1 SHORT-TERM EXPOSURE OF ACETAZOLAMIDE IN THE PHARMACOLOGIC TREATMENT OF CHRONIC METABOLIC ALKALOSIS IN NEONATES AND INFANTS

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Purpose of Study: To evaluate the effects on electrolyte homeostasis and acid-base balance of acetazolamide administered to ameliorate the metabolic alkalosis associated primarily with diuretic therapy in neonates and infants with chronic respiratory insufficiency.

Methods Used: Infants and neonates who received acetazolamide (3-5 mg/kg/dose intravenously every 6 hours up to 4 doses) in the NICU of Childrens Hospital Los Angeles between January 2006 and October 2007 were identified. A retrospective chart review was conducted to obtain patient demographics, concurrent diuretics, electrolyte supplements, parenteral nutrition, number of acetazolamide doses, results of serum metabolic panel(s) and blood gas analyses, and urine output during the 24 hours of the study.

Summary of Results: Eighty-nine patients receiving 129 courses of acetazolamide were identified and included. Fifty, 42, 17 and 20 patients received 1, 2, 3, and 4 doses of acetazolamide, respectively. Calculated serum bicarbonate (36.9 ± 4.1 vs. 31.5 ± 4.3 mEq/L, P < 0.001) and BE (10.0 ± 3.4 vs. 4.8 ± 4.0 mEq/L, P < 0.001) were significantly reduced following 24 hours of acetazolamide administration. During the same time interval, a statistically significant decrease in serum pH (7.41 ± 0.06 vs. 7.37 ± 0.06, P < 0.001) and creatinine (0.38 ± 0.19 vs. 0.43 ± 0.19, P < 0.001) and an increase in serum chloride concentration (98.9 ± 5.3 vs. 101.3 ± 5.5 mEq/L, P < 0.001) from baseline were noted. There were no significant differences in serum sodium, potassium, blood urea nitrogen, and urine output. After acetazolamide administration, 4 patients developed uncompensated respiratory acidosis (pH < 7.25) with pCO2 > 40 mEq/L.

Conclusions: Short-term exposure to acetazolamide for the pharmacologic treatment of chronic metabolic alkalosis associated with diuretic therapy in neonates and infants with chronic respiratory insufficiency results in a decrease in metabolic alkalosis with a 3% incidence of “overshoot” acidosis. More data are needed to establish the safety and efficacy of short-term acetazolamide to correct diuretic associated metabolic alkalosis in this patient population.

2 CHITOSAN-MEDIATED IN UTERO GENE THERAPY FOR CYSTIC FIBROSIS

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Purpose of Study: In utero gene replacement is a novel treatment paradigm for the prenatal and postnatal monogenic disorders. Traditional viral vector-mediated gene delivery carries the risks of endogenous virus recombination and random insertion into the genome, resulting in oncogenesis. To increase safety, non-viral gene delivery systems using complex polymers are currently under investigation. The purposes of our studies are: 1) to use a non-viral vector (chitosan nanoparticles) containing reporter gene Green Fluorescent Protein (GFP) to transfet HEK 293T cells in vitro; 2) to use chitosan containing reporter gene firefly luciferase (LUC) to transfect Calu-3 (a CF submucosal gland cell line) cells in vitro; and 3) to perform in utero GFP gene delivery via intra-amniotic injection of chitosan-pGFP construct; and analyze post-natal pup tissues and maternal tissues for transgene presence and expression.

Methods Used: HEK293T cells were transfected with chitosan-pGFP and GFP positive cells were visualized after 48 hours using direct fluorescence microscopy. Calu-3 cells were transfected with either chitosan-pLUC or naked pLUC, and LUC positive cells were analyzed by luminometer at 48 hrs post-transfection. Time-mated CD-1 pregnant dams underwent laparotomy on gestational day 16 (term = 21d), and individual amniotic sacs were injected with chitosan-pGFP. Following spontaneous delivery, pups and dams were sacrificed on post-natal day 1. All tissues were examined for GFP transgene presence and expression by DNA PCR, qRT-PCR, and whole mount fluorescent microscopy.

Summary of Results: Transfection of HEK293T and Calu-3 was seen with the chitosan-pDNA constructs, suggesting that chitosan is functional as a vector to deliver genes into cells in culture. In vivo transfection of fetal mice via intra-amniotic injections of chitosan-GFP resulted in GFP expression in lungs and intestines. Maternal mice were negative for DNA transfection.

Conclusions: Chitosan appears to be an effective vector for gene delivery both in vitro and to fetal mice. Successful transfection of Calu-3 human cystic fibrosis submucosal gland cell line suggests that these target cells for CF gene therapy are transfetable with chitosan-DNA. Chitosan shows early promise as a transgene delivery system for the purpose of in utero gene replacement therapy.

3 MODULATON OF REGULATORY T LYMPHOCYTES BY KILLER DENDRITIC CELLS

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Purpose of Study: In addition to their primary role as initiators and regulators of the immune response, emerging evidence indicates that dendritic cells (DC) are also endowed with a direct killing activity. The goal of this work was to evaluate whether activated killer DC were able to negatively modulate regulatory T cells (Treg), major components of tumor-induced immunosuppression.

Methods Used: DC were generated from bone marrow cells harvested from femurs and tibiae of BALB/c mice and cultured for five days in complete medium (RPMI, Gibco/BRL) supplemented with 10% Fetal Bovine Serum (Gibco). Day 5 DC were added to 96-well plates and were activated with either the TLR-4 agonist lipopolysaccharide (LPS) or with the synthetic bacterial lipopeptide Pam3Cys-SK4 (Invivogen) (a TLR-2 agonist). Regulatory T cells were isolated from the spleen and lymph nodes of BALB/c mice using a mouse CD44/CD25® Regulatory T cell isolation kit and an autoMACS separator according to manufacturers’ instructions (Miltenyi Biotec, Auburn). Activated DC were cultured for 24 hours with CD44/CD25+ Treg or with conventional CD44/CD25+ T lymphocytes (ratio 1:1). The number of dead lymphocytes was then evaluated at the end of the co-culture using trypsin blue.

Summary of Results: Our data indicated that LPS or Pam3Cys-SK4 - activated DC triggered death of 58.8% and 40% of CD44/CD25+ Treg, respectively, compared to 4.4% when Treg were incubated with non-activated DC. The percentage of dead CD44/CD25+ T lymphocytes was not modified by the presence of the DC in the culture. Analysis by flow cytometry after staining of the cells with propidium iodide (eBioscience) and anti-CD4 indicated that LPS-activated DC were more cytotoxic against Treg compared to non-activated DC or to DC activated with Pam3Cys-SK4.

Conclusions: Murine bone marrow-derived dendritic cells activated with LPS are capable of inducing death of a proportion of regulatory T cells. Further studies are required to evaluate the significance of these findings in vivo and to determine whether these findings may be reproduced in humans.
4 FRUCTOSE CONSUMPTION IN RHESUS MACAQUES AS A MODEL FOR ACCELERATED DEVELOPMENT OF DYSLIPIDEMIA AND INSULIN RESISTANCE

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Purpose of Study: To evaluate the effects of a fructose-supplemented diet on the lipid metabolism, adipocytokine hormones, and insulin sensitivity in rhesus macaques.

Methods Used: Thirty-two adult male rhesus macaques, age 12 to 20 years, were studied (body weight = 16.4 ± 0.4 kg). At baseline, all animals had fasting glucose concentrations <100 mg/dl, fasting insulin concentrations <100 µU/ml, fasting triglyceride concentrations <100 mg/dl, and a percent body fat >20%. In addition to a standard ad libitum diet (26% energy as protein, 14% energy as fat, and 60% energy as carbohydrate), all animals were provided 500 ml/day of a fruit-flavored 15–20% fructose-sweetened beverage. Total and percent body fat were determined by DEXA and glucose tolerance and insulin sensitivity were assessed with intravenous glucose tolerance tests (IVGTTs) at baseline, 6, and 12 months. Fasting glucose, insulin, total cholesterol, HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), triglyceride (TG), apolipoprotein-A1 (ApoA1), apolipoprotein-B (ApoB), adiponectin, and leptin concentrations were measured at baseline, 1, 3, 6, 9, and 12 months.

Summary of Results: One year of fructose consumption in rhesus macaques significantly increased body weight (+1.5 ± 0.6 kg, P < 0.01), fat mass (+4.5 ± 2.0%, P < 0.001), percent fat mass (+4.5 ± 2.0%, P < 0.001), the area under the curve (AUC) for glucose during an IVGTT (+12 ± 4%, P < 0.01), and fasting insulin (+124 ± 21%, P < 0.01), TG (+96 ± 12%, P < 0.001), leptin (+44 ± 7%, P < 0.001), and ApoB (+17 ± 9%, P < 0.01) concentrations. Moreover, one year of fructose consumption significantly decreased fasting HDL-C (-12 ± 6%, P < 0.01) and adiponectin (-31 ± 12%, P < 0.01) concentrations. In addition, four animals (12% of the study population) developed significantly increased fasting glucose concentrations (171 ± 7 mg/dl, P < 0.001) and overt diabetes.

Conclusions: Fructose-fed rhesus macaques represent a novel non-human primate model of accelerated development of the metabolic syndrome and will be useful for investigating the pathophysiology, prevention, and treatment of insulin resistance and dyslipidemia.

WSCL, WAP, WSPR, WSMRF
Student Subspecialty Award Poster Session
6:00 PM
Thursday, January 29, 2009

5 FEASIBILITY OF A WALKING SCHOOL BUS PROGRAM TO PREVENT OBESITY IN HISPANIC ELEMENTARY SCHOOL CHILDREN

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Purpose of Study: Hispanic children have the highest prevalence of being overweight or obese in the US at 42.8%. Walking to school is an affordable mode of transportation that may help reduce this high prevalence. The purpose of this study was to assess the feasibility of a 10 week trial of the Walking School Bus (WSB) Program among a population of Hispanic elementary school students as a strategy to prevent obesity.

Methods Used: Kindergarten through 5th grade students who lived within a one mile radius of the participating school were recruited. Children walked on designated routes to and from school supervised by parent volunteers. Four health themes were emphasized: (1) get up and play, (2) turn off your television, (3) eat five servings of fruit and vegetables per day, and (4) reduce soda and juice intake. Pre/post questions taken from CDC 2005 Youth Risk Behavior Survey, 24-hour diet recalls, and height and weight measurements were performed to assess health outcomes.

Summary of Results: Among the 28 children who initially enrolled, three dropped out. Remaining 25 were Hispanic with 56% reporting that Spanish was the preferred language at home, ages were 5–11 years, and 64% were female. Seventy-six percent of participants walked an average of three or more times per week. BMI percentile remained fairly stable from 50.8% pre-WSB to 49.3% post-WSB (P = 0.1). According to pre/post surveys, participants increased physical activity from a mean of 4.3 to 5.3 days/week (P = 0.08) and increased their consumption of fruit from 0.83 to 1.59 servings/day (P = 0.01). Vegetable intake more than doubled according to 24-hour diet recalls (P < 0.001). There were no significant changes in television viewing time and soda/ juice intake.

Conclusions: The WSB program was feasible with no excessive weight gain in the group of children and self-reported obesity reduction behavior changes. The WSB with health themes may be an important childhood obesity prevention strategy from a public health promotion perspective.

6 HOW DOES AUDITORY SENSORY GATING IN NEWBORNs WITH PRENATAL DRUG AND/OR NICOTINE EXPOSURE DIFFER FROM NEWBORNs WITH NORMAL PRENATAL EXPOSURES?

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Purpose of Study: This study looked at the effect of prenatal multi-drug and nicotine exposure on sensory auditory gating in infants. Auditory sensory gating, using a paired-click paradigm, provides a physiological measure of the brain’s ability to disregard irrelevant information (Adler, 1985). It is related to attentional control. Evoked responses (ERPs) to the paired clicks are recorded and compared using a ratio (T/C Ratio) of peak amplitudes following the auditory stimuli (Stimulus 2; Test/Stimulus 1; Conditioning). Individuals with intact auditory gating tend to exhibit ratios of less than 0.4 (Seigel, 1984). We hypothesized that infants prenatally exposed would exhibit a deficit in auditory sensory gating as compared to infants with no prenatal exposure.

Methods Used: Auditory ERPs were collected on 18 case (i.e., infants born to poly-drug abusing mothers) and 27 control infants. Continuous EEG was recorded from site Cz and used in ERP analysis. Bipolar electrooculagram (EOG) and electromyogram (EMG) were used to help determine when the infant entered active sleep. To investigate whether auditory sensory gating differed based on prenatal exposures to drugs, the mean T/C ratios for cases and controls were compared using a student’s t-test with a two-sided alpha of .05. All procedures were approved and monitored by the Colorado Multiple Institutional Review Board.

Summary of Results: Cases and controls did not differ in gestational age, size, gender, or race and ethnicity. Latencies and amplitudes of ERPs for conditioning and test clicks were similar. Controls were found to have lower T/C ratios (mean T/C ratio = 0.46) than cases (mean T/C ratio = 0.62).

Conclusions: This is the first study to evaluate auditory sensory gating in infants prenatally exposed to illicit drugs. Infants with prenatal drug exposures were found to have deficits in auditory sensory gating when compared to infants with no prenatal drug exposures. Auditory sensory gating deficits indicate attentional difficulties, and while we cannot say whether that these infants will continue to exhibit problems with attention in the future, it appears that they may have trouble filtering out irrelevant information presently.

7 TRANSFORMING GROWTH FACTOR-BETA PATHWAY POLYMORPHISMS AND AORTIC ROOT DILATATION IN KAWASAKI DISEASE PATIENTS

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Purpose of Study: Kawasaki disease (KD) is a pediatric systemic vasculitis that causes aortic root dilatation in approximately 15% of patients (pts). Other syndromes associated with aortic root dilatation include Marfan and Loeys-Dietz syndromes, which result from increased levels of transforming growth factor-beta (TGF-β) due to point mutations in genes in the signaling pathway. TGF-β is a multifunctional protein affecting proliferation, apoptosis, differentiation, and collagen synthesis. We postulated that genetic variation in the TGF-β pathway might influence aortic root dilatation in KD.
Methods Used: We measured aortic root dimensions on echocardiograms performed during the acute and convalescent period in 109 KD pts (75% Caucasian, 13% Hispanic, 1% Asian, 11% mixed ethnicity). Measurements were normalized for body surface area and expressed as z-scores. Subjects were classified as dilated if the z-score for the aortic annulus or sinus was ≥2 on any echo. Genotypes for all haplotype-tagged single nucleotide polymorphisms (SNPs) for TGF-β, TGF-β receptor 1 (R1), and TGBFR2 were determined using a custom Illumina® Oligo Pool Assay. Case-control analysis was performed using general linear models.

Summary of Results: Two intrinsic SNPs in TGBFR1 were found to have a nominal P < 0.05 under the allelic and dominant models. rs10733710 was positively associated with aortic root dilatation in both the allelic (P = 0.02, OR 2.73, 95% CI 1.18-6.29) and dominant (P = 0.02, OR 3.35, 95% CI 1.15-9.76) models. rs6478974 was negatively associated with aortic root dilatation in both the allelic (P = 0.05, OR 0.47, 95% CI 0.21-1.04) and dominant (P = 0.01, OR 0.25, 95% CI 0.10-0.73) models. Haplotype analysis using a moving window of 2 identified a protective (P = 0.02) and risk (P = 0.01) haplotype in TGBFR1.

Conclusions: Excess signaling through the TGF-β pathway may lead to a spectrum of aortic root pathology ranging from mild (KD) to severe (Marfan). Immunohistochemistry of KD aortic roots and additional genotyping of TGF-β pathway SNPs may further elucidate the role of TGF-β in KD pathogenesis.
they produce "microwords" that are much shorter and less accurate than conventional Sanger sequencing. These factors have prevented their use for applications including de novo genome assembly, full length cDNA sequencing, metagenomics, and the interrogation of non-unique sub-sequences of assembled genomes. Towards addressing these limitations, we sought to develop strategies that enabled the grouping and assembly of microwords derived from the same kilobase-scale fragments.

Methods Used: As a proof-of-concept, we randomly sheared genomic DNA from Pseudomonas aeruginosa to ~1.2 kb and cloned the fragments into pUC19, a standard cloning vector. The resulting plasmid library was processed to a shotgun sequencing library such that one end of each library molecule corresponds to the vector-insert junction, and the other end to a random breakpoint internal to the kilobase-scale fragment associated with that junction. With paired-end sequencing on a next-generation platform (Illumina GA), we obtained pairs of microwords corresponding to each of these ends. Each group of shotgun microwords associated with the same vector-insert junction "tag" was considered to be derived from the same kilobase-scale fragment, and was assembled in silico to one or more consensus "subassemblies."

Summary of Results: A total of 22,284 groups representing 10.1 million shotgun microwords were individually subjected to subassembly using the phrap algorithm. A total of 86,012 subassemblies resulted, each of which was derived from at least 2 shotgun microwords. The average total length of subassemblies derived from each group was 607 bp, with an average of 3.8 subassemblies per group. The average size of the longest subassembly from each of the 22,284 groups was 306 bp, and the longest subassembly was 1017 bp. Manual review of a subset of the longest subassemblies demonstrated that the assemblies were accurate and that the accuracy of consensus base calls was significantly improved over the raw microwords.

Conclusions: We show that next-generation, massively parallel DNA sequencing can be adapted to obtain long, high-accuracy reads, significantly extending the application of this technology.

12 AUTOMATED CLINICAL INFORMATION SYSTEM IMPROVES PATIENT CARE

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Purpose of Study: Studies have shown that poor quality medical care can result from time constraints and fragmentation of care causing delays in treatment and/or inconsistent documentations. Following a root cause analysis of patient deaths in the liver transplant program at the University of Washington (UW) from 2003–2006, the program identified immunosuppressive drug toxicities as the leading cause of patient morbidity after discharge from the hospital. Due to the increasing volume of post transplant patients, the time to adjust medications sometimes required 3 days following laboratory results. This extended period also caused inconsistent documentation. To address these concerns, the UW liver transplant program developed and instituted an automated clinical support system that consolidated clinical information needed for immunosuppressive medication review.

Methods Used: To study the effect of the new automated clinical informatics system, data was collected on 428 consecutive liver transplant patients receiving tacrolimus between Jan 2004–Apr 2008.

Summary of Results: Using the automated system reduced the time to make medication adjustment to less than 1 hour. The 127 patients on the automated system had a creatinine clearance at one year (87.5 ± 32.9 ml/min) significantly higher (P = 0.008) than the creatinine clearance (74.4 ± 30 ml/min) in those 301 patients using the old paper chart system. The incidence of tacrolimus toxicity in one year was significantly lower (P = 0.05) in those being monitored with the automated system (18%) vs being monitored with the paper charting system (30%). The incidence of rejection within one year was significantly lower (P = 0.001) in patients being monitored with the automated system (7%) vs being monitored with the paper charting system (27%). In a formal cost-effective analysis the automated system demonstrated absolute cost-effectiveness compared to the paper charting system cost $322 to monitor a patient for one year with a 97% quality of life compared to the paper charting system cost of $1790 with an 89% quality of life.

Conclusions: These results are one of the first to demonstrate that an automated clinical information system for monitoring chronic drug maintenance is cost-effective. In conclusion, an automated clinical informatics system improves the management of immunosuppressive drugs in transplant patients and improves the quality of patient care and life.

13 FEEDBACK REGULATION OF p53/microRNA 34a/BCL6 CIRCUITRY IN B-CELL DIFFERENTIATION

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Purpose of Study: Three decades of studies have placed p53 at the center of the tumor-suppressor network. Only recently, microRNA 34a (miR-34a) has been identified to be transcriptionally activated by p53, demonstrating for the first time the tumor-suppressor role of small, non-coding RNAs in the p53 network. BCL6, whose translocation to the immunoglobulin loci is responsible for 40% of diffuse large B-cell lymphoma, has been shown to suppress p53 expression in germinal-center B cells. Interestingly, the 3′ untranslated region (3′ UTR) of BCL6 contains miR-34a binding sites, as predicted by multiple computational algorithms. This study aims to test the hypothesis that miR-34a is a crucial negative regulator of BCL6 post-transcriptionally, and therefore, is important in regulating germinal center formation and B cell differentiation.

Methods Used: In vitro plasma differentiation assay was used to purify a B lymphocyte (B220+) population and a plasma cell (B220+ CD138+) population from mouse spleens. RNA levels were quantified by RT-qPCR.

Summaried of Results: The plasma differentiation assay show that as B cells differentiate into plasma cells, BCL6 mRNA level goes down, while miR-34a and p53 mRNA levels increase. To characterize this regulatory circuitry further, 293T cells were transfected with an inducible vector expressing BCL6 with its 3′ UTR and a vector containing p53 promoter upstream of a luciferase reporter. When the expression of BCL6 was induced, the p53 promoter was repressed, resulting in a 70% reduction in luciferase activity. More interestingly, when we also over-expressed miR-34a at the same time, a 50% increase in luciferase activity was noticed, suggesting that miR-34a down-regulates BCL6, leading to de-repression of the p53 promoter.

Conclusions: While the initiating event during this germinal center B cell to plasma cell transition remains elusive, our data suggests that it is potentially regulated by a positive feedback loop involving p53, miR-34a, and BCL6, specifically p53->miR-34a->BCL6->p53. Future studies will be conducted to further examine this putative positive feedback loop and address its physiological relevance in the context of B-cell differentiation and malignancy.

14 EFFECTS OF SPECIFIC SINGLE-NUCLEOTIDE POLYMORPHISMS IN A LUPUS-ASSOCIATED HAPLOTYPE OF COMPLEMENT RECEPTOR 2 ON ALTERNATIVE SPlicing

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Purpose of Study: A common three-single-nucleotide polymorphism (SNP) haplotype in the complement receptor 2 (CR2/CD21) gene is associated with systemic lupus erythematosus (SLE). SNP2 and SNP3 of the haplotype are located in exon 10, directly 5′ of the alternatively spliced exon 11 that is preferentially expressed in follicular dendritic cells (FDC). Alleles at these SNPs may influence splicing, alter relative amounts of CR2 long and short isoforms, and contribute to lupus susceptibility.

Methods Used: To determine the effect of SNP2, SNP3, and two SNPs in exon 11 on splicing, CR2 genomic DNA from introns 9 to 12 containing the minor allele for all four SNPs was cloned into an exon-trapping vector (pL53m). A second plasmid containing all major alleles was generated by site-directed mutagenesis. Both plasmids were transiently transfected into Raji (B cell) and HK (FDC) lines. Relative amounts of vector-derived mRNA including or excluding exon 11 were determined by quantitative RT-PCR. The relative amount of each isoform in primary B cells from healthy human subjects was also assessed.

Summary of Results: In Raji cells transfected with the major allele construct, levels of transcripts excluding exon 11 were 8.8-fold higher than those including it, whereas they were 13-fold higher in cells with minor alleles. Similarly, in HK cells, transcript levels excluding exon 11 were 4-fold and 12-fold higher with major and minor alleles respectively. In primary B
cells from subjects with major alleles at all four SNPs (n = 3), short isoflom mRNA levels were 1.3-fold higher than long, while in subjects with all minor alleles (n = 2), they were 3-fold higher.

Conclusions: In conclusion, the major alleles of four SNPs in exon 10 and 11 of the CR2 gene decrease the splicing efficiency of exon 11 in vitro and in vivo. Identification of the specific SNPs involved and characterization of their effects on protein expression and function will broaden our understanding of the role of CR2 in the pathogenesis of lupus.

15 CHITOSAN NANOPARTICLES FOR ANTIMICROBIAL TREATMENT AGAINST CUTANEOUS PATHOGENS

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Purpose of Study: Skin infections are a major concern due to the increasing prevalence of antibiotic resistance in two of the most common bacteria: Staphylococcus aureus and Propionibacterium acnes. Methicillin-resistant S. aureus (MRSA) is responsible for an estimated 18,000 deaths each year while 60-70% of P. acnes are resistant to common antibiotics. One potential new antimicrobial is chitosan, a derivative of the crustacean shell chitin. It is a polymeric cation with broad spectrum and low toxicity towards mammalian cells. The positively charged chitosan molecule is thought to interact with the negatively charged bacterial cell membrane and cause cell lysis. This mechanism of killing makes it difficult for bacterial resistance to develop. Studies on nasal and oral drug delivery have also found chitosan to enhance paracellular transport of drugs across the epithelium by opening tight junctions. Alginate, a polymer extracted from brown algae, can be used with chitosan to form nanoparticles (NP) with antimicrobial activity that can also enhance delivery of other therapeutics.

Methods Used: Alginate was first gelated to form the core of the NP using CaCl2 to cross-link its guluronic acid units. Chitosan was then dissolved in acidic water and added to alginate under sonication to promote homogenous mixing. The NP was then precipitated out of solution using a centrifuge and washed several times. It was finally resuspended in distilled water and ready for use. The bactericidal activity of the NPs and controls were assessed using colony forming unit (CFU) assays. The two bacteria used for testing were P. acnes and S. aureus. Effectiveness of killing was judged relative to no treatment.

Summary of Results: Chitosan’s bactericidal activity was found to be pH dependent, with optimal killing at pH 6. In addition, S. aureus appears much less susceptible to chitosan’s antimicrobial activity than P. acnes. Alginate was shown to be non-bactericidal at all the pH’s tested.

Conclusions: Future formulations of chitosan-alginate NP’s need to take into account the pH of the environment and the pathogen targeted. Further antimicrobial activity of chitosan and NP will need to determined using in vivo skin infection model.

16 ASSESSMENT OF AUTonomic DAMAGE IN DIABETICS USING AN ISOMETRIC HANDGRIP TEST

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Purpose of Study: Isometric handgrip exercise was evaluated for its usefulness as an assessment of autonomic damage associated with type II diabetes.

Methods Used: Fifteen young adult control subjects (30.6 ± 8.6 years), 15 senior control subjects (65.8 ± 8.8 years), and 15 type II diabetics (63.4 ± 14.4 years) whose average body fat percentages were 40.1 ± 12.9, 36.1 ± 9.3, and 39.6 ± 15.5%, respectively, participated. Cutaneous blood flow and perspiration during isometric exercise may be a viable tool to determine the extent of autonomic damage associated with diabetes.

Summary of Results: Cutaneous blood flow and perspiration response rates were greatest in the younger controls (P < 0.05), significantly less in the older controls (P < 0.05), and significantly even less in subjects with diabetes (P < 0.05).

Conclusions: Recent studies show that there is an impaired release of or bioavailability of nitric oxide from vascular endothelial cells associated with damage from diabetes. Since vasodilation and perspiration are mediated by nitric oxide release, it is not surprising that the present study demonstrated significantly impaired vasodilation and sweating in diabetic subjects. Ultimately, local changes in cutaneous blood flow and perspiration during isometric exercise may be a viable tool to determine the extent of autonomic damage associated with diabetes.

17 ULTRASOUND IMAGING OF THE FETAL CISTERNA MAGNA: DIFFERENTIATION OF MEGA CISTERNA MAGNA FROM DANDY-WALKER VARIANT BY RATE OF GROWTH OF THE FETAL CISTERNA MAGNA IN THE SECOND AND THIRD TRIMESTERS

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Purpose of Study: Mega cistern magna (MCM) and Dandy-Walker variant (DWW) represent a spectrum of cystic posterior fossa malformations within the Dandy-Walker complex. Due to their shared embryology and frequently overlapping appearance on prenatal ultrasound, differentiation is particularly challenging. However, discrimination between these posterior fossa lesions is critical for improved prognosis and prenatal counseling. The purpose of this study was to evaluate the growth of the fetal cisterna magna from the second through third trimester by transabdominal sonography of fetuses with MCM and DWV to identify distinguishing characteristics that may assist in diagnosis.

Methods Used: Sequential second and third trimester transabdominal sonograms of fetuses with MCM and DWV were retrospectively evaluated. In the standard axial plane, the anteroposterior (AP) diameters of the fetal cisterna magna were measured and charted against gestational age. The neurodevelopmental outcome of each fetus was retrospectively reviewed.

Summary of Results: From 2000 to 2008, adequate second and third trimester transabdominal sonography for 11 fetuses with DWV and 17 with MCM was identified in our ultrasound database. The cisterna magna growth ranged from 0.16–0.74 mm/week for DWV’s (mean, 0.38 ± 0.17 mm/week) and 0.08–0.98 mm/week (mean, 0.53 ± 0.22 mm/week) for MCM’s. The area under the ROC curve for differentiating MCM from DWV was 0.735 with a 95% confidence interval of 0.53–0.882. A critical value of 0.48 mm/week for the growth slope corresponds to a sensitivity of 52.9% and a specificity of 90.0% for prediction of MCM (P = 0.0128) for selecting MCM vs. DWV. On evaluation of postnatal neurodevelopmental outcome, all 17 (100%) fetuses with MCM were found to be developing normally, whereas 2 (18%) of the fetuses with DWV were developmentally normal.

Conclusions: On average, fetuses diagnosed with MCM appeared to have a moderately increased rate of cisterna magna growth relative to that of fetuses diagnosed with DWV. This characteristic may support the differentiation of MCM and DWV on prenatal ultrasound.

18 BRAIN INJURY AND AMPLITUDE-INTEGRATED ELECTROENCEPHALOGRAM IN PRETERM INFANTS

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Purpose of Study: Preterm infants are at risk for brain injury and adverse neurodevelopmental outcome. Amplitude-integrated electroencephalogram (aEEG) measures brain function and shows maturation of the background pattern with increasing postmenstrual age. The impact of brain injury on aEEG maturation is not known. The aim of this study was to quantitatively describe the effect of postmenstrual age and brain injury on aEEG.

Methods Used: This was a prospective cohort study including infants born <34 weeks gestation with aEEG and magnetic resonance imaging (MRI) in the newborn period. Exclusion criteria were evidence of congenital malformation or TORCH infection. Infants were considered to have significant brain injury if any of the following were present on magnetic resonance imaging: white matter injury (greater than 3 areas of grade III injury hypertension (greater than 2 mm), intraventricular hemorrhage > grade II, ventriculomegaly (largest atrial ventricular diameter >8–10 mm). A neurological examination was performed within 24 hours of MRI using standard criteria. A single-channel Olympic 6000 monitor was used to record aEEG within 48 hours of MRI. The total aEEG score was calculated using the system described by Burdjalov et al. The relationship between total aEEG score and postmenstrual age and brain injury was assessed using linear regression for repeated measures.
Summary of Results: Twenty-six infants with 33 aEEG tracings were included in this study. Eight (31%) had brain injury as defined above. Total aEEG score was significantly associated with perinatal age (r = 0.87, P < 0.001). For infants without brain injury, total aEEG score rose by 0.8 points (95% confidence interval: 0.6-2 points) with each week increase in perinatal age. Infants with brain injury had a trend toward lower scores that was not significant (P > 0.06). The effect of brain injury did not depend on perinatal age.

Conclusions: There were quantifiable changes in aEEG recordings with increasing perinatal age. The lower scores on aEEG in infants with brain injury were not statistically significant in this small cohort.

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PHYSIOLOGIC VITAMIN D HORMONE 1,25(OH)_{2}D_{3}
HAS SPATIAL AND TEMPORAL-SPECIFIC ACTIONS
DURING PERINATAL PULMONARY MATURATION
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Purpose of Study: The mechanisms leading to increased surfactant synthesis and secept thinning, the key features of perinatal lung maturation, remain incompletely understood. Using in vitro models, we have shown that the physiologic Vitamin D steroid hormone 1,25(OH)_{2}D_{3} (1,25D) may be an important paracrine/autocrine effector of perinatal lung maturation. However, its role under in vivo conditions has not been examined. We hypothesized that 1,25D administered in vivo will promote alveolar maturation by increasing surfactant synthesis and secept thinning. In this study, we determined alveolar type II (ATII) and fibroblast differentiation and lung morphometry following parental administration of 1,25D to rat pups.

Methods Used: Sprague-Dawley rat pups were administered saline (control) or 1,25D (5 ng/kg) once daily up to 3 weeks. After sacrifice the lungs were examined for markers of ATII cell and fibroblast differentiation and morphometry on postnatal days 1, 7, 14, and 21. The markers of ATII cell and fibroblast differentiation examined by Western hybridization included Surfactant Protein (SP-B), SP-C, Cholinephosphate Cytidylyltransferase-α (CCCT-α), Parathyroid Hormone-Related Protein (PTHRP) and its receptor, Peroxisome Proliferator-Activated Receptor (PPARγ), and Bcl/Bax ratio.

Summary of Results: 1,25D administration significantly increased the expression of key ATII cell and fibroblast differentiation markers as well as increased alveolar counts, but paradoxically, it increased septal thickness (P < 0.05 vs control for both). With 1,25D administration the Bcl/Bax ratio also increased significantly at all time points examined.

Conclusions: Vitamin D administration to neonatal pups increased ATII cell and fibroblast differentiation, alveolar counts, which was accompanied by an increase in septal thickness. This increase along with increased Bcl/Bax ratio suggests increased fibroblast proliferation, likely due to inhibited apoptosis. We conclude that spatial and temporal-specific actions of Vitamin D play a critical role in perinatal pulmonary maturation by stimulating key alveolar epithelial-mesenchymal interactions and lipofibroblast proliferation/apoptosis.

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DEVELOPMENTAL EXPRESSION AND FUNCTION OF COLLAGEN TYPE XI IN ZEBRAFISH
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Purpose of Study: Collagen Type XI (Col XI) plays an important role in the embryonic development of many species. Human mutations in Col XI result in Marshall and Stickler Type 2 syndromes which are characterized by abnormalities in craniofacial and ear development. Collagen Type XI knockdown experiments were performed by microinjection of an anti-sense morpholino. Morphant embryos were then stained with alcin blue to detect abnormal alerin cartilage in craniofacial structures.

Summary of Results: Col XI knockdown experiments were performed by microinjection of an anti-sense morpholino. Morphant embryos were then stained with alcin blue to detect abnormal alerin cartilage in craniofacial structures.

Conclusions: This study confirms the viability of zebrafish as a model organism for the study of Col XI and provides evidence for a functional role of Col XI in craniofacial bone development. Further studies will focus on determining isomorph specific expression patterns in the tissues already described and elucidating the functions of the several Col XI isoforms in craniofacial and ear development.

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ELEVATED ACTIVITY OF MATRIX METALLOPROTEINASE-2 AND -9 IS ASSOCIATED WITH INCREASED STIFFNESS, MEDIOL CALCIFICATION AND VATOSOMOT DYNYNCTION OF ARTERIAL VASCULARITY IN PATIENTS WITH END-STAGE KIDNEY DISEASE
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Purpose of Study: Arterial stiffening and medial calcification contribute to increased cardiovascular mortality in patients with chronic kidney disease (CKD). Matrix metalloproteinase (MMP) -2 and -9 play a crucial role in vascular remodeling and maintaining matrix integrity and structural stability. We hypothesized that in the macro-vascularity of CKD patients, especially those on dialysis (Stage 5), MMP-2 and -9 would be elevated, leading to elastic fiber fragmentation and arterial stiffening. Such abnormal structural changes would, in turn, lead to demonstrable vasomotor dysfunction.

Methods Used: During living donor kidney transplantation, inferior epigastric arteries (EIA) from recipients [non-dialysis (ND-EGA) = 11; dialysis (D-EGA) = 22] were harvested for mechanical, histological, functional, and molecular studies.

Summary of Results: Stiffness coefficient of D-EGA was 30% greater than that of ND-EGA. Movat’s staining showed elastic fiber fragmentation and a marked reduction of the external elastic lamina (EEL)/media ratio in D-EGA. Medial calcium/phosphate deposition, demonstrated by von Kossa stain, strongly correlated with the increased stiffness coefficient in D-EGA (r = 0.61, P < 0.05). Both stiffness coefficient and medial calcium/phosphate deposition in D-EGA were negatively correlated with the phenylephrine-induced contraction (r = 0.406, r = 0.443, P < 0.05, respectively). These correlations were absent in ND-EGA. In D-EGA, the expression level and gelatinolytic activity of both MMP-2 and -9 were elevated, and the activity of MMP-2 negatively correlated with the EEL/media ratio (r = 0.60, P < 0.05).

Conclusions: The impaired vasomotor function of EGA from Stage 5 CKD patients correlated with composite measures of arterial stiffening, elastic fiber disorganization, and medial calcification. These findings were correlated with increased levels of MMP-2 expression and activation. Therefore, elevated MMP-2 activity may be the molecular basis for the adverse cardiovascular events in patients with end-stage kidney disease.
tested the hypothesis that the estrogen-mediated attenuation of the cannabinoid inhibition of glutamatergic synaptic input takes place on a rapid time scale.

Methods Used: Whole-cell patch clamp recordings were performed using hypothalamic slices prepared from ovariectomized female guinea pigs. We evaluated glutamatergic synaptic input in ARC neurons by monitoring the frequency and amplitude of miniature excitatory postsynaptic currents (mEPSCs). Slices were perfused for 10–15 minutes with either 100 nM estradiol benzoate (EB) or its ethanol vehicle. Baseline data was obtained over 3–4 minutes, after which both steroid- and vehicle-treated slices were subsequently exposed to varying concentrations of the cannabinoid CB1 receptor agonist WIN 55,212-2, yielding 3–4 minutes worth of additional data upon equilibration of the drug in the slice in order to evaluate the change in mEPSC frequency and amplitude. The recorded neurons were subsequently identified via immunohisto-fluorescence using phenotypic markers for POMC neurons.

Summary of Results: In cells from vehicle-treated slices, WIN 55,212-2 elicited a dose-dependent decrease in mEPSC frequency but not amplitude. EB treatment rendered the cannabinoid less effective in reducing mEPSC frequency, manifest by a rightward-shift in the agonist dose-response curve. These effects were observed in identified POMC neurons from both vehicle- and EB-treated slices.

Conclusions: This study demonstrates that estrogen rapidly diminishes the cannabinoid-mediated inhibition of glutamatergic input onto ARC POMC neurons. Such findings may be applied to feeding behavior regulation as well as elucidation of a membrane-bound estrogen receptor signal transduction pathway.

23 COBINAMIDE AND DOS MONITORING-A POTENTIAL NEW TREATMENT APPROACH FOR MASS CASUALTY CYANIDE POISONING

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Purpose of Study: To determine the ability of inhaled cobinamide to rapidly reverse cyanide (CN) toxicity using diffuse optical spectroscopy (DOS).

Methods Used: Cyanide toxicity was induced in New Zealand white rabbits using a standard 10 mg intravenous CN infusion model developed in our laboratory. Quantitative DOS monitoring of physiologic effects of cyanide toxicity were performed continuously during cyanide toxicity and treatment concurrently with standard arterial and venous blood gas sampling, and cyanide levels. Animals were treated with aerosolized cobinamide (83.5 mg or 240.6 mg), or controls; and response to therapy measured.

Summary of Results: In cells from vehicle-treated slices, WIN 55,212-2 yielded 3–4 minutes worth of additional data upon equilibration of the drug in the slice in order to evaluate the change in mEPSC frequency and amplitude. The recorded neurons were subsequently identified via immunohisto-fluorescence using phenotypic markers for POMC neurons.

Conclusions: This study demonstrates that estrogen rapidly diminishes the cannabinoid inhibition of glutamatergic synaptic input on ARC neurons. Such findings may be applied to feeding behavior regulation as well as elucidation of a membrane-bound estrogen receptor signal transduction pathway.

24 OP-1 ENHANCES OSTEOGENESIS IN OSTEOPROGENITOR CULTURES CHALLENGED WITH POLYMETHYL METHACRYLATE PARTICLES

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Purpose of Study: Periprosthetic osteolysis results in part from the biologic reactions of bone cells and osteoprogenitors to orthopedic wear debris. Previous studies have shown that polymethylmethacrylate (PMMA) particles inhibit the differentiation, proliferation, and mineralization of osteoprogenitor cells in vitro. OP-1 (BMP-7), a growth factor that induces bone formation, may potentially stimulate osteogenesis in osteoprogenitor cells inhibited by PMMA particles. In this study, we exposed MC3T3-E1 osteoprogenitor cells challenged with PMMA particles to OP-1, and analyzed the time-dependent effects of this growth factor on the osteogenesis of these cells.

Methods Used: Confluent cultures of MC3T3-E1 osteoprogenitor cells (ATCC) were challenged with PMMA particles (1–10 μm, Polysciences) at doses of 0.000, 0.075, 0.150, and 0.300% v/v for 20 days, starting from the first day (Day 1) of differentiation in osteogenic medium. These cells were exposed to OP-1 (200 ng/ml) during the following days of osteogenic culture/particle treatment: (1) days 1–20, (2) days 4–20, and (3) days 1–4. Control cells were challenged with PMMA particles throughout this 20-day period but were not exposed to OP-1. Mineralization was measured by von Kossa staining with NIH Imaging quantification of the total area of stained matrix after the 20-day culture period.

Summary of Results: MC3T3-E1 cells challenged with PMMA particles showed a dose-dependent decrease in mineralization. The exposure of these cells to OP-1 during days 1–20, 4–20, and 1–4 of culture/particle treatment resulted in significant increases in mineralization. At each particle dose, cells treated with OP-1 at these different time periods showed similar levels of increased mineralization, which signifies that the first four days of osteogenic differentiation (days 1–4) was a sufficient time window for osteoprogenitor cells to respond to the stimulatory effects of OP-1.

Conclusions: This study has shown that OP-1 stimulates the osteogenesis of MC3T3-E1 osteoprogenitor cells that have been inhibited by PMMA particles in vitro. Clinically, the administration of OP-1 to the site of osteolysis in total joint replacement may increase bone formation by stimulating the osteogenic differentiation of osteoprogenitor cells.

Behavior and Development
Concurrent Session
8:30 AM
Friday, January 30, 2009

25 HOW DOES AUDITORY SENSORY GATING IN NEWBORN WITH PRENATAL DRUG AND/OR NICOTINE EXPOSURE DIFFER FROM NEWBORN WITH NORMAL PRENATAL EXPOSURES?

A. Herrndon, S. Hunter, R. Ross University of Colorado, Denver School of Medicine, Aurora, CO.

Purpose of Study: This study looked at the effect of prenatal multi-drug and nicotine exposure on sensory auditory gating in infants. Auditory sensory gating, using a paired-click paradigm, provides a physiological measure of the brain’s ability to disregard irrelevant information (Adler, 1982) and is related to attentional control. Evoked responses (ERPs) to the paired clicks are recorded and compared using a ratio (T/C Ratio) of peak amplitudes following the auditory stimuli (Stimulus 2; Test/Stimulus 1; Conditioning). Individuals with intact auditory gating tend to exhibit ratios of less than 0.4 (Seigel, 1984). We hypothesized that infants prenatally exposed would exhibit a deficit in auditory sensory gating as compared to infants with no prenatal exposure.

Methods Used: Auditory ERPs were collected in 18 case (i.e., infants born to poly-drug abusing mothers) and 27 control infants. Continuous EEG was recorded from site Cz and used in ERP analysis. Bipolar electrooculogram (EOG)
and electromyogram (EMG) were used to help determine when the infant entered active sleep. To investigate whether auditory sensory gating differed based on prenatal exposures to drugs, the mean T/C ratios for cases and controls were compared using a student’s t-test with a two-sided alpha of .05. All procedures were approved and monitored by the Colorado Multiple Institute Review Board.

Summary of Results: Cases and controls did not differ in gestational age, size, gender, or race and ethnicity. Latencies and amplitudes of ERPs for conditioning and test clicks were similar. Controls were found to have lower T/C ratios (mean T/C ratio = 0.46) than cases (mean T/C ratio = 0.62). Consistent with prior studies, individuals with schizophrenia have impaired sensory gating. The importance of this finding is that impaired sensory gating is associated with impaired attention, and therefore treatment of this abnormality could improve some of the symptoms of schizophrenia. Acute nicotine administration improves P50 sensory gating deficits in nonsmoking family members of individuals with schizophrenia and in individuals with schizophrenia who abstain from nicotine overnight. However, tachyphylaxis may limit the ability of nicotine to reverse P50 sensory gating deficits on a chronic basis. The purpose of this study is to see if individuals who identify themselves as smokers have different P50 sensory gating levels than those who are nonsmokers.

Methods Used: Subjects for this study participated in a larger study, The Consortium on the Genetics of Schizophrenia (COGS). The P50 auditory potential was measured for 899 subjects. Of these, 310 were controls, 170 were individuals who had a diagnosis of schizophrenia as determined by the Diagnostic Interview for Genetic Studies criteria, and 409 were family members of schizophrenic individuals. Smoking status (smoker or nonsmoker) was established by self report.

Summary of Results: Forty-two (14%) of the controls, 76 (45%) of the individuals with schizophrenia, and 59 (14%) of the family members reported they were smokers. As a group, individuals with schizophrenia had a higher mean P50 ratio than controls (0.63 ± 0.478 vs. 0.36 ± 0.310). Family members (0.50 ± 0.351) did not have a significantly different mean P50 ratio when compared to individuals with schizophrenia and controls. Within each diagnostic group, being a smoker was not associated with having a lower P50 sensory gating ratio.

Conclusions: Consistent with prior studies, individuals with schizophrenia have impaired sensory gating. While nicotine may transiently improve P50 sensory gating, chronic nicotine dosing (i.e. tobacco smoking) is not associated with improved sensory gating. A longitudinal study of change in smoking status among the smoking groups is needed to explore whether there is a cohort effect.

26 CHRONIC TOBACCO USE AND P50 SENSORY GATING
M.E. Guess1, L.F. Martin2, R. Freedman1,2, A. Olincy2 1VA Eastern Colorado Health Care System, Denver, CO and 2University of Colorado Denver School of Medicine, Aurora, CO.

Purpose of Study: Individuals with schizophrenia and some of their family members have the diminished ability to suppress the auditory evoked potential to the second of two clicks. This is called impaired P50 sensory gating. The importance of this finding is that impaired sensory gating is associated with impaired attention, and therefore treatment of this abnormality could improve some of the symptoms of schizophrenia. Acute nicotine administration improves P50 sensory gating deficits in nonsmoking family members of individuals with schizophrenia and in individuals with schizophrenia who abstain from nicotine overnight. However, tachyphylaxis may limit the ability of nicotine to reverse P50 sensory gating deficits on a chronic basis. The purpose of this study is to see if individuals who identify themselves as smokers have different P50 sensory gating levels than those who are nonsmokers.

Methods Used: Subjects for this study participated in a larger study, The Consortium on the Genetics of Schizophrenia (COGS). The P50 auditory potential was measured for 899 subjects. Of these, 310 were controls, 170 were individuals who had a diagnosis of schizophrenia as determined by the Diagnostic Interview for Genetic Studies criteria, and 409 were family members of schizophrenic individuals. Smoking status (smoker or nonsmoker) was established by self report.

Summary of Results: Forty-two (14%) of the controls, 76 (45%) of the individuals with schizophrenia, and 59 (14%) of the family members reported they were smokers. As a group, individuals with schizophrenia had a higher mean P50 ratio than controls (0.63 ± 0.478 vs. 0.36 ± 0.310). Family members (0.50 ± 0.351) did not have a significantly different mean P50 ratio when compared to individuals with schizophrenia and controls. Within each diagnostic group, being a smoker was not associated with having a lower P50 sensory gating ratio.

Conclusions: Consistent with prior studies, individuals with schizophrenia have impaired sensory gating. While nicotine may transiently improve P50 sensory gating, chronic nicotine dosing (i.e. tobacco smoking) is not associated with improved sensory gating. A longitudinal study of change in smoking status among the smoking groups is needed to explore whether there is a cohort effect.

27 CORRELATING STRUCTURAL-FUNCTIONAL PARAMETERS IN THE DEVELOPING BRAIN DURING IMPLIED LANGUAGE LEARNING
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Purpose of Study: Children have an amazing ability to learn new languages; however, the neural underpinnings of the language-learning process are not well characterized. The aim of this study is to evaluate relationships between cortical thickness and brain activation in language-relevant cortices in typically developing children.

Methods Used: Previously, we demonstrated functional magnetic resonance imaging (fMRI) signal increases over time in bilateral perisylvian language regions (superior temporal gyrus; STG) while children attempted to learn words from an artificial language based solely on the statistical and prosodic cues available in a continuous speech stream. Using these images, structural MRI (sMRI) of 15 individuals was analyzed using High-dimensional Continuum Mechanical Warping Algorithms to align the functional and structural scans. Correlation analyses were performed on each participant’s statistical functional activation map during word segmentation and their average cortical thickness maps.

Summary of Results: Positive correlations between thickness and signal increases in left STG and inferior frontal gyrus (IFG), as well as a negative correlation between these measures in right STG were observed. These areas where cortical thickening is observed during development. Cortical thinning was associated with decreased activity in the dorsal frontal cortex.

Conclusions: Our results support the idea that the left hemisphere becomes more dominant with increased experience with a native language. Children also seem to rely less on the dorsal frontal cortex as the language cortices take over.

28 UNDERIDENTIFICATION OF ANXIETY AND ATTENTIONAL SYMPTOMS IN CHILDREN WITH CHROMOSOME 22Q11.2 DELETION SYNDROME
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Purpose of Study: Chromosome 22q11.2 deletion syndrome (22q11.2DS) is the most common microdeletion syndrome, occurring in 1/2000-4000 births. Learning and emotional issues are common, with 30–50% with ADHD and 30–40% with anxiety disorders. This study evaluated how often children with 22q11.2DS are being identified and treated for these symptoms.

Methods Used: As part of a larger study on neurocognition in children with 22q11.2DS, 45 children ages 7–14 received developmental evaluations, including clinical interviews and behavioral questionnaires, such as the SNAP-IV for symptoms of ADHD. Using McNemar’s chi-square test, parental report of prior diagnosis of ADHD was compared with a history of ADHD symptoms elicited during evaluation. Descriptive analysis of significant anxiety symptoms elicited was also performed.

Summary of Results: We identified more children with clinically significant symptoms of ADHD or anxiety than expected based on a previous diagnosis of ADHD or any anxiety disorder. A prior diagnosis of ADHD was present in 27% (12/45) compared to 44% (20/45) who met SNAP-IV/DSM-IV criteria for ADHD based on parental report (P = 0.04). A prior diagnosis of anxiety disorder was reported in 16% (7/45), while parents reported daily anxiety in 45% of children (20/45), excessive worrying in 58% (19/45), perseveration in 47% (21/45), and skin picking in 38% (17/45). Ten of 12 (83%) with a prior diagnosis of ADHD were taking stimulant medication, which was 45% of the 22 who met ADHD criteria after our assessment. Half of those with a prior diagnosis of anxiety disorder (3/7) were taking SSRIs, while only 20% (4/20) of children whose parents reported daily anxiety were on SSRIs. We recommended medication for 65% and CBT for all with clinically meaningful symptoms of anxiety.

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Conclusions: Despite the documented increased risk for ADHD and anxiety disorders in children with 22q11.2DS, these problems remained undetected and untreated in our sample. There is a need for increased awareness and diagnosis of these conditions so that medical and behavioral interventions can be provided to improve functional outcomes at school and home.

29 SENSITIVITY OF THE AUTISM DIAGNOSTIC OBSERVATION SCHEDULE FOR CHILDREN WITH AUTISM SPECTRUM DISORDERS AND CO-OCCURRING ANXIETY SYMPTOMS

K. Hornburg, A. Blakeley-Smith, K. Ridge, S. Hepburn, J. Reaven
University of Colorado Denver School of Medicine, Aurora, CO.

Purpose of Study: Individuals with autism spectrum disorders (ASD) are at increased risk for developing anxiety symptoms compared to the general population. The purpose of this study is to examine the relationship between clinical anxiety symptoms and the presentation of an autism spectrum disorder. The current study investigates the sensitivity of the Reciprocal Social Interaction score of the Autism Diagnostic Observation Schedule (ADOS) to co-occurring anxiety symptoms. Because the ADOS is often used for diagnostic evaluation for autism, anxiety-associated differences in performance might explain individual differences in presentation, thus indicating the need for a more in-depth assessment of anxiety symptoms.

Methods Used: The dataset was assembled from data obtained in two other studies (CPEA Longitudinal Network; Reaven et al., in preparation). The subjects were children ages 6-14 with an autism spectrum diagnosis based on the Autism Diagnostic Interview-Revised (ADI-R) and the ADOS-G. Subjects were classified as “anxious” if they scored above the 90th percentile on the anxiety subscale of the Developmental Behavior Checklist - Primary Carer version (DBC-P). A Reciprocal Social Interaction composite score for each subject was calculated by summing the score for each individual item in the Reciprocal Social Interaction portion of the ADOS, with higher scores indicating greater impairment. The group means were compared using a one-way ANOVA.

Summary of Results: The study included 71 subjects, 45 in the Non-Anxious group and 26 in the Anxious group. The groups were matched for age, Full Scale IQ, Verbal IQ, and Nonverbal IQ. The means for the Reciprocal Social Interaction composite score were not significantly different between groups. The Non-Anxious group mean score was 11.56, and the Anxious group mean score was 12.65, F (1,69) = 1.183, P = 0.280.

Conclusions: Based on the current study, anxiety symptoms do not appear to be associated with degree of social impairment in children with autism spectrum disorders. Limitations of the study will be discussed. Further research is needed to investigate how co-occurring anxiety affects the presentation of ASD.

Acknowledgements: Cure Autism Now (CAN)

30 GASTROINTESTINAL DISORDERS IN CHILDREN WITH AUTISM SPECTRUM DISORDER FROM MULTIPLEX FAMILIES IN THE AGRE DATABASE

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1UC Davis M.I.N.D. Institute, Sacramento, CA and 2Children’s Hospital Los Angeles, Los Angeles, CA.

Purpose of Study: To determine the prevalence of gastrointestinal (GI) disorders in children with autism spectrum disorder (ASD) from multiplex families (two or more affected children) compared to unaffected siblings. Preliminary data was also obtained to determine if autism may be a risk factor associated with having celiac disease.

Methods Used: Presence of GI problems of all children (18 years or younger) from 351 multiplex families participating with the Autism Genetic Resource Exchange (AGRE) Consortium was analyzed. ASD diagnoses were determined by pediatric neurologists using in-home clinical exams, the ADI-R and ADOS-G. Furthermore, to determine if autism alone is associated with having celiac disease, 35 randomly selected children with autistic disorder, but without any known risk factors for celiac disease (e.g. GI symptoms, family history, and autoimmune disease) were screened for celiac antibodies (tissue transglutaminase IgA antibodies, endomyseal antibodies, and total IgA).

Summary of Results: From 351 families, 652 children had an ASD and 168 were unaffected siblings. Having adjusted for family clustering, we found significantly more GI problems in children with ASD (278/652; 43%) than unaffected siblings (20/164; 12%) (P < 0.0001). The two most common GI problems in children with ASD were constipation (20%) and chronic diarrhea (19%), whereas gastroesophageal reflux (4.9%) and constipation (3.7%) were most common in their unaffected siblings. Our multivariate analysis showed autism (adjusted OR = 5.3) was highly associated with GI disorders. There was no association between presence of GI problems and sex, age, maternal or paternal education, or current use of medications. In addition, none of the 35 children with autism had elevated celiac serologies.

Conclusions: The presence of GI problems in this population of children with ASD is 43%, which is higher than previous reports. Children with ASD had 5.3 times the odds of having a GI problem than unaffected siblings. None of the randomly selected subjects with autism, but no risk factors for celiac disease, had positive celiac serologies, however, a larger sample size is needed to determine the exact prevalence of celiac disease in children with autism.

Acknowledgements: Cure Autism Now (CAN)

31 CHANGES IN SELF-ESTEEM IN OVERWEIGHT CHILDREN PARTICIPATING IN A MEDICALLY SUPERVISED AND PSYCHOLOGICALLY MONITORED RISK FACTOR REDUCTION PROGRAM

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Purpose of Study: The impact of obesity on the self-esteem during childhood is still controversial. The spectrum of studies covers those which report little or no influence up to those which suggest a casual relationship of obesity and self-esteem in children. We aimed to assess the parental and child perception of children’s self-esteem who participated in a medically supervised and psychologically monitored risk factor reduction program (RFR) for overweight children.

Methods Used: This report includes data from 967 children, who joined the RFR 12-week program and were evaluated by the psychologist, from 01/2006 to 08/2008. We measured their self-esteem perceptions with the Child Health Questionnaire (CHQ) pre and post program. Answers to CHQ-Self-esteem domain were transformed into a score from 0 to 100 (worst to best) for statistical analysis. We used for statistical comparison tables for U.S. school children.

Summary of Results: The group had 489 boys and 478 girls, with mean age of 11.3 ± 2.6 years (range: 6 to 18) and mean BMI Z-score of 2.29 ± 0.35. Race distribution was: 60% Hispanic, 22% Caucasian, 7% African-American, 25% Asian, and 9% Other. 61% of children complete the 12-week program. At entry, the whole group showed self-esteem scores significantly lower than U.S. school children; by week 12, parents and children perceived significant improvement in children’s self-esteem. Table summarizes results. Logistic analysis did not show influences of parent’s level of education, current employment status or marital status in children’s self-esteem score or success in changes in BMI Z-score.

Conclusions: In this group of overweight children: 1-Children perceived their self-esteem higher than their parents did. 2- Parents and Children scored the children’s self-esteem lower than U.S. school children. 3- Parents’ marital status, current employment or education level did not influence the parental perception of children’s self-esteem or success in the RFR program.
referral practices of primary care physicians treating adolescents. Survey questions included: practice setting; estimates of the number of adolescents seen annually and of the percent of adolescents in their practice with substance use or psychiatric disorders; current screening, treatment referral and follow-up methods; knowledge of published screening guidelines; perceived barriers, satisfaction ratings and suggestions for improving this system of care. All procedures were approved and monitored by the Colorado Multiple Institutional Review Board.

Summary of Results: Of five physicians interviewed (3 pediatric private practices, 1 university-based family practice, and 1 county-hospital affiliated adolescent medicine clinic), all estimated that >50% of adolescents used or abused substances and 3 estimated >40% had psychiatric disorders. 4/5 used self-administered questionnaires developed by their practice group; 1 reported non-standardized screening based on clinical judgment. None of the physicians used published screening practice guidelines. Referral practices were driven by patients’ insurance provider lists. All reported low satisfaction ratings with substance and mental health treatment. Low satisfaction ratings were attributed to poor treatment access and lack of clinical progress information or follow-up recommendations from referral agencies.

Conclusions: Although most physicians in this pilot study use some mental health and substance screening measures, low satisfaction ratings may indicate that initiatives to improve standardized screening and referral practices in primary care settings may be ineffective without concomitant improvement in systemic and economic barriers to mental health and substance treatment access and continuing care.

33 EATING THE EFFICACY OF APPETITE AWARENESS TRAINING IN THE TREATMENT OF EATING DISORDERS IN A MILIEU-BASED PROGRAM: A PILOT STUDY

A.A. Cirona1, M. Solomon2, C. Nab1, J. Hagman1,2 (1University of Colorado Denver School of Medicine, Denver, CO and 2The Children’s Hospital, Aurora, CO.)

Purpose of Study: Appetite dysregulation is a common feature of eating disorders (EDs). Appetite awareness training (AAT) is a form of cognitive behavioral therapy designed to address this feature of ED psychopathology by increasing interoceptive awareness of hunger and fullness. AAT involves attending a weekly group and completion of daily appetite monitoring forms in which individuals rate their satiety level before and after eating. It has been shown to be an effective treatment in adult women with binge eating disorder and bulimia nervosa, but has not yet been evaluated in an adolescent population, milieu-based programs, or individuals with anorexia nervosa. The purpose of the present study was to evaluate the efficacy of AAT in the ED Treatment Program, a milieu-based setting, at The Children’s Hospital in Denver.

Methods Used: There were five outcome measures, three of which were collected at baseline and at four weeks (Mizex Anorectic Cognition Scale; Interoceptive Awareness Questionnaire; and the Preoccupation with Eating, Weight, and Shape Scale); the other two were completed daily (appetite monitoring forms completed by patients, and the Ease of Eating form, completed by staff).

Summary of Results: Eleven patients were enrolled in the study with an average age of 17.4 years. The group appeared to be an important addition to the milieu program and provide a method by which patients were better able to understand appetite signals.

Conclusions: AAT provided a useful group therapy experience for adolescent and young adult patients in a milieu-based therapy program. Patients and staff reported that the focus of the group was helpful in processing awareness of appetite cues throughout the day. Future efforts are underway to incorporate AAT throughout the week and to enhance patients’ use of the AAT monitoring scales in and outside of the program.

34 TRAUMA EXPOSURE AND COPING MECHANISM IN ERIITREAN REFUGEES: AN EXPLORATORY STUDY

B.W. Belay, D. Savin University of Colorado Denver School of Medicine, Aurora, CO.

Purpose of Study: East Africa is a region of tremendous political and social upheaval. Refugees from this region have resettled in many countries, including the United States. Despite recognition of the enormous mental health needs in East African refugees, there is little literature formally assessing the degree of trauma exposure or the types of coping strategies employed by this group. This lack of knowledge may be partially attributable to the lack of culturally valid assessment tools. The purpose of this pilot study is to identify traumatic life events in Eritrean refugees and explore what adaptations of existing measures are necessary to identify coping strategies employed by this population.

Methods Used: Open-ended interviews were conducted with 10 Eritrean refugees and asylees between the ages of 23 and 47 who migrated to the United States after 1998 (7 Males and 3 females). The Horn of Africa Needs Assessment was used by integrating questions from the Ways of Coping Checklist (WCC), Coping Orientation to Problems Experienced (COPE) and the Connor-Davidson Resilience Scale(CDRS). Additional questions included in the interview reflected domains pertinent to the Eritrean history and traditions projected to give insights on culturally relevant coping strategies. Resulting transcription of the interviews were analyzed and types of trauma and coping strategies categorized.

Summary of Results: Types of traumatic stressors identified included combat-related trauma, physical torture, detention, sexual harassment, natural disasters and culture shock. Identified coping strategies included faith and religion, family and community support, positive reinterpretation, use of herbs and alcohol as well as various spiritual practices deeply rooted in the Eritrean culture.

Conclusions: Trauma exposure was common and severe in this population. General categories of coping mechanisms identified in Eritrean refugees were similar to coping strategies recognized in other regions of the world. The use of specific herbs, traditional ceremonies and certain spiritual rituals were unique to this population. Future studies or clinical work with this or similar populations may benefit by integration of these newly identified strategies.

35 HOW OVERWEIGHT CHILDREN IMPACTS FAMILY DOMAINS

B. Cred1, W.N. Evans1,2, R.J. Acherman1,2, G.A. Mayman1,2, H. Restrepo1,2 (1Children’s Heart Center Nevada, Las Vegas, NV and 2Children’s Heart Center Nevada, University of Nevada, School of Medicine, Las Vegas, NV.)

Purpose of Study: The role of parents in treatment of childhood obesity is multifaceted and crucial. Conflicts among family priorities often make it difficult for parents to help their children develop healthy lifestyles. Our aim was to assess the family impact in a group of overweight children who participated in a medically supervised and psychologically monitored risk factor reduction program (RFR) for overweight children.

Methods Used: This report includes data from 591 children and their parents, who finished the RFR 12-week program and were evaluated by the psychologist, from 01/2006 to 08/2008. Four areas of family domain (emotional impact, impact on parents’ time, family cohesion and family activity) were assessed using the Child Health Questionnaire (CHQ) pre and post program. Answers to CHQ were transformed into scores for statistical analysis. We used for comparison tables for U.S. school children.

Summary of Results: The group had 300 boys and 291 girls, with mean age of 11.3 ± 2.6 years (range: 7 - 18) and mean BMI Z-score of 2.27 ± 0.33. Parents’ marital status: 11% divorced, 65% married, 17% single, and 7% no reported. At week 1, parents’ and children’s scores were significantly lower (P< 0.001) than the norm for US school children. By the end of program both groups’ scores improved significantly, but without reaching the norms. Logistic analysis did not show differences in parents’ level of education, current employment status or current marital status in any of the scores under assessment.

Conclusions: 1-Parents perceived the obesity in their children significantly affecting the family domains. 2- RFR program helps significantly to improve both groups family’s perceptions. 3- Parents’ marital status, current employment or education level did not influence the perception of any of family domains.
Cardiovascular I
Concurrent Session
8:30 AM
Friday, January 30, 2009

36
TRANSFORMING GROWTH FACTOR-BETA PATHWAY POLYMORPHISMS AND AORTIC ROOT DILATATION IN KAWASAKI DISEASE PATIENTS

K.O. Lin1, D. Molkara1,2, J.R. Frazer1,2, C. Shimizu1, S. Jain1, S. Sun1, A.L. Baker1, J.W. Newburger2, S. Davila1,M.L. Hibberd1, J.C. Burns1,2 1University of California, San Diego School of Medicine, La Jolla, CA; 2Research Children’s Hospital San Diego, San Diego, CA.

Purpose of Study: Kawasaki disease (KD) is a pediatric systemic vasculitis that causes aortic root dilatation in approximately 15% of patients (pts). Other syndromes associated with aortic root dilation include Marfan and Loeys-Dietz syndromes, which result from increased levels of transforming growth factor-beta (TGF-β) due to point mutations in genes in the signaling pathway. TGF-β is a multifunctional protein affecting proliferation, apoptosis, differentiation, and collagen synthesis. We postulated that genetic variation in the TGF-β pathway might influence aortic root dilatation in KD.

Methods Used: We measured aortic root diameters on echocardiograms performed during the acute and convalescent period in 109 KD pts (75% Caucasian, 13% Hispanic, 1% Asian, 11% mixed ethnicity). Measurements were normalized for body surface area and expressed as z-scores. Subjects were classified as dilated if the z-score for the aortic annulus or sinus was ≥2 on any echo. Genotypes for all haplotype-tagged single nucleotide polymorphisms (SNPs) for TGF-β, TGF-β receptor 1 (R1), and TGFBR2 were determined using a custom Illumina® Oligo Pool Assay. Case-control analysis was performed using general linear models.

Summary of Results: Two intronic SNPs in TGFBR1 were found to have a nominal P < 0.05 under the allelic and dominant models. rs10733710 was positively associated with aortic root dilation in both the allelic (P = 0.02, OR 2.73, 95% CI 1.18-6.29) and dominant (P = 0.02, OR 3.35, 95% CI 1.15-9.76) models. rs6478974 was negatively associated with aortic root dilation in both the allelic (P = 0.05, OR 0.47, 95% CI 0.21-1.04) and dominant (P = 0.01, OR 0.25, 95% CI 0.09-0.73) models. Haplotype analysis using a moving window of 2 identified a protective (P = 0.02) and risk (P = 0.01) haplotype in TGFBR1.

Conclusions: Excess signaling through the TGF-β pathway may lead to a spectrum of aortic root pathology ranging from mild (KD) to severe (Marfan). Immunohistochemistry of KD aortic roots and additional genotyping of TGF-β pathway SNPs may further elucidate the role of TGF-β in KD pathogenesis.

37
ROSUVASTATIN SUPPRESSES THE DEVELOPMENT OF EXPERIMENTAL ABDOMINAL AORTIC ANEURYSMS IN MICE THROUGH THE INDUCTION OF HEME OXYGENASE-1

J. Azuma1, R.J. Wong2, T. Morisawa2, M. Hsu1,2, D.K. Stevenson2, P.S. Tsao1 1Stanford University School of Medicine, Stanford, CA and 2Stanford University school of medicine, Stanford, CA.

Purpose of Study: Several authors have reported potential beneficial effects of statins in reducing abdominal aortic aneurysm (AAA) expansion in a manner independent of its cholesterol-lowering properties. We previously demonstrated that statins selectively induce heme oxygenase-1 (HO-1) expression and, as a consequence, may reduce oxidative stress in vascular cells. The purpose of this study was to assess the effect of statins on the progression of AAA expansion.

Methods Used: Angiotensin II (Ang II, 1.0 mg/kg/min) was infused into 8-wk-old male ApoE−/− mice for 2 wks via osmotic minipumps. Mice were then treated with daily IP injections of vehicle (VEH, n = 8) or 5 mg/kg of rosuvastatin (RV, n = 10) for 5 wks starting 3 wks prior to pump implantation. At the end of Ang II infusion, suprarenal (SR) and infrarenal (IA) diameters were measured post-mortem. AAA severities were scored at 1 (SR IA diameter ratio ≥2), 2 (SR/IA diameter ratio >2), or 3 (presence of dissection). HO enzyme activity in AAA was determined by gas chroma-
tography and expressed as pmol CO/h/mg fresh weight (FW).

Summary of Results: RV treatment did not significantly affect either body weight gain or plasma total cholesterol and triglyceride levels. Progression and severity of AAA expansions were higher in VEH-treated mice compared to RV-treated mice (SR/IA diameter ratios: 2.3 ± 0.2 vs. 1.6 ± 0.2, respectively, P < 0.05). Overall HO enzyme activity was not significantly different between VEH- and RV-treated mice (43 ± 7 vs. 51 ± 6 pmol CO/h/mg FW, respectively). But when categorized by AAA severity, HO activity in Type 2 expansions were significantly higher following rosuvastatin treatment compared to mice treated with vehicle (31 ± 3 vs. 58 ± 9 pmol CO/h/mg FW, respectively, P < 0.05).

Conclusions: We conclude that RV inhibits the progression of AAA expansion through the induction of HO activity. Development of specific targeted therapies that induce HO-1 may be a new therapeutic strategy for the prevention of AAA disease.

38
L-4F, AN HDL MIMETIC PEPTIDE, INHIBITS PLATELET AGGREGATION


Purpose of Study: Forty percent of patients with atherosclerosis have normal or elevated high-density lipoprotein (HDL) levels, supporting both pro- and anti-inflammatory roles for HDL cholesterol. Inflammatory oxidized phospholipids have also been shown to promote platelet aggregation. We previously reported that 4F, an apoA-I mimetic peptide, binds oxidized phospholipids with very high affinity. We therefore hypothesized that L-4F would inhibit platelet aggregation.

Methods Used: One-year-old female apoE null mice on regular chow diet were injected subcutaneously with L-4F or vehicle control. Blood was collected into sodium citrate anticoagulant solution and pooled from 8-10 mice for each experiment. Platelets were collected from normal human donors and C57BL/6 control mice. Platelet aggregation studies were conducted using a PAP-4 aggregometer.

Summary of Results: After five days of treatment with L-4F at 1 mg/kg/day, total platelet aggregation and slope (maximum rate of aggregation) were significantly inhibited in response to arachidonic acid (AA) (P < 0.001), collagen (P = 0.0004) and ADP (P < 0.01) and lag time was significantly increased in response to arachidonic acid (AA) (P = 0.048), collagen (P = 0.0021) and ADP (P = 0.0079). A single L-4F injection significantly inhibited platelet aggregation for up to 72 hours. After two weeks of treatment, aggregation to AA (P < 0.01), collagen (P < 0.01) and ADP (P < 0.001) was significantly inhibited in ApoE null mice implanted with osmotic pumps delivering L-4F at a continuous dose of 0.01 mg/kg/day. Thromboxane A2 (TXA2) synthase activity, as measured by the production of TXB2, was significantly reduced in platelets from L-4F treated mice (P < 0.001), and SC-560 (a COX-1 inhibitor) further decreased TXB2 and platelet aggregation was significantly reduced in platelets from L-4F treatment mice compared to VEH-mice (43 ± 7 vs. 31 ± 3 T

Conclusions: L-4F significantly inhibited platelet aggregation by decreasing maximum response and slope while increasing lag time after the addition of AA, collagen and ADP. This inhibition was accompanied by a significant increase in bleeding time and a reduction of TXB2 levels in apoE null mice suggesting that the anti-platelet activity of L-4F may be mediated in part by inhibition of TXA2 synthase.

39
EXERCISE-INDUCED AORTIC HEME OXYGENASE ACTIVITY IS ASSOCIATED WITH ATTENUATION OF EXPERIMENTAL ABDOMINAL AORTIC ANEURYSM DISEASE

G.M. Schultz1, M.M. Tedesco1, T. Morisawa2, J. Azuma2, R.J. Wong2, D.K. Stevenson2, R.L. Dalman1 1Stanford University, Stanford, CA and 2Stanford University, Stanford, CA.

Summary of Results: RV treatment did not significantly affect either body weight gain or plasma total cholesterol and triglyceride levels. Progression and severity of AAA expansions were higher in VEH-treated mice compared to RV-treated mice (SR/IA diameter ratios: 2.3 ± 0.2 vs. 1.6 ± 0.2, respectively, P < 0.05). Overall HO enzyme activity was not significantly different between VEH- and RV-treated mice (43 ± 7 vs. 51 ± 6 pmol CO/h/mg FW, respectively). But when categorized by AAA severity, HO activity in Type 2 expansions were significantly higher following rosuvastatin treatment compared to mice treated with vehicle (31 ± 3 vs. 58 ± 9 pmol CO/h/mg FW, respectively, P < 0.05).

Conclusions: We conclude that RV inhibits the progression of AAA expansion through the induction of HO activity. Development of specific targeted therapies that induce HO-1 may be a new therapeutic strategy for the prevention of AAA disease.

<table>
<thead>
<tr>
<th>Profile</th>
<th>HO Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>Triglyceride (mg/dL)</td>
</tr>
<tr>
<td>VEH</td>
<td>41±3/7</td>
</tr>
<tr>
<td>RV</td>
<td>458±27</td>
</tr>
</tbody>
</table>

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Purpose of Study: Resistive aortic hemodynamic conditions promote inflammation within the infrarenal (IR) aortic wall and increase AAA disease risk. Lower extremity exercise offsets these conditions and may limit AAA progression by upregulating heme oxygenase-1 (HO-1), a stress response gene of particular interest as promoter region polymorphisms have been linked to human AAA disease risk. This study was designed to quantify the effects of exercise on aortic wall shear stress (WSS), HO activity, and AAA growth.

Methods Used: Apo E-/- male mice were infused with Angiotensin II (1.0 mg/kg/min) via minipumps. Exercise (EA) mice (n = 5) had continuous access to exercise wheels and ran voluntarily. Normal activity (NA) mice (n = 5) did not have access to wheels. Resting maximum suprarenal (SR) and IR aortic diameters (d) and mean aortic velocities (V) were monitored weekly with ultrasound (VisualSonics Inc). SR aortic WSS (dynes/cm²) was calculated as WSS = 8µV/d, where µ is blood viscosity (0.035 dynes/s/cm²). Wild-type C57BL mice were used to determine the effect of exercise on aortic HO activity. At 14 days, aortae from exercising (n = 8, EW) and normal activity (n = 8, NW) mice were pooled, and HO activity was quantified via gas chromatography and expressed as fold change from controls.

Summary of Results: EA mice ran 4.9 ± 3.4 km/day. SR aortic WSS was greater in EA mice than in NA mice at all time points (P > 0.05). EA mice had smaller average aneurysm diameters after 4 days (Fig. 1). EWT mice ran 8.7 ± 3.6 km/day. Aortic HO activity was greater in EW than NW mice (Fig. 2).

Conclusions: Voluntary wheel exercise increases SR aortic WSS, promotes HO activity, and limits experimental AAA progression. This effect may be the result of flow-induced regulation of HO activity within the aorta.

Figure 1

Figure 2

40 AFTERDEPOLARIZATIONS OCCUR IN CARDIOMYOCYTES DERIVED FROM HUMAN EMBRYONIC STEM CELLS AND INDUCED PLURIPOTENT STEM CELLS

J.A. Gantz, M. Laflamme
University of Washington, Seattle, WA.

Purpose of Study: Human Embryonic Stem Cells (hESCs) are a promising candidate for cell-based cardiac tissue repair because they have shown remarkable in vitro growth capacity and because they have been successfully differentiated into proliferating human cardiomyocytes (CMs). Induced Pluripotent Stem (iPS) cells are exciting candidates for cardiac therapies because they have shown similar CM differentiation capability while sidestepping the ethical controversy surrounding hESCs. To be an effective therapy, exogenous cardiac tissue implants will need to match the electrical stress responses of healthy human cardiac cells. Afterdepolarizations (Phase II/III/IV oscillatory depolarizations) are known to be a major contributor to triggered tachyarrhythmias. Mouse stem cell-derived CMs have previously exhibited a low threshold for stress-induced afterdepolarizations and have raised concerns about the safety of stem cell-derived cardiac tissue implantation. Our initial observations of hESC- and iPS-derived CMs have demonstrated afterdepolarizations warranting further investigation of these cells’ arrhythmogenic potential.

Methods Used: Wild-type H7 female hESCs derived from NIH cell line WA07 were directly differentiated in a monolayer culture by sequential exposure to 100 ng/ml human recombinant activin A and 10 ng/ml human recombinant bone morphogenic protein 4 as previously described. Spontaneously beating CMs were subsequently transferred and cultured on 0.1% PEI pre-treated, 2% gelatin coated glass coverslips. Action potentials were recorded under perfusion of 10 mM HEPES buffer (pH 7.4 at 37°C) with and without the addition of 10 μM isoproterenol using perforated-patch current-clamp techniques.

Summary of Results: Human ESC-derived CM action potential recordings collected in this work have shown afterdepolarization inducibility under the influence of 10 μM isoproterenol. In addition, we have successfully recorded the action potential of a spontaneously-beating, IPS-derived CM and confirmed that it exhibits human CM action potential characteristics, including spontaneous afterdepolarizations, both previously un-published findings.

Conclusions: Afterdepolarization demonstration in hESC- and IPS-derived human CMs calls for the further study of arrhythmogenic behavior in these cells if they are to be safe candidates for human transplantation.

41 AFos INHIBITS PHENYLEPHRINE MEDIATED CONTRACTILE DYSFUNCTION BY ALTERING PHOSPHOLAMBN AND TROPONIN T PHOSPHORYLATION

M. Jeong1, J. Walker1, W. Colucci2, R. Moore3, C. Vinson4, C. Long1
1University of Colorado Denver, Aurora, CO; 2Boston University, Boston, MA; 3University of Colorado Boulder, Boulder, CO and 4National Cancer Institute, Bethesda, MD.

Purpose of Study: Previously we found that inhibition of activator protein-1 (AdAFos) in neonatal rat ventricular myocytes subjected to phenylephrine (PE) treatment inhibited the expression of the pathologic gene while maintaining myocyte growth. We now extend these observations to the adult rat ventricular myocyte (ARVM) with the hypothesis that inhibiting PE mediated expression of the pathologic gene while preserving myocyte hypertrophy will lead to improvement in myocyte function.

Methods Used: See results

Summary of Results: As seen in the NRVM, PE treatment resulted in significant increase in newly synthesized protein in βGal control and AFos groups (P < 0.05 vs βGal or AFos). Induction of the pathologic gene profile was seen in response to PE treatment in the βGal group, ie, expression of β-myosin heavy chain, brain natriuretic peptides, and skeletal actin was increased, whereas expression of α-myosin heavy chain was repressed (P < 0.05 vs βGal). In AFos expressing ARVMs, the induction of the pathologic gene expression was inhibited (P < 0.05 vs βGal+PE). PE treated βGal group exhibited depressed myocyte shortening, contraction and relaxation velocities, systolic and diastolic calcium levels, and exponential time decay (P < 0.05 vs βGal). The contractile and calcium handling dysfunction seen in PE treated βGal myocytes were improved in myocytes expressing AFos (P < 0.05 vs βGal+PE). Although we did not see a change in total phospholamban in response to PE treatment in both βGal or AFos groups, PE treatment lead
to a significant decrease in phosphorylation of phospholamban at serine 16 (ser16 PLB) in the βGal group (P < 0.05 vs βGal) and phosphorylation was maintained in AFos expressing ARVMs (P < 0.05 vs βGal-PE). Additionally, PE treatment led to increased phosphorylation of troponin T (TnT) and AFos expression inhibited this phosphorylation event.

Conclusions: Phosphorylation treatment lead to contractile and calcium handling dysfunction due to the changes in phosphorylation state of ser16 PLB and TnT. AFos expression inhibited PE mediated PLB and TnT phosphorylation changes, and displayed improved contractility and calcium handling.

Purpose of Study: L.T. Hegerova

University of Washington, Seattle, WA.

STEM CELLS

CARDIAC DIFFERENTIATION OF INDUCED PLURIPOTENT

42 IMMEDIATE HYPOThERMIA, AND NOT DELAYED, INDUCTION IMPROVES LEFT VENTRICULAR FUNCTION AND ATTENUATES LV REMODELING IN ACUTE MYOCARDIAL INFARCTION

E.B. Juneman1,2, H. Raasch2, T. Hagerty2, J. Lancaster3, S. Goldman1,2, H. Thai1,2
1Southern Arizona VA, Tucson, AZ and 2University of Arizona, Tucson, AZ.

Purpose of Study: Recent studies evaluating hypothermia suggest it may be a novel therapy in preserving myocardial function following an ischemic event. This study was designed to determine what effects immediate vs. delayed hypothermia would on cardiac function following myocardial infarction.

Methods Used: We ligated the left coronary artery of adult male Sprague-Dawley rats to induce MI. We then measured LV hemodynamics and assessed LV function and chamber dimensions by echocardiography three weeks after induction of hypothermia (temperature <28o C). A normalheath control group (temperature >34o C) was similarly studied. The hypothermic groups were divided into immediate hypothermia (IH) versus 20 minutes delayed hypothermia (DH).

Summary of Results: After MI and induction of hypothermia, the LV End Diastolic Pressure (LVEDP) decreased (P < 0.05) in IH rats (8.5 ± 1.3 mmHg) as compared to DH rats (16.5 ± 2.5 mmHg) and decreased (P < 0.05) as compared to normalheath rats (26.0 ± 3.0 mmHg). Similarly, LV systolic pressure in normothermic rats (109 ± 4.3 mmHg) was higher (P < 0.05) than IH rats (86 ± 2.3 mm Hg) and LV systolic pressure in DH rats (102 ± 3.6 mmHg) was higher (P < 0.05) than IH rats. IH preserved LVEF compared to normothermia (58 ± 5.0 vs. 37 ± 3.3%, P < 0.05) although DH did not preserve LVEF (37.8 ± 3.5%). The displacement of the anterior infarcted region was normalized in the IH animals (0.21 ± 0.01 vs. 0.05 ± 0.02 cm, P < 0.005) and not normalized in the DH (P = NS). LV remodeling (LV systolic and diastolic chamber dilation) was also attenuated in the IH animals. In animals with DH, the LVF was not improved compared to normothermic (38 ± 3.5 vs. 37 ± 3.3%, P = NS). There were no significant differences in LV systolic pressure and anterior displacement between DH and normothermic animals after MI.

Conclusions: Induction of immediate hypothermia after acute MI limits LV remodeling, preserves LV function and restores regional wall motion in the infarcted LV segment. Delayed hypothermia did not demonstrate these changes. Our findings suggest that hypothermia may be a viable therapeutic option in the treatment of acute myocardial ischemic injury, if applied early.

SUMMARY OF RESULTS:

The reliable generation of reasonably homogenous populations of cardiomyocytes from hiPSCs represents a significant advance in the development of myocardial cell therapies.

Purpose of Study: To determine that in patients with systemic lupus erythematosus (SLE), Libman-Sacks endocarditis is a common cause of stroke, transient ischemic attacks (TIA), and focal brain injury on magnetic resonance imaging (MRI). This finding could have important diagnostic and therapeutic implications since currently vasculitis, cerebritis, and hypercogulability are considered the most common pathogenic mechanisms.

Methods Used: 35 patients with diagnosis of SLE (32 women, mean age 40) and 15 age and gender matched healthy volunteers (13 women, mean age 37) underwent clinical evaluation, brain MRI, and transesophageal echocardiography (TEE).

Summary of Results: 1) Fourteen patients (40%) had a past or acute stroke/TIA; 2) 15 of 34 patients (41%) and 2 controls (13%) had focal brain injury on MRI (P = 0.09); and 3) 21 patients (60%) had Libman-Sacks endocarditis on TEE [valve vegetations (46%), valve thickening (60%), and valve regurgitation in 29%] as compared to 1 control (7%) (P < 0.01). Libman-Sacks vegetations and valve thickening were more common in patients with stroke/TIA (Table 1) or focal brain injury on MRI (Table 2).

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Conclusions: Libman-Sacks endocarditis is a cause of cerebral macro or micro-embolism resulting in stroke/TIA and focal brain injury. Thus, in patients with SLE with focal neurologic deficits or brain injury, cardiacembolism should be considered.

**TABLE 1.** Association of Libman-Sacks Endocarditis with Acute and Past Stroke/TIA in Patients with SLE

<table>
<thead>
<tr>
<th>Valve Abnormality</th>
<th>Stroke or Transient Ischemic Attack</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (n=23)</td>
<td>7 (33%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Past (n=10)</td>
<td>5 (50%)</td>
<td></td>
</tr>
<tr>
<td>Acute (n=4)</td>
<td>4 (100%)</td>
<td></td>
</tr>
<tr>
<td>Vegetations (n=16)</td>
<td>5 (31%)</td>
<td></td>
</tr>
<tr>
<td>Thickening (n=21)</td>
<td>5 (24%)</td>
<td></td>
</tr>
<tr>
<td>Regression (n=10)</td>
<td>5 (50%)</td>
<td></td>
</tr>
<tr>
<td>Any Abnormality (n=21)</td>
<td>5 (24%)</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 2.** Association of Libman-Sacks Endocarditis with Focal Brain Injury on MRI in Patients with SLE

<table>
<thead>
<tr>
<th>Valve Abnormality</th>
<th>Focal Brain Injury Old or Recent Cerebral Infarcts</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (n=5)</td>
<td>No (n=29)</td>
<td></td>
</tr>
<tr>
<td>Vegetations (n=16)</td>
<td>5 (100%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Thickening (n=20)</td>
<td>5 (100%)</td>
<td></td>
</tr>
<tr>
<td>White or Mixed</td>
<td>15 (78%)</td>
<td>0.00</td>
</tr>
<tr>
<td>Vegetations (n=16)</td>
<td>8 (89%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Thickening (n=20)</td>
<td>8 (89%)</td>
<td>12 (48%)</td>
</tr>
</tbody>
</table>

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**RIGHT VENTRICULAR REMODELING IN EISENMENGER’S SYNDROME: A THREE-DIMENSIONAL ANALYSIS**

L. Strizich
University of Washington, Seattle, WA.

**Purpose of Study:** This study analyzes six patients with Eisenmenger’s Syndrome in order to better understand the remodeling of the right ventricle associated with this etiology of pulmonary hypertension (PH).

**Methods Used:** Cardiac MRI of each patient were manually traced in 2D to create 3D reconstructions of the right ventricle (RV), which were sliced into 20 cross-sections from apex to base. RV shape was analyzed according to various parameters. The hearts were divided into two subgroups, three univentricular (UV) hearts and three hearts with post-tricuspid lesions (PTL), and compared to nine normal hearts using ANOVA.

**Summary of Results:** Shape analysis showed that both the UV group and the PTL group were larger and rounder than the normal group. Specifically, significant differences found between the UV group and the normal population included: end diastolic (ED) and end systolic (ES) volume indexes (ED 214 mL/mm² ± 10, P < 0.001; ES 144 mL/mm² ± 22, P < 0.001), RV length in ED and ES (ED 63 mm±5, P = 0.01; ES 55 mm±4, P = 0.001), ejection fraction (39 mL/9, P = 0.002), and normalized area and eccentricity (P < 0.05). Significant differences between the PTL group and the normal population included: RV length ED and ES (ED 62 mm±4, P = 0.01; ES 51 mm±5, P = 0.01), the angle of the tricuspid annulus at ED and ES (ED 44±15, P = 0.01; ES 39±10, P = 0.02), the ejection fraction (33 mL/8, P < 0.001), and normalized area and eccentricity (P < 0.05).

**Conclusions:** While significant differences were found between the right ventricles of study and control groups, because of the small size and the heterogeneity of the congenital defects analyzed, the RV remodeling patterns in patients with PH due to Eisenmenger’s are still unclear. It is important to understand the RV remodeling pattern in this group of patients because right heart failure is a significant cause of death in this population. To better understand the remodeling process and to correlate it with patient morbidity and mortality will require greater numbers of Eisenmenger’s patients and the sub-classification of patients by etiology and anatomy. This work was funded by the National Institutes of Health through the NIH Roadmap for Medical Research, Grant #: T1I RR 025-16-01.

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**COVALENT MODIFICATION OF KEAP1 BY 1-PALMITOYL-2,5,6-EPoxyisoProSTANE E2-SN-GlycoR3-phoSPHAdIChOLINe STIMULATES NRF2-DEPENDENT HEME-OXYGENASE PRODUCTION IN HUMAN AORTIC ENDOThELIAL CELLS**

K. Matinpour, M. Mazzotta, A. Watson
d Geffen School of Medicine, UCLA, Los Angeles, CA.

**Purpose of Study:** Atherosclerosis is the leading cause of morbidity in developed countries and it is believed that oxidized phospholipids have an instrumental role in its development. Oxidized phospholipids can react covalently with proteins, and lipids rendering them dysfunctional and antigenic. Consequently, an inflammatory response can occur. Keap1, a cytoplasmic negative regulatory protein, is thought to play an instrumental role in numerous diseases ranging from cancer to cardiovascular disease via interactions with several transcription factors such as Nrf-2. However, the mechanism by which Keap1 removes its inhibition has not been well elucidated. Keap1’s various cysteine residues enable it to possibly function and facilitate as a sensory protein for free radical and oxidative compounds via covalent modification. Our proposed mechanism of this reaction is that through covalent modification of Keap1 by specific oxidized phospholipids, Keap1 removes its inhibition on its associated transcription factors and enables gene and protein expression.

**Methods Used:** For further understanding, biotin-labeled oxidized 1-Palmityl-2-arachidonoyl-sn-glycero-3-phosphoethanolamine (PAPE) products were incubated with human recombinant Keap1, and human aortic endothelial cells. The covalent interaction was monitored by western blot analysis using streptavidin-HRP.

**Summary of Results:** Streptavadin-HRP recognized Keap1 treated with Ox-PAPE-N-Biotin but not Keap1 treated with unoxidized PAPE-N-Biotin.

**Conclusions:** The data suggests that oxidation was required for modification via Michael addition with cysteine residues on Keap1.

Endocrinology I
Concurrent Session
8:30 AM
Friday, January 30, 2009

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**GENETIC NATURE OF INSULIN CLEARANCE, AN UNDErSTUDYEd METABOlIC TRABoT**

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**Purpose of Study:** Diabetes affects 7-8% of adults in the U.S. and is a major cause of cardiovascular disease. Insulin resistance and impaired insulin secretion are considered essential to the development of diabetes. The role of dysregulated insulin clearance (removal of insulin from the circulation) is largely unknown. We previously documented a high heritability of insulin clearance in a prior study of Hispanics. In this study our goal was to confirm the high heritability and conduct a genome-wide linkage scan for insulin clearance.

**Methods Used:** Hyperinsulinemic-euglycemic clamps were performed in 536 subjects from 162 Hispanic families ascertained via a family history of hypertension. Insulin clearance is obtained from the steady state plasma infusion rate divided by SSPI; because the infusion rate is the same for all subjects, SSPI directly reflects insulin clearance. Heritability estimates and a genome-wide linkage scan (utilizing 388 microsatellites) were conducted using a variance components approach implemented in the program SOLAR.

**Summary of Results:** The age-, sex- and BMI-adjusted heritability of insulin clearance was 70.5%, indicating that the majority of the phenotypic variance is due to genetic factors. Two linkage peaks with a LOD = 2 for SSPI were identified in this cohort (chr 15 @ 67 CM, LOD = 2.49 and chr 20 @ 54 CM, LOD = 2.73). These loci harbor several promising candidate genes for insulin clearance during the euglycemic clamp. Insulin clearance is the insulin infusion rate divided by SSPI; because the infusion rate is the same for all subjects, SSPI directly reflects insulin clearance. Heritability estimates and a genome-wide linkage scan (utilizing 388 microsatellites) were conducted using a variance components approach implemented in the program SOLAR.

**Conclusions:** We have demonstrated that insulin clearance is a highly heritable trait in two distinct Hispanic cohorts, and now have identified chromosomal loci that may harbor genes that regulate insulin clearance. Identification of these genes may lead to improved modalities of risk assessment, diagnosis, prevention, and therapy of diabetes. A better understanding of how the body clears insulin will also be relevant to many other hyperinsulinemic disorders, such as the metabolic syndrome and polycystic ovary syndrome.

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Purpose of Study: To evaluate the relationship between insulin resistance-associated metabolic parameters and anthropometric measurements with sugar-sweetened beverage intake and physical activity.


Participants: A total of 6,967 individuals aged 12-19 years.

Main Exposure: Sugar-sweetened beverage consumption and physical activity levels.

Outcome Measures: Glucose levels, insulin levels, a homeostasis model assessment of insulin resistance, total cholesterol levels, HDL-cholesterol levels, LDL-cholesterol levels, triglyceride levels, total cholesterol/HDL-cholesterol ratios, non-HDL-cholesterol/HDL-cholesterol ratios, triglyceride/HDL-cholesterol ratios, systolic blood pressure, diastolic blood pressure, height, weight, waist circumference, body mass index, and ponderal index.

Summary of Results: Low sugar-sweetened beverage intake was associated with a lower homeostasis model assessment of insulin resistance (P < 0.001), higher HDL-cholesterol levels (P < 0.001), lower triglyceride levels (P < 0.001), a lower total cholesterol/HDL-cholesterol ratio (P = 0.002), a lower non-HDL-cholesterol/HDL-cholesterol ratio (P = 0.002), a lower triglyceride/HDL-cholesterol ratio (P < 0.001), a lower systolic blood pressure (P < 0.001), and a lower waist circumference (P < 0.001); alternatively, high physical activity levels were associated with a lower homeostasis model assessment of insulin resistance (P < 0.001), a trend towards lower total cholesterol levels (P = 0.06), lower LDL-cholesterol levels (P = 0.004), and a lower ponderal index (P < 0.001).

Conclusions: Low sugar-sweetened beverage intake and high physical activity levels appear to have complementary health benefits and are associated with improved insulin resistance-associated metabolic parameters and anthropometric measurements in adolescents.

50 THE LIPID AND WEIGHT CHANGE ASSOCIATED WITH BETA-BLOCKER IN TYPE 2 DIABETES

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Purpose of Study: Bet-blocker (BB) is one of the important pharmacological agents in the treatment of CAD and CHF. However, its unfavorable effects on glucose and lipid metabolisms are of clinical concern, especially in diabetic patients. We sought to examine these effects in our type 2 diabetic outpatients.

Methods Used: A Retrospective chart review was conducted on 1032 patients with type 2 diabetes in our clinic at VACCHS. Data on BMI, fasting lipid and glucose, A1c were collected; other measured parameters included age, sex, BP and medications. T test and multiple linear regression models were used for statistical analysis.

Summary of Results: More than 98% of the patients were males; age 69.5 years; BMI 29.96; BP 126.8/67.3 mmHg; TC 143 mg/dl; HDL 44 mg/dl; LDL 85 mg/dl; TG 70 mg/dl; Glucose 136.8 mg/dl; A1c 6.7%. The medication profiles were as follows: atenolol 22%, metoprolol 22%, other beta-blockers 1%; statins 63.7%. Lab results reported to have much favorable metabolic effects on lipids and glucose in type 2 diabetes and therefore may have a special therapeutic role in patients with both diabetes and CAD or CHF. Due to relatively older age and much more male patients in this study, the results should be interpreted with caution. Further studies are warranted in more representative population.

51 ACUTE CONSUMPTION OF VERY LOW CARBOHYDRATE MEALS LOWERS POSTPRANDIAL CONCENTRATIONS OF INSULIN AND LEPTIN

M. Kumagai, J. Smith, S. Bergman, J. Jordan, A. Clemons, M. Gillingham, B. Duell, D. Stadler Oregon Health and Science University, Portland, OR.

Purpose of Study: Persons following very low carbohydrate (VLC) diets report “food disinterest” that may contribute to reduced food intake and greater weight loss than other weight reduction diets. Acute changes in weight regulation hormones that affect hunger and satiety may contribute to this heightened response. This study uses a random-order, crossover design to test the hypothesis that acute consumption of VLC meals leads to decreased postprandial insulin and leptin concentrations compared to high complex carbohydrate (HC) meals.

Methods Used: Seven healthy normal-weight adults completed two 4-day controlled dietary phases separated by at least a 3-day wash-out phase. Participants consumed a standard diet [51% carbohydrate (CHO), 14% protein, 35% fat] for 3 days, and VLC (4% CHO) or HC (58% CHO) breakfast and lunch meals on the 4th day. VLC and HC test meals provided 10 kcal/kg body weight. Pre- and postprandial concentrations of insulin and leptin were measured in blood samples obtained half-hourly and hourly for 9.5 h. Area under the curve (AUC) and time to maximum response for each analyte was determined for each diet, with differences between diets compared using paired t-tests; time to peak response was also examined for correlations between insulin and leptin.

Summary of Results: Patterns of change in concentration over time and areas under the curve for insulin and leptin were significantly different between the VLC and HC diets; 91 ± 13.2 vs 259 ± 29.7 μU/ml, P = 0.0002 and 3.5 ± 0.7 vs 4.7 ± 1.0 ng/ml(P < 0.001). The statistical significance remained the same after adjusting for time to peak response was also examined for correlations between insulin and leptin.

Conclusions: Acute consumption of VLC meals compared to HC meals resulted in significantly different postprandial patterns of change and lower AUCs for insulin and leptin. The impact that insulin has on circulating leptin concentrations and the influence of these and other weight regulation hormones on hunger and satiety is our current focus of investigation.

52 NON-DIABETIC ARE AT HIGH RISK FOR DEVELOPING PERSISTENT DIABETES MELLITUS AFTER LIVER TRANSPLANT

L.E. Aguirre1,2, M. Sheikh-Ali3, B. McNeel1 1University of New Mexico, Albuquerque, NM; 2University of Florida, Jacksonville, FL and 3Mayo Clinic, Jacksonville, FL.

Purpose of Study: To study the occurrence of diabetes in non-diabetic liver transplant recipients at the Mayo Clinic Jacksonville, Florida.

Methods Used: Method: Methods Used: Retrospective chart analysis of 275 consecutive orthotopic liver transplants (OLT) conducted at the Mayo Clinic for 13 months. Inclusion criteria: Patients with end-stage-liver disease and no history of diabetes mellitus (DM) undergoing OLT at the Mayo Clinic between 2003 and 2004. Exclusion criteria: Pre-existing DM, renal failure, prior history of solid organ transplantation. Blood glucose data was collected at the time of OLT evaluation and at 3 different time points post-OLT. Diabetes was defined following the current American Academy of Clinical Endocrinologists guidelines.

Summary of Results: 122 out of 275 patients met study criteria. Most of our study population consisted of males (84%) of Caucasian ethnicity (64%) and had a family history of DM. The incidence of DM after OLT was 95% at 1 week, 38% at 4 months and 34% at 1 year. Intriguingly, patients that were classified as diabetic at both 1 week and 4 months post-OLT remained diabetic even after discontinuation of all stressors that are known to cause hyperglycemia.

Conclusions: Non-diabetic patients undergoing OLT are at high risk for developing DM. The risk of persistent DM at 1 year post-OLT is high in patients with a family history of DM and those diagnosed with DM at 1 week and 4 months post-OLT. These findings suggest that agressive glucose monitoring and diabetes treatment should be emphasized before and after OLT for both diabetic and non-diabetic patients.
53 VITAMIN D (1,25D) INHIBITS CARDIOMYOBLASTS CELL PROLIFERATION BY PROMOTING CELL CYCLE ARREST AND ENHANCES CARDIOMYOTUBES FORMATION WITHOUT INDUCING APOPTOSIS

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Purpose of Study: Cardiomyocyte disease remains the leading cause of death in the US. Low levels of 25(OH)D are associated with a higher risk of myocardial infarction in a graded manner, even after controlling for factors known to be associated with coronary artery disease. A growing body of evidence suggests that people who are deficient in 25(OH) D have higher risks of cancer, diabetes, autoimmune diseases and recently heart attacks.

Cardiac hypertrophy has been observed in rats deficient in 25(OH)D and in the hearts of vitamin D-receptor knockout mice. We examined the role of 1,25D (the active form of vitamin D) on cardiomyocyte proliferation, apoptosis, cell phenotype, cell cycle progression and differentiation into cardiomyotubes. Rat H9c2 cardiomyocytes were incubated with 1,25D in a time course manner and at different concentrations in order to assess, first, if this cardiomyocyte cell line expresses the VDR (vitamin D receptor) and also the initiation of cell cycle changes at which 1,25D exerts its effects and have statistical significance in cell proliferation by different approaches.

Methods Used: Cell proliferation was evaluated by formazan assay and for the expression of PCNA. Apoptosis was evaluated by TUNEL assay and select apoptotic related genes such as Bcl-2 and Casp3. The biological activity of 1,25D was assessed by change in expression and sub-cellular localization of VDR. Changes in cell phenotype were studied by following cells in vivo for 7 days through a noninvasive fluorocrome (PHK2). The expression of genes related to the cell cycle was analyzed by RT2PCR microarrays after total RNA isolation.

Summary of Results: The addition of 1,25D to H9c2 cardiomyocytes cells: 1) inhibits cell proliferation; 2) enhances cardiomyocytes formation; 3) exerts a protective effects against apoptosis and 4) promotes a generalized decreased in the expression of genes related to the regulation of the cell cycle such as: Cyclins A1, C, and E and Cdk2a and Cdk4.

Conclusions: The results of the present study suggests that reversing vitamin D deficiency could contribute to the prevention of cardiovascular disease and other related cardiac conditions by down regulating excess cell proliferation and promoting myotube formation.

54 PRESENTING COMPLAINTS OF PEDIATRIC PATIENTS WITH HYPERTHYROIDISM

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Purpose of Study: We characterized the presenting signs and symptoms of children ultimately diagnosed with hyperthyroidism.

Methods Used: We performed a retrospective chart review of pediatric patients evaluated for hyperthyroidism between December 1999 and July 2008. A search of ICD 9 codes revealed 68 patients. We reviewed medical records for the following: 1) chief complaint at initial visit; 2) additional symptoms present; 3) number of visits prior to diagnosis; 4) type of practitioner seen prior to diagnosis; 5) duration of symptoms; 6) past medical history; 7) laboratory studies at diagnosis; 8) patient age and gender; and 9) presence of major behavioral problems.

In 5 cases, the initial chief complaint was unknown. These patients were included for behavioral analyses.

Summary of Results: Cardiac symptoms were the most common presenting symptom in children diagnosed with hyperthyroidism (23.8 percent). 17.4 percent of patients were incidentally diagnosed after a physical exam for an unrelated purpose, 9.5 percent presented with fatigue, and 6.3 percent complained of weight loss. 6.3 percent were diagnosed after screening laboratory blood draws. Additionally, 6.3 percent of patients were diagnosed following an initial evaluation for mood symptoms.

A secondary analysis revealed 14 of 68 patients (including the 4 who presented with mood symptoms) with major behavioral problems at presentation.

Conclusions: Cardiac manifestations were the most common reason for our patients to seek medical care; this is the first study to demonstrate this high incidence of cardiac complaints among children with hyperthyroidism. Delayed diagnosis occurred in many due to the time spent evaluating suspected cardiac disease. Thyroid screening labs should thus be considered in all children with cardiac symptoms.

55 ASSESSMENT OF MAXIMAL CORTISOL SECRETION RATES IN SECONDARY ADRENAL INSUFFICIENCY (AI) PATIENTS AND IN HEALTHY CONTROLS USING ADVANCED NUMERICAL MODELING METHODS

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Purpose of Study: The cosyntron stimulation test for diagnosis of secondary AI (SAI) has low sensitivity (57%), and gold standard tests such as insulin tolerance and metanephrine tests have limited utility. Assessment of cortisol secretion rate may provide a better diagnostic tool for evaluation of adrenal function; however usual methods are cumbersome and yield average cortisol secretion rates. Numerical methods provide an alternative approach to estimation of cortisol secretion rates; our primary study objective was to apply numerical methods in order to model the time course of cortisol sampled total cortisol during cosyntron stimulation. We also sought to determine whether dexemethasone (DEX) suppression influences cortisol secretion or clearance rates, and how its use affects the concept that maximal cortisol secretion rates are decreased in subjects with SAI than in control subjects.

Methods Used: Advanced numerical modeling methods involving solving 3 simultaneous non-linear system of differential equations that describe free, cortisol binding globulin (CBG)-bound, and albumin-bound cortisol compartments. The solutions for free cortisol secretion and clearance rates accounted for measured concentrations of CBG and albumin and match a time series of cortisol concentrations obtained during the high-dose (250 mcg) cosyntron stimulation test. We assume a uniform (maximal) cortisol secretion rate during the 60-minute of the test. All subjects were tested with both placebo and DEX (1 mg at 2300 hr) pretreatment.

Summary of Results: The solution of differential equations indicates that cortisol secretion rate is not proportional to total cortisol 60-minute after cosyntron. These equations fit to preliminary data in SAI and control subjects yield adequate goodness of fit (median R2 = 0.94) and demonstrated expected decrease in maximal cortisol secretion rate in subjects with SAI. Administration of DEX had no effect on maximal cortisol secretion or clearance rates.

Conclusions: Advanced numerical modeling techniques permit calculation of maximal cortisol secretion rate under dynamic (non-steady) conditions during the 60-minute cosyntron stimulation test.

56 REPRIMO EXPRESSION AND FUNCTION IN PITUITARY TUMORS

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Purpose of Study: Gonadotropinomas, which produce α, LHβ, and/or FSHβ subunits, represent 35% of pituitary tumors. They pose a diagnostic challenge, and their pathogenesis is unknown. Identification of pituitary tumor-specific genes may provide markers of aggressiveness and lead to a better understanding of the pathophysiology of these tumors. Reprimo (RPRM), is a mediator of the p53-mediated cell cycle arrest at the G2 phase. RPRM is hypermethylated in some cancers blocking its transcription and silencing this cell cycle “brake”, ultimately resulting in increased growth and tumorigenesis. We identified RPRM as decreased 13-fold in DNA array analysis of gonadotropinomas vs. normal pituitaries and asked if its suppression may play a role in pituitary tumorigenesis.

Methods Used: Affymetrix U133 Plus2.0 Array was utilized to compare gene expression profiles of ten gonadotropinomas with nine normal pituitaries. αT3 mouse gonadotroph cells were transfected with vector or RPRM plasmid to create a model of RPRM overexpression in pituitary cells. To assess RPRM methylation, the bisulphite converted RPRM promoter(30 CpG) was PCR-amplified and sequenced. RPRM expression was analyzed by RTPCR.
Summary of Results: Semiquantitative RTPCR showed that RPRM mRNA levels were consistently lower in gonadotropinomas compared to normal pituitary, suggesting the results of the DNA arrays. Immunohistochemistry revealed overexpression of RPRM in αT3 gonadotroph cells triggered a 10-fold increase in cleaved caspase 3 after 48 h serum starvation compared to controls as an index of apoptosis. These data suggested that repression of RPRM would lead to protection from programmed cell death. RPRM promoter methylation was detected in 3 out of 10 gonadotropinomas and 0 out of 10 normal pituitaries, suggesting hypermethylation may play a partial but not universal role in RPRM function.

Conclusions: RPRM is downregulated in human pituitary tumors compared to normal pituitary at the transcript and mRNA level. Overexpression of RPRM increased rates of apoptosis in a gonadotroph cell-line, consistent with its role as a p53 cell cycle mediator. RPRM is variably methylated in pituitary tumors, suggesting its role as a tumor suppressor is mediated through multiple mechanisms.

Antigen Tolerance and Immune Response

58 anti-CTLA-4 therapy induces hypopituitarism in metastatic prostate carcinoma

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Purpose of Study: Antigen T-cell responses are important in the immune response to cancer. Anti-CTLA-4 therapy has been shown to induce autoimmune phenomena in a small proportion of patients. The purpose of this case report is to describe the first two cases of hypopituitarism in prostate cancer patients undergoing experimental therapy with anti-CTLA-4 therapy.

Methods Used: A pilot trial of ipilimumab (IP), an anti-CTLA-4 antibody, was performed in melanoma, renal cell, ovarian, and prostate cancers.

Case Report: Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) is a receptor that inhibits T-lymphocytes and promotes antigen tolerance. Anti-CTLA-4 antibody represents a novel approach to cancer treatment through disruption of immune tolerance to antigens on tumor cells. They are currently under investigation for malignant melanoma, renal cell, and prostate cancers. Anti-CTLA-4 therapy induces autoimmunity. In fact, autoimmunity is a marker of responsiveness to therapy and tumor regression. Presumed autoimmune hypophysitis (AH) is seen in about 5% of patients treated with anti-CTLA-4 antibody for melanoma and renal cell carcinoma. A pilot trial of ipilimumab (IP), an anti-CTLA-4 antibody, failed to reveal any cases of AH in patients with prostate cancer. We describe the first two cases of hypopituitarism in prostate cancer patients undergoing experimental therapy with IP.

Both of our patients exhibit many of the previously described characteristics of the 17q21.31 deletion syndrome and have deletions that encompass the MAPT gene. In addition, our first patient has a history of joint dislocations and oligodontia and both have long toes, features which have not been previously described as part of the clinical phenotype.

Conclusions: Both of our patients exhibit many of the previously described characteristics of the 17q21.31 deletion syndrome and have deletions that encompass the MAPT gene. In addition, our first patient has a history of joint dislocations and oligodontia and both have long toes, features which have not been previously described as part of the clinical phenotype.

59 Chromosome 17q21.31 deletion syndrome: a report of two new patients and review of the literature

J. Hogue, A. Slavotinek USCF, San Francisco, CA.

Purpose of Study: The rapidly increasing use of array comparative genomic hybridization (array CGH) in patients with mental retardation has facilitated the identification of novel microdeletion and microduplication syndromes, one of which is the 17q21.31 deletion syndrome. Since it was first reported in 2006, a total of 25 patients with this deletion syndrome have been reported. Patients have been noted to show similar characteristics including variable developmental delay, a friendly and amiable personality, hypotonia, a long face, and a pear-shaped nose. We report two additional patients with deletions in the 17q21.31 region in an attempt to further characterize the clinical phenotype.

Methods Used: Information on the patients was compiled and compared and a literature review was completed.

Summary of Results: Our first patient is an 11 year old girl with a history of congenital dislocation of the hips, global developmental delay, mild mental retardation, hypotonia, a friendly and amiable personality, easily controlled seizures, joint laxity, patellar dislocation, and congenital absence of the upper lateral incisors bilaterally. Physical examination is notable for blonde hair and blue eyes, a high forehead, mildly upslanting palpebral fissures, a bulbous and broad nasal tip, prominent ear lobes, a narrow palate, an everted lower lip, long toes, valgus deviation of the hallucema, and pes planus. Array CGH analysis revealed a 453 kb region copy number decrease within the 17q21.31 region.

Our second patient is a 28 month old boy with a history of global developmental delay, hypotonia, failure to thrive, cryptorchidism, easily controlled seizures, thinning of the corpus callosum on MRI, and a friendly and outgoing personality. His physical exam is notable for a broad and prominent forehead, upslanting palpebral fissures, a broad nasal root, cupped helices, a small chin, and long toes. Array CGH analysis revealed a 676 kb region copy number decrease within the 17q21.31 region.

Conclusions: Both of our patients exhibit many of the previously described characteristics of the 17q21.31 deletion syndrome and have deletions that encompass the MAPT gene. In addition, our first patient has a history of joint dislocations and oligodontia and both have long toes, features which have not been previously described as part of the clinical phenotype.

60 Eukaryotic elongation factor-2 kinase (EEF2K) downregulation correlated with de novo DNA methylation and decreased DNA accessibility in neonatal IUGR rat liver

Q. Fu, R.A. McKnight, X. Yu, C.W. Callaway, R.H. Lane University of Utah, Salt Lake City, UT.

Purpose of Study: The rapidly increasing use of array comparative genomic hybridization (array CGH) in patients with mental retardation has facilitated the identification of novel microdeletion and microduplication syndromes, one of which is the 17q21.31 deletion syndrome. Since it was first reported in 2006, a total of 25 patients with this deletion syndrome have been reported. Patients have been noted to show similar characteristics including variable developmental delay, a friendly and amiable personality, hypotonia, a long face, and a pear-shaped nose. We report two additional patients with deletions in the 17q21.31 region in an attempt to further characterize the clinical phenotype.

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Conclusions: Both of our patients exhibit many of the previously described characteristics of the 17q21.31 deletion syndrome and have deletions that encompass the MAPT gene. In addition, our first patient has a history of joint dislocations and oligodontia and both have long toes, features which have not been previously described as part of the clinical phenotype.
Purpose of Study: It has been shown that uteplacental insufficiency (UPI) alters protein synthesis in IUGR. One of the key regulators of protein synthesis is eEF2K, which regulates protein synthesis by phosphorylating and inactivating eEF2. eEF2K is a classic Cpg island gene. It is well known that DNA hypermethylated and decreased DNA accessibility in the promoter region are related to transcription repression. We hypothesized that UPI would affect hepatic eEF2K expression by altering eEF2K DNA methylation and possibly DNA accessibility in neonatal IUGR rats.

Methods Used: IUGR rat model was generated by bilateral uterine artery ligation. Real-time RT-PCR and Western blotting were used to quantify hepatic eEF2K mRNA and protein levels. Bisulfiite sequencing was used to detect in vivo DNA methylation. The M.Ssfl methyltransferase (MMT) footprinting assay was used to determine nucleosome position and test DNA accessibility.

Summary of Results: IUGR animals had decreased hepatic eEF2K mRNA and protein levels of 70%* and 40% (P = 0.06) respectively. 45 CpG sites around the transcription start site (TSS) from -282 to +217 on the eEF2K gene were analyzed. Increased Cpg methylation between -206 and -282 occurred in IUGR relative to control (13% vs 0%, 29% vs 10%, 29% vs 10%*). There was no Cpg methylation downstream of -206 in both control and IUGR groups. The position of 2.5 nucleosomes around the TSS was mapped by MMT footprinting. The -1 nucleosome was highly accessible in both groups, while -2 and +1 nucleosomes had significantly decreased accessibility in IUGR relative to control. (P < 0.05)

Conclusions: UPI downregulates hepatic eEF2K expression in neonatal IUGR rats. This downregulation is correlated with de novo DNA methylation in the promoter region. Reduced DNA accessibility in both the promoter and 5'untranslated region are related to transcription repression. We hypothesized that UPI regulates protein synthesis in IUGR. One of the key regulators of protein synthesis is eEF2K, which regulates protein synthesis by phosphorylating and inactivating eEF2. eEF2K is a classic Cpg island gene. It is well known that DNA hypermethylated and decreased DNA accessibility in the promoter region are related to transcription repression. We hypothesized that UPI would affect hepatic eEF2K expression by altering eEF2K DNA methylation and possibly DNA accessibility in neonatal IUGR rats.
for hydrogen bonding. Lysine and arginine are similar in side chain structure and pK, while histidine has a ring side chain and variable pK depending on ionic environment.

METHODS USED:

K.P. Cusmano-Ozog, A. Kwan, G.M. Enns, T.M. Cowan

1 Stanford University, Stanford, CA and 2 Stanford University, Stanford, CA. PURPOSE OF STUDY: Etymalonan Encephalopathy (EE) is an autosomal recessive disorder caused by mutations in the ETHE1 gene. Biochemical findings include elevated C4- and C5- acylcarnitines and a characteristic pattern of urine organic acids. Clinical findings include petechiae, acrocyanosis and diarrhea. Neurological symptoms typically present in infancy accompanied by abnormal brain lesions on MRI. Death in early childhood is common, with survival ranging from 3–16 years in reported patients. We describe an atypical EE patient who has later age of onset, longer survival, and uncommon milder clinical features.

METHODS USED: Retrospective chart review.

Summary of Results: The proband is a 24-year-old female whose parents are consanguineous. She developed chronic diarrhea at 2 years of life and symptoms of Raynaud’s disease began at age 5 years. Developmental milestones were delayed and a full scale IQ at 7 years was 59. She completed high school in special education classes. The patient began complaining of headaches at age 10 years; EEG and brain MRI were normal. Repeat MRI performed 14 years of age was also normal. At 16 years, she experienced decreased strength in her lower extremities, resulting in fatigability, poor coordination and frequent stumbling. Babinski sign was positive bilaterally, and reflexes were brisk. EMG and NCV studies showed nonspecific abnormalities. Acylcarnitine profile showed elevated C4, C5, C6, and C10:1 acylcarnitines. Urine organic acids showed elevated ethylmalonic and methylsuccinic acids as well as isobutyrylglycine and isovalerylglycine. Molecular studies demonstrated a deletion of the entire ETHE1 gene on both chromosomes with absence of the ETHE1 protein on fibroblasts by Western blot analysis.

Conclusions: We present a patient with characteristic biochemical findings, deletion of ETHE1 with an atypical neuropathic presentation, mild course, and absence of MRI findings who remains alive at age 24 years. To our knowledge this represents the oldest surviving case of EE, and broadens phenotypic spectrum of EE beyond previously reported cases. The relationship between clinical phenotype and ETHE1 genotype remains unknown. We recommend that the diagnosis of EE be considered in any patient with chronic diarrhea, acrocyanosis, developmental delay and neurologic symptoms, regardless of age or severity of symptoms.

65 VASCULAR AND AUDITORY FEATURES IN CARDIO-FACIO-CUTANEOUS SYNDROME

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Purpose of Study: To evaluate the ocular and audiologic features in patients with cardio-facio-cutaneous (CFC) syndrome as reported in a parental survey and to determine whether a genotype/phenotype correlation exists. CFC is a congenital disorder caused by mutations in genes of the Ras/MAPK pathway — BRAF, MEK1, and MEK2. CFC is characterized by cardiac defects, distinctive craniofacial appearance, cutaneous abnormalities and developmental delays.

METHODS USED: A detailed questionnaire regarding ocular and audiologic clinical features was sent to a cohort of over 50 CFC patients with known molecular diagnosis.

Summary of Results: We received information from 27 CFC patients with confirmed molecular diagnosis. Parents reported visual and auditory problems in 26/27 patients. All patients had cognitive delay. The most common ocular features that parents noted were problems with depth perception 16/27 and abnormal head posture 14/27. Other commonly reported manifestations were refractive errors 17/27, strabismus 15/27, amblyopia 15/27, nystagmus 10/27, droopy eye lids 10/27 and optic nerve hypoplasia 2/27. Only one patient had cataracts. Hearing abnormalities included hearing impairment 7/27, sensitivity to loud noises 20/27, small ear canals 19/27, excess ear wax 21/27 and ear tube placement 15/27 patients. Majority of patients reported BRAF mutations and no gender/mutation specific phenoypeic correlations were found.

Conclusions: The high occurrence of cognitive delay and visual features such as strabismus, amblyopia and nystagmus suggest that Ras/MAPK pathway plays an important role in CNS development including human visual pathway and ocular alignment control. Majority of children exhibited sensitivity to loud noises and had features such as small ear canal and excess wax suggesting the important role of Ras/MAPK pathway in development of auditory system. Our results demonstrate that these patients require routine ophthalmologic and ENT evaluation and are likely to benefit from interventions in the management of the visual and auditory symptoms. Further characterization of the ocular and auditory manifestations in a larger number of mutation positive CFC patients will contribute towards the understanding of the pathogenesis of this syndrome.

66 DYSTOSIS MULTIPLEX-LIKE SKELETAL FINDINGS IN ALBRIGHT HEREDITARY OSTEODYSTROPHY

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Purpose of Study: The term “Albright hereditary osteodystrophy” (AHO) describes the skeletal phenotype associated with mutations in GNAS1, which encodes the stimulatory G-protein α subunit. Individuals with AHO have short stature, obesity, and short metacarpals. Maternal origin of the altered allele additionally leads to developmental difficulties and polyendocrinopathy including parathyroid hormone resistance. We present a patient with AHO secondary to maternally inherited GNAS1 mutation. Our patient’s atypical skeletal findings delayed diagnosis; his case expands the reported skeletal manifestations, which we will review in the context of genetic and epigenetic pathogenesis.

METHODS USED: Retrospective review of case records and the relevant medical literature was performed.

Summary of Results: Our patient presented at ten months with congential hypothyroidism, imperforate anus, brachymelia without brachydactyly, and obesity. Skeletal survey showed broad ribs and undertubulation of the long bones, suggestive of dystosis multiplex; urine glycosaminoglycans and oligosaccharides were normal. He experienced seizures at 23 months, leading to discovery of hypocalcemia and elevated parathyroid hormone. Examination of his mother showed short limbs and brachymetaphalangia. Sequencing of GNAS1 revealed a missense mutation corresponding to Lys44Arg, which was predicted to be disease-causing.

Conclusions: The association of brachymetaphalangia and short stature, though seen in a variety of syndromes, often prompts consideration of AHO. These features’ independence of the parent-of-origin effect displayed by the endocrine aspects of the disorder has been explained by tissue-specific imprinting of GNAS1. However, as this family illustrates, these skeletal findings are not universal, even among those who have severe endocrine manifestations of the disorder. The range of reported skeletal findings includes such diverse entities as vertebral anomalies, fibrous dysplasia, and heterotopic ossification. Some individuals have no skeletal manifestations. The dystosis multiplex-like findings in our patient further expand the phenotypic spectrum and emphasize the importance of considering this diagnosis in a variety of clinical scenarios.
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ESTIMATING THE PREVALENCE OF HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT) IN PATIENTS WITH JUVENILE POLYS (JP) USING A CLINICAL INFORMATICS SYSTEM

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Purpose of Study: Mutations in the gene SMAD4 have been associated with JP and HHT. The hypothesis of this study is that analysis of HHT-associated diagnoses in a population of patients with pathologically confirmed JP will be found at a higher frequency than in a control group of age and gender-matched controls with adenomatous polyps.

Methods Used: The anatomic pathology information system was queried to identify all patients with juvenile polyps since 1995. A total of 113 patients were identified. A population of age and gender matched controls was created. Queries of the electronic data warehouse for ICD-9 codes that represent the manifestations of HHT (e.g. epistaxis 784.7, pulmonary AV malformation 417.0 or 747.3) were compared between the two populations.

Summary of Results: Preliminary analysis of the 113 JP patients identified 27 (24%) with GI hemorrhage and 3 (2.6%) with epistaxis. Only one patient had both GI hemorrhage and epistaxis. No patients were found with a diagnosis of AV malformation, angiodyplasia of the GI tract or HHT.

Conclusions: Based on these preliminary data, no JP patients were able to be definitively diagnosed with HHT based solely on the informatics inquiry. Only one patient has possible HHT based on the presence of both GI hemorrhage and epistaxis. Additional analyses to be presented include assessment of the control group with comparison to the JP group and the results of chart review of all patients with a history of either GI hemorrhage or epistaxis to address limitations of the informatics inquiry to capture other clinically relevant information necessary for the diagnosis of HHT.

Conclusions: It can be reasonably concluded that the prevalence of HHT in a population of patients with JP is quite low—probably 1% or less. While information should be sought regarding associated diagnoses and family history, HHT surveillance in this population cannot be justified at the present time.

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DEXTROCARDIA DIAGNOSED AFTER ONE MONTH OF AGE ACCOMPANIED BY FEWER SERIOUS CARDIAC MALFORMATIONS

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Purpose of Study: To assess the relationship between dextrocardia (D), cardiac malformations (CM), and age at diagnosis (DX). A primary care clinician in pediatrics, family practice, or obstetrics may encounter a fetus, infant, or child with dextrocardia (D), discovered by fetal ultrasound, physical exam, or chest X-ray. Dextrocardia is associated with serious CM. However, the relationship between age at dextrocardia discovery and the incidence of CM has not been reported.

Methods Used: We report patients with dextrocardia evaluated between 1988 and 2008.

Summary of Results: We identified 56 patients: 32 males and 24 females. Median age at DX: 20 months (range: prenatal to 12 years). CM: 29/56 (52%), situs solitus (SS): 18/56 (32%), situs inversus (SI): 25/56 (45%), and situs ambiguous (SA): 13/56 (23%). CM in situs ambiguous group: 12 (92%), situs solitus group: 11/56 (19%), and in situs inversus group: 6 (24%). Of the 29 CM, 11 (38%) had AV canals, 7 (24%) L-TGA, 3 (10%) single ventricles, and 8 (28%) other. Age at DX of Dextrocardia: 14 prenatal, 22 neonatal, and 20 >1 month. CM by age: Prenatal: 10/14 (71%), neonatal 16/22 (73%), and >1 month 3/20 (15%). Mean age at DX: Dextrocardia with CM: 9.8 months and without CM: 28.7 months (P = 0.001). In dextrocardia with SA, CM: 11/12 (92%). In dextrocardia with SS: CM: 10/13 (77%) for those diagnosed prenatal and/or neonatal, and CM: 1/5 (20%) for those diagnosed >1 month (P = 0.04).

Conclusions: A fetal or a neonatal diagnosis of dextrocardia increased the risk for serious CM. The risk for CM decreased if dextrocardia was diagnosed beyond 1 month of age. The incidence of CM was highest in those with situs ambiguous, followed by situs solitus, and lowest in situs inversus.
71  AUTOMATED CLINICAL INFORMATION SYSTEM IMPROVES PATIENT CARE

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Purpose of Study: Studies have shown that poor quality medical care can result from time constraints and fragmentation of care causing delays in treatment and/or inconsistent documentations. Following a root cause analysis of patient deaths in the liver transplant program at the University of Washington (UW) from 2003-2006, the program identified immunosuppressive drug toxicities as the leading cause of patient morbidity after discharge from the hospital. Due to the increasing volume of post transplant patients, the time to adjust medications sometimes required 3 days following laboratory levels. This extended period also caused inconsistent documentation. To address these concerns, the UW liver transplant program developed and instituted an automated clinical support system that consolidated clinical information needed for immunosuppressive medication review.

Methods Used: To study the effect of the new automated clinical informatics system, data was collected on 428 consecutive liver transplant patients receiving tacrolimus between Jan 2004-Apr 2008.

Summary of Results: Using the automated system reduced the time to make medication adjustments from 2004 to 2008. The 12-month period in 2004 on the automated system had a creatinine clearance at one year (87.5 ± 32.9 ml/min) significantly higher (P = 0.008) than the creatinine clearance (74.4 ± 30.0 ml/min) in those 301 patients using the old paper chart system. The incidence of tacrolimus toxicity in one year was significant lower (P = 0.05) in those being monitored with the automated system (18%) vs being monitored with the paper charting system (30%). The incidence of rejection within one year was significantly lower (P = 0.001) in patients being monitored with the automated system (7%) vs being monitored with the paper charting system (27%). In a formal cost-effectiveness analysis the automated system demonstrated absolute dominance over the paper charting system. The automated system cost $322 to monitor a patient for one year with a 97% quality of life compared to the paper charting system cost of $1790 with an 89% quality of life.

Conclusions: These results are one of the first to demonstrate that an automated clinical information system for monitoring chronic drug maintenance is cost-effective. In conclusion, an automated clinical informatics system improves the management of immunosuppressive drugs in transplant patients and improves the quality of patient care and life.

72  ASSOCIATION OF NATIONAL INSTITUTES OF HEALTH FUNDING LEVELS WITH UNITED STATES DISEASE BURDEN MEASURES


Purpose of Study: The United States (US) National Institutes of Health (NIH) is the largest public source of medical research funding in the United States. There is government and public concern that research funding does not correlate with US disease burden. In 1998, Congress asked the Institute of Medicine (IOM) to review the NIH apportionment process. Thereafter, Gross et al (NEJM 1999; 340:188) published a study analyzing the relationship between NIH condition-specific funding and US disease burden measures, finding disability-adjusted life-years (DALY’s) were the strongest predictor. We perform a comprehensive update assessing the 10-year impact of the IOM criteria.

Methods Used: This cross-sectional study compared US disease-specific burden and sociopolitical measures from 2004 to NIH funding levels in 2008. Data on burden was collected from the Global Burden of Disease Project led by the World Health Organization; figures on hospital stays, emergency TV reports, and charity revenue were other sociopolitical factors analyzed. All predictors and the NIH funding level underwent log-transformation. Standard univariate analyses were employed. The a priori primary multivariate linear regression analysis included all public health needs measures. All other predictors were then singly added to this model and the significance of their contribution assessed with the F-statistic.

Summary of Results: The median NIH funding for the 29 conditions analyzed in 2006 was $335 million, ranging from $17 million for peptic ulcer disease to $2.9 billion for HIV/AIDS. The primary multivariate analysis found a significant relationship only between DALY’s and NIH funding (P<0.045). No markers of scientific quality and opportunity nor sociopolitical factors were important.

Conclusions: In 2006, NIH funding was significantly related only to the US public health needs measure of disease-specific DALY’s. Thus, in this 10-year assessment of the 1998 IOM NIH funding priority-setting criteria implementation, no significant changes in factors influencing NIH funding levels were detected.

73  DOES THE J-1 VISA WAIVER PROGRAM MEET THE NEEDS OF WASHINGTON STATE’S POOR AND UNDERSERVED?

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Purpose of Study: The Federal J-1 Visa Waiver program allows each state to annually recruit 30 foreign medical graduates, who recently completed U.S. residency training while on J-1 (student) visas, to work in underserved rural and inner city settings. We sought to determine whether the J-1 visa waiver program was meeting its goal of increasing the number of physicians in Washington State’s underserved areas.

Methods Used: All J-1 visa waiver physicians assigned to employers in the state between 1995 and 2003 were identified, tracked where possible through public databases to their current locations, and surveyed by written questionnaire about their experiences in and subsequent to the program.

Summary of Results: Of the 155 physicians assigned to employers, 143 (92%) were tracked and sent surveys, of whom 75 (52%) returned them. Based on the returned surveys, Washington State J-1 visa waiver physicians remained with their J-1 waiver employers 18 [0–120] (median [range]) months longer than their required commitment period, and remained in practices serving primarily underserved populations for 25 [0–120] consecutive months after fulfilling their commitment period. After leaving their J-1 waiver employers, 74% of physicians who undertook their period of service in rural areas moved towards more urban areas, and 65% of respondents still live in the state. While the majority of physicians were Asian, Latin American physicians (62%) were most likely to leave the state after completing their obligations (P < 0.05), with 46% of them relocating to Texas and Florida. Whereas most expressed satisfaction with the program, 23 felt employers should have shown them more respect. Further, 8 of 13 respondents who changed employers during their J-1 waiver periods cited an exploitive or disreputable employer as the reason.

Conclusions: In summary, in Washington State the J-1 Visa Waiver program has successfully increased the number of physicians in underserved areas, who frequently stay beyond their obligation. Policy changes at a national level, allowing physicians to obtain waivers in states where they intend to settle long-term, could result in better retention in underserved areas following completion of their commitments.

74  IMPEDIMENTS TO AN UNDERSERVED WORKFORCE SOLUTION: BARRIERS TO FAMILY MEDICINE RESIDENT TRAINING IN COMMUNITY HEALTH CENTERS

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Purpose of Study: The chronic problem of health workforce shortages in community health centers (CHCs) has become a crisis. One potential workforce solution is training partnerships between family medicine residencies (FMRs) and CHCs. This solution builds on previous work that has demonstrated a positive correlation between depth of exposure to underserved settings and recruitment and retention to these areas following graduation. Our investigation evaluates the barriers to training family medicine residents in CHCs.

Methods Used: As part of a national survey, all US family medicine residency directors were asked to list up to three barriers to training residents in CHCs. Using grounded theory, three coders group the responses into representative barrier codes. Frequencies of barriers were tabulated, and a comparative analysis examined differences in barriers between FMRs that currently train with CHCs (CHC-affiliated FMRs) and FMRs that do not currently train with CHCs (non-affiliated FMRs.)

Summary of Results: A total of 226 residents (64%) answered the open-ended survey item about barriers to CHC-FMR affiliation, with an average
of 1.78 barriers listed. The number and percentage of barriers in order of frequency are: 65 residen(ies) (29%) cited Governance as a barrier to affiliated. 59 (26%) cited. Administrative complexity; 54 (24%) cited. Financial considerations; 48 (21%) cited Leadership; 41 (18%) cited Access; and 41 residences (18%) cited that there were no barriers to training in CHCs or that CHC training was unneeded. There was a significant association between being a CHC-affiliated FMR and the citation of Financial considerations compared to being a non-affiliated FMR (P < 0.001). Administrative complexity was also associated (P < 0.01) with being a CHC-affiliated FMR. Conversely, there was a significant association between being a non-affiliated FMR and the citation of Leadership (P < 0.001).

Conclusions: This study illustrates the barriers to CHC-FMR partnerships, and how these barriers differ by CHC-affiliation status. CHC-FMR barrier data have not been reported on a nationwide scale. In light of the current workforce crisis, this information could assist stakeholders in the formation and maintenance of CHC-FMR partnerships.

75 THE EFFECT OF SHOULDER DYSTOCIA SIMULATION TRAINING ON ACTUAL DYSTOCIA CHART DOCUMENTATION

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Purpose of Study: Simulation training is used to enhance resident management of shoulder dystocia complication. Since it is one of the most common causes of litigation in Obstetrics, documentation must be accurate and complete. A study evaluating documentation post shoulder dystocia simulation demonstrated that less than 25% of residents recorded 10/15 crucial items for chart documentation of a shoulder dystocia complication. The goal of this study was to evaluate the effectiveness of simulation training on the quality of actual shoulder dystocia delivery documentation.

Methods Used: Starting in 2004, all residents at University of Washington Ob-Gyn residency program have participated in shoulder dystocia simulation training that includes a written note regarding the events that took place during the shoulder dystocia simulation. We evaluated 62 pre training notes whose primary writers are OB residents from the years of 2001–2003, family medicine residents, and certified nurse midwives. To evaluate post training documentation, we reviewed 33 notes from the years 2005–2007, whose primary writers are OB residents who have participated in simulation training. We evaluated the delivery documentation on the presence of 9 components that were each designated one point.

Summary of Results: There was an overall increase in the mean from 4.2 (SD ± 1.3) pre training to 5.6 (SD ± 1.1) post training (P<0.01). We observed an increase in frequency in 8 of the 9 components evaluated. 4 items were present in 90–100% of post training documentation: position of fetal head (100%), head to shoulder delivery time (94%), maneuver documentation (100%), and classification as shoulder dystocia (100%). However, some areas were still lacking in post simulation training documentation and 3 important items were present in less than 20% of the notes: quantification of traction on the fetal head (18%), presence of symmetrical Moro response in the baby (18%), and communication with the patient regarding the events of delivery (0%).

Conclusions: Simulation training of shoulder dystocia with simulated documentation is associated with improved actual post delivery documentation. Although many areas of documentation improved, several items were still missing and chart documentation needs to further be perfected.

76 Effects of Body Mass Index (BMI) in Children Hospitalized with Asthma

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Purpose of Study: Overweight status has been associated with increased asthma prevalence and morbidity in the pediatric population. However, the effects of BMI in children hospitalized with asthma have not been fully studied. The purpose of this study was to examine the association of BMI with hospital length of stay (LOS), costs, pediatric intensive care unit (PICU) admissions and hospital/emergency department (ED) readmission rates.

Methods Used: We performed a retrospective study of children age 2–17 years discharged from Primary Children Medical Center (PCMC), a tertiary care children’s hospital in the Intermountain West, with a primary ICD-9 diagnosis of asthma between Jun 2004 and Dec 2006. Patient information was retrieved through the enterprise data warehouse, including LOS, cost, PICU admissions and any subsequent hospital or ED visits within 12 months of hospital discharge. Weight and height were extracted manually and were used to calculate BMI. Patients with other chronic medical conditions were excluded. Patients were stratified into 3 categories: underweight (BMI percentile<5), normal weight (BMI percentile 6–84) and overweight (BMI percentile >84). Cox and multivariate linear and logistic regression analyses were used to determine whether BMI was associated with LOS, cost, PICU and hospital readmissions, after controlling for age, gender, race, casemix severity index and insurance type.

Summary of Results: Overall 662 patients were discharged with the primary ICD-9 diagnosis of asthma during the study period: 56.6% male and 43.4% female. The median age was 5 year. 9.1% of patients were underweight, 63.4% had normal weight and 27.5% were overweight. After controlling for covariates, increased in BMI was associated with increased hospital/ED readmissions (P = 0.047) and decreased PICU admissions (P = 0.028). Median LOS and cost consistently increase with increasing BMI; this association did not reach statistical significance.

Conclusions: Overweight children with asthma had more hospital and ED readmissions and tended to have longer hospital LOS, larger cost and fewer PICU admissions. Obesity appears to be an independent risk factor for asthma exacerbations but may be protective in terms of asthma severity. Further research is needed to confirm these findings.

77 COMMUNITY SOCIOECONOMIC STATUS AND PROVISION OF BYSTANDER CARDIOPULMONARY RESUSCITATION IN OUT-OF-HOSPITAL CARDIAC ARREST

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Purpose of Study: While neighborhood socioeconomic status (SES) has been linked to multiple health outcomes, we studied its association with provision of bystander cardiopulmonary resuscitation (CPR) during out-of-hospital cardiac arrest (OHCA). We further analyzed the data by narrowing the measure of SES from the standard census tracts to block groups and incident location.

Methods Used: This study was a retrospective, cohort analysis of cardiac arrests occurring in private residences in King County, Washington from January 1, 1999 to December 31, 2005 (n = 2,618). Demographic and care data collected on each OHCA included arrest location, victim’s age and sex, witnessed status, collapsing rhythm, and EMS response time. Neighborhoods were defined as census tracts and block groups, and neighborhood SES was measured using multiple measures from 2000 census data (education, employment, median household income, race/ethnicity). Incident location SES was measured using year 2000 tax-assessed valuation calculated as value-per-unit. Logistic regression models were used to analyze the socioeconomic data assessed as continuous variables and as quartiles against three outcomes: bystander CPR, citizen CPR, and dispatch-assisted CPR.

Summary of Results: After adjusting for demographic and care factors, neighborhood SES measured by multiple population-level census variables showed no significant effect on any subgroup of CPR at either the tract or block group level. A secondary analysis of only OHCA occurring in public locations (n = 607) and a tertiary analysis including all OHCA (n = 3,225) showed similar results to the primary analysis. Higher SES as defined by tax-assessed value-per-unit of the incident location was positively associated with bystander CPR (P < 0.01)*, citizen CPR (P < 0.01)*, and dispatch-assisted CPR (P < 0.01)*. [*For each subsequent quartile referenced to the lowest quartile]

Conclusions: Neighborhood SES is not a reliable predictor of CPR provision during OHCA. There is no difference in CPR provision when defining neighborhoods as larger census tracts or smaller block groups. Higher incident location SES shows an association with increased provision of CPR. SES as measured by tax-assessed value-per-unit is a more precise and better predictor of CPR receipt in out-of-hospital cardiac arrest.

78 EVALUATING DISCLOSURE AND OFFER PROGRAMS TO ENHANCE THE RESPONSE TO MEDICAL INJURIES

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Purpose of Study: Medical liability insurance crises and the Institute Of Medicine’s report on medical errors have drawn attention to the inadequacy of the malpractice system. Proposals to reform the system have proven to be
politically untenable. Disclosure and Offer (D&O) programs have emerged as alternative compensation systems that operate within the framework of current malpractice law. D&O programs follow the general framework of disclosure of a medical injury, followed by an offer of compensation. To date, critical appraisal of such programs remains sparse.

**Methods Used:** A review of published literature related to the compensation of patients suffering medical injuries, including analysis of malpractice epidemiology, examination of the emergence of D&O programs, and analysis of results from existing programs at COPIC insurance company and the University of Michigan Health System.

**Summary of Results:** Since 2000, a handful of insurers have introduced D&O programs. Programs at COPIC insurance company, and the University of Michigan Health System (UMHS) are at the forefront of this movement, and each has published data from their unique experiences. COPIC has handled 4870 cases, paying an average of $5,286 per compensated incident. COPIC spends two to three times less money managing each case than under traditional claims management. UMHS has reduced risk management costs by two thirds, and has reduced the average resolution time to half what it was at the program’s inception. Both programs report improved patient, physician and lawyer satisfaction, as compared to tort litigation. Of concern, while COPIC operates a ‘no-fault’ compensation model, it has enumerated criteria that preclude some injured patients from utilizing the program. Furthermore, the programs’ financial burdens will likely soar as incident detection improves. Examining objections to system reform provides additional clues about stakeholder concerns likely to emerge as discussions of program expansion occur.

**Conclusions:** Despite leaving unresolved the lingering political turmoil over current malpractice law, D&O programs offer a reasonable strategy for insurers looking to proactively advance the cause of injury compensation. Potential hurdles to dissemination may be overcome by better understanding stakeholder concerns, and by working with these groups during the genesis of new D&O programs.

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**79 EFFICACY OF NEONATAL CARE EDUCATION FOR EXPECTANT MOTHERS IN A LIMITED-RESOURCE HOSPITAL**


**Purpose of Study:** To determine the efficacy of teaching expectant mothers the early signs of neonatal illness as a way to help reduce neonatal mortality in limited-resource countries.

**Methods Used:** With local pediatricians, we developed a 10-minute, written educational module on neonatal care. We developed and tested self-administered written tests to determine if the module had an educational value for mothers. Written tests were administered to determine mothers’ knowledge before and immediately after the module. Tests were self-administered or completed with providers’ help when mothers were not literate. When possible, women were retested after delivery.

**Summary of Results:** During spring of 2008, we recruited 101 pregnant women in antenatal clinics (mean age = 28.5 yrs, mean gestational age = 35 wks). Study participants were highly educated by Lao standards, over 50% of women had >8 yrs of schooling, and 28% had >12 yrs of education. The education module increased women’s knowledge of neonatal care by 10% on immediate posttest (81% to 91%, P < 0.001). The major areas of improvement were temperature control (thermometer use, knowledge of normal temperatures) and umbilical cord care. On linear regression, maternal education (P = 0.025) and number of prior births (0.037) predicted higher pretest scores; only maternal education predicted higher posttest scores (P = 0.010). Improvement in test scores did not differ between less-educated women (0-8 yrs) and more-educated women. On repeat testing after delivery, women (n = 47) had scores similar to their immediate posttest (93%), suggesting they understood the educational message (P > 0.001).

**Conclusions:** A brief written and pictographic educational intervention increased expectant mothers’ knowledge of basic newborn care. This effect was seen among women with a wide range of formal education (0-16 yrs) and was retained into the early postpartum period when this knowledge is relevant. We speculate that maternal antenatal education during routine prenatal care is an inexpensive and effective intervention that could improve neonatal moratility and mortality in developing countries.
3) drug dosage; or 4) whether the RARs and RXRs are present in the tumors. In addition, we have tested whether tazarotene therapy combined with a HH pathway inhibitor cyclopamine could have a synergistic effect against BCC carcinogenesis. Both agents can inhibit BCC as single agents. A BCC cell line, ASZ001, was treated with tazarotene or cyclopamine alone, or in combination. Combined treatment at the highest suboptimal concentration (5 μM) resulted in the greatest reduction of cell proliferation suggesting that a combined treatment of a retinoid and a HH pathway inhibitor may have greater effect than a single agent alone.

**Summary of Results:**

**Methods Used:** Proteasome function was assayed using fluorogenic substrates. In-vitro and in-vivo.

**Purpose of Study:** To evaluate the potential accuracy of three dimensional volumetric measurements of tumors by thin slice computed tomography using a phantom model.

**Methods Used:** A gelatin phantom consisting of 55 polymethyl methacrylate (PMMA) spheres spanning diameters from 1.6 mm to 25.4 mm was fabricated and scanned using thin slice (0.625 mm) CT (GE Lightspeed 16). Three different scans covering different scan field of view dimensions (20, 30, and 40 cm) were made, and images were reconstructed using three CT kernels (standard, lung, and bone). Contiguous thin slice images were averaged to produce CT images with greater thicknesses (1.25, 2.50, and 5.0 mm). Visually adaptive thresholding techniques were used to segment the PMMA spheres from the gelatin background, where a total of 2970 spherical volumes were evaluated across the permutations studied.

**Summary of Results:** The general trends in the volumetric results are predictable, where smaller slice thickness and larger sphere diameters produce more accurate volume assessment than larger slice thickness and smaller sphere diameter. The measured volumes were larger than the actual volumes by a common factor depending on slice thickness; for the 2 cm DFOV, 0.625 mm slices were on average 16%, 1.25 mm slices were 17%, 2.5 mm CT slices were 27%, and 5.0 mm slices produced 70% overestimates of volume (mm³). The accuracy was improved using a smaller DFOV. It was found that the bone reconstruction algorithm produced the most accurate tumor volume estimates, followed by the lung algorithm and the standard algorithm. Estimates of measurement precision were also made, and for a 30 cm DFOV, the bone kernel and 1.25 mm slices, the 95% confidence intervals and coefficients of variation (COV) for volume measurement were 0.326–0.747 mm³ (COV = 40%) for the 1.6 mm diameter sphere, 125–151 mm³ (COV = 11%) for the 6.4 mm sphere, and 8810–9820 mm³ (COV = 0.71%) for the 25.4 mm diameter sphere.

**Conclusions:** The results of this investigation provide guidance for CT protocol development and may guide the development of more advanced techniques to promote quantitatively accurate CT volumetric analysis of tumors.

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**THE PROTEASOME INHIBITOR NPI-0052 TARGETS GLIOMA STEM CELLS AND RADIOSENSITIZES Glioblastomas in-Vitro and in-Vivo**

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**Purpose of Study:** Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor in adults, and even after multimodal treatment the prognosis is poor. The ubiquitin-proteasome pathway is critical for many basic cellular processes, and its inhibition sensitizes cells to ionizing radiation. In this study we used NPI-0052, a novel proteasome inhibitor in combination with radiation and studied its effects on primary and established GBM cell lines in-vitro and in-vivo.

**Methods Used:** Proteasome function was assayed using fluorescent peptides, self-renewal capacity was monitored in sphere-forming assays, and clonogenic cell survival and tumor growth delay were assessed.

**Summary of Results:** NPI-0052 selectively killed GBM stem cells in-vitro and sensitized GBMs to ionizing radiation in-vitro and in-vivo.

**Conclusions:** NPI-0052 enhanced the efficiency of the standard treatment of GBM. Our study provides, for the first time, a rationale to combine NPI-0052 with radiation in patients suffering from GBM.

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**PULMONARY EMBOLISM SEVERITY INDEX’ VS ‘PULSE-OXIMETRY’ IN RISK STRATIFICATION OF PULMONARY EMBOLISM PATIENTS IN THE EMERGENCY DEPARTMENT**

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**Purpose of Study:** To evaluate the use of two different risk stratification tools in the identification of pulmonary embolism (PE) patients in the emergency department (ED) who have low risk for in-hospital adverse outcomes or complications requiring hospitalization procedures.

**Methods Used:** Electronic medical record was retrospectively searched for all patients diagnosed with PE in a single large urban ED from June 2004 to June 2008 by trained researchers for triage vital signs, prior co-morbidities, adverse short term outcomes requiring hospital interventions (defined as respiratory failure, hypotension requiring pressors, and hemodynamic impairment requiring thrombolitics) and lastly death. We retrospectively applied the two risk stratifying tools, Pulmonary Embolism Severity Index (PESI) and Pulse-Oximetry, to the ED PE patients to classify them as high or low risk for morbidity or mortality. The performance of these classifications was then assessed using actual patient complications and outcomes from the duration of that hospital stay.

**Summary of Results:** 168 PE patients were identified from the ED electronic medical record. The overall rate of adverse outcomes was 7.1% (12/168), including a 3.0% mortality rate. A pulse oximetry cutoff of 92.5% saturation would have classified 64.9% (109/168) patients as low risk, of which 3.7% (4/109) had an adverse outcome, and 35.1% (59/168) patients as high risk, of...
which 13.6% (8/59) had an adverse outcome. The PESI would have classified 54.2% (91/168) patients as low risk, of which 2.2% (2/91) required hospitalization and 0 died. The remaining 45.8% (77/168) were classified as high risk, with an adverse outcome rate of 13.0% (10/77). We found a PESI cutoff of II to have a sensitivity of 83% (95% CI = 52–98%), specificity of 57% (49–65%), negative predictive value of 98% (92–100%). A Pulse oximetry cutoff of 92.5% oxygen saturation had a sensitivity of 64% (31–89%) and specificity of 67% (59–74%) for adverse events.

Conclusions: Our data indicates the Pulmonary Embolism Severity Index is potentially a reliable and practical identifier of low-risk patients with PE (who are potential candidates for less costly, non-monitored therapy.)

Summary of Results: 87,586 colon cancer cases were identified including 53,907 (63%) proximal, 5,855 (7%) descending and 30,511 (30%) sigmoid cancers. A larger proportion of sigmoid cancers presented at stage I when compared to proximal cancers (29.3% vs. 17.3%, \( P < 0.001 \)). Proximal cancers also had a larger proportion with poorly differentiated tumor grade (25.9% vs. 14.3%, \( P < 0.001 \)). After adjustment for stage, grade, treatment and other relevant clinical variables, sigmoid cancers had decreased CRC-specific mortality compared to proximal tumor (Hazard Ratio .88, 95% CI 0.84–0.89). There were no differences in treatment rendered when each colon subsite was stratified by stage.

Conclusions: In this large population-based analysis, sigmoid colon cancers were observed to have earlier stage at presentation, lower grade, and improved overall and CRC-specific survival.

88 SECOND PRIMARY MALIGNANCIES IN YOUNG WOMEN WITH ENDOMETRIAL CANCER
M. Naqvi, D. Chase, W. Brewster University of California, Irvine, Irvine, CA.

Purpose of Study: The objective of this study was to document the rate of second primary tumors in women with endometrial cancer less than 60-years-old.

Methods Used: An analysis was performed of data from the Surveillance, Epidemiology, and End Results (SEER) Program during the years 1975–2001. Cases of endometrial cancer were included if the endometrial cancer was the primary cancer. Sites of second primaries were considered in women under 50 and between 50-60. Cases of sarcomas and lymphomas were excluded. Observed rates were compared with expected rates based on age, sex, race, year and site-specific rates in the SEER program. Age-standardized Incidence Rates (SIR) were calculated and reflect the observed over expected rates. Rates were also calculated among white and non-white cases.

Summary of Results: 32,816 women were identified with endometrial cancer diagnosed as their first primary cancer under 60. Among women diagnosed with endometrial cancer as their first malignancy under 50, 12.1% developed subsequent primary cancers. The top 4 elevated SIRs for second primaries in women under the age of 50 were: mediastinum and other respiratory organs (SIR 20.62;95% CI 2.5–74.5), colorectal (SIR 3.05;95% CI 12.64–3.49), acute myeloid leukemia (SIR 2.81;95% CI 1.45–4.91), and non-lymphocytic leukemia (SIR 2.12;95% CI 1.21–3.45). The top 4 elevated SIRs for second primaries in women between 50 and 60 were: non-Hodgkin’s lymphoma (SIR 3.91;95% CI 11.07–10.02), colorectal (SIR 3.64;95% CI 12.51–12.52), kidney (SIR 3.24;95% CI 11.05–7.56), and ovary (SIR 2.53;95% CI 1.09–4.99). The highest rate in white women was for appendiceal cancers (SIR 1.86;95% CI 1.04–3.07) whereas the highest rate for non-white women was in skin melanoma (SIR 3.67;95% CI 1.47–7.55).

Conclusions: The risk of second primaries related to mismatch repair deficiencies in women diagnosed with endometrial cancer less than 60 years is highest for colorectal cancers. Kidney and biliary tract cancers also show high SIRs in this population. Lymphomas and leukemias, although not related to mismatch repair deficiencies, manifest as frequent second primaries in both age groups. Racial disparities exist in the rates of certain cancer types. Future research should focus on the incidence of these disparities as well as establishing screening programs for second primaries in these young women.
the escape of nitrite-derived NO from the RBC and its bioavailability in the circulatory system. To test the hypothesis that NO produced from the reaction between nitrite and deoxyhemoglobin escapes the erythrocyte as N$_2$O, as evidenced by S-nitrosation of plasma proteins.

**Methods Used:** Human and sheep blood samples were adjusted to 50% oxyhemoglobin saturation by equilibration with gas mixtures of CO$_2$, O$_2$, and N$_2$. pH was adjusted to 7.4 ± 0.1. Sodium nitrite solution was added to an initial concentration of 50 μM. Samples were collected at baseline and 10 min following nitrite addition for measurement of S-nitrosated proteins by the western blot biotin-switch assay.

**Summary of Results:** The incubation of nitrite with whole blood resulted in the S-nitrosation of plasma proteins. Albumin was the major protein nitrosated in both human and sheep samples. Larger unidentified blood proteins were also S-nitrosated. There was no evidence of hemoglobin S-nitrosation following addition of nitrite.

**Conclusions:** The biotin switch method provides a viable assay to identify S-nitrosated proteins via a western blot. The major protein S-nitrosated via the nitrite reductase pathway was plasma albumin in blood from both humans and sheep. The finding of increased plasma S-nitrosation following nitrite addition to blood provides evidence of the escape of nitrite-derived NO from the erythrocyte.

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**SURVIVAL DISPARITIES IN NON-SMALL CELL LUNG CANCER PATIENTS RECEIVING RADIATION TREATMENT: AN INVESTIGATION OF RACE AND GENDER**

Y. Khanal1, J. Eaton2, J. Pakish1, P. Venl1, R. Martins1, L. Carr1, K. Eaton1, T. Quang1, S. Patel1

**University of Washington, Seattle, WA and 2University of Washington, Seattle, WA.**

**Purpose of Study:** Multiple studies evaluating non-small cell lung cancer disparities reveal male gender and African American race are independent predictors for poorer outcome. Studies postulate gender disparities may arise from biological differences, while racial disparities may be an issue of access to healthcare. This study aims to evaluate the prognostic factors affecting survival of non-small cell lung cancer patients receiving radiation treatment at the University of Washington hospitals and to investigate whether race and gender disparities persist at the level of access to radiation treatment.

**Methods Used:** A retrospective review of 604 patients receiving radiation treatment for non-small cell lung cancer from 1994-2008 at any of the University of Washington hospitals was conducted. Race, age, stage at presentation, radiation treatment length, radiation treatment breaks, and length of time from initial diagnosis to death or last follow-up were recorded. Only those lung cancer patients who had all the preceding information in their medical records were included - totaling 485 records.

**Summary of Results:** Of the 485 records, 79 patients had a lung malignancy other than non-small cell lung cancer, 34 patients did not have race coded in their charts— these patients weren’t included. Of a final 372 patients, there were 306 Caucasian, 32 African American, 34 Asian American and 134 female, 238 male patients. Cox regression models showed male gender [hazard ratio (HR), 1.34; P-value = 0.027] and stage at presentation [stage III: HR, 1.93; P-value = 0.001, stage IV: HR, 2.46; P-value < 0.001] were significantly associated with shorter survival. In these analyses, race had no significant effect on length of survival.

**Conclusions:** In this study, racial survival disparity was not an issue for patients receiving radiation treatment. However, gender and stage at presentation were predictors for poorer survival. These results suggest race differences in lung cancer survival disappear at the level patients have access to radiation treatment, supporting the notion that gender survival differences are likely the result of biologic differences, while racial survival disparities may be an issue of healthcare access.

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**CD30 POSITIVE ANAPLASTIC LARGE CELL LYMPHOMA (ALCL) MIMICKING LANGERHANS CELL HISTIOCYTOSIS (LCH)**

N. Ezra, G. Van Dyke, S. Binder

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

**Case Report:** Cutaneous T-cell lymphomas (CTCL) are uncommon and complex malignancies that constitute a rare subset of non-Hodgkin’s lymphomas of T-cell origin. CTCLs are a diverse group of disorders that display a wide range of clinical and histopathological presentations primarily involving the skin. A less common cutaneous T-cell lymphoma variant is CD30 positive Anaplastic Large Cell Lymphoma (ALCL). We report on a 56-year-old female with a clinical and histopathological presentation consistent with a histiocytosis and immunohistochemistry suggestive of anaplastic large cell lymphoma. The constellation of histologic and immunologic features favored a CD30 lymphoproliferative disorder of T-cell lineage even though there were accompanying numerous dendritic histiocytes and Langerhans cells. Although there was a large number of CD1a positive Langerhans cells and dendritic cells present, the sheets of CD30 positive atypical lymphoid cells which express T-cell markers was consistent with CD30 positive lymphoproliferative disease and favors CD30 positive Anaplastic Large Cell Lymphoma (ALCL) over Langerhans histiocytosis. The absence of ALK staining favored a primary cutaneous origin. This case signifies a CD30+ anaplastic large cell lymphoma of skin clinically and histopathologically mimics a Langerhans Cell Histiocytosis (LCH).

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**FEEDBACK REGULATION OF P53/MICRORNA 34A/BCL6 CIRCUITRY IN B-CELL DIFFERENTIATION**

J.L. Zhao1,2, D. Rao2,3, D. Baltimore1

1University of Washington, Seattle, WA and 2University of California Institute of Technology, Pasadena, CA and 3UCLA, Los Angeles, CA.

**Purpose of Study:** Three decades of studies have placed p53 at the center of the tumor-suppressor network. Only recently, microRNA 34a (miR-34a) has been identified to be transcriptionally activated by p53, demonstrating for the first time the tumor-suppressor role of small, non-coding RNAs in the p53 network. BCL6, whose transcription to the immunoglobin loci is responsible for 40% of diffuse large B-cell lymphoma, has been shown to suppress p53 expression in germinal-center B cells. Interestingly, the 3’ untranslated region (3’UTR) of BCL6 contains miR-34a binding sites, as predicted by multiple computational algorithms. This study aims to test the hypothesis that miR-34a is a crucial negative regulator of BCL6 post-transcriptionally, and therefore, is important in regulating germinal center formation and B cell differentiation.

**Methods Used:** In vitro plasma differentiation assay was used to purify a B lymphocyte (B220+) population and a plasma cell (B220+ CD138+) population from mouse spleens. RNA levels were quantified by RT-qPCR.

**Summary of Results:** Results based on in vitro plasma differentiation assay show that as B cells differentiate into plasma cells, BCL6 mRNA level goes down, while miR-34a and p53 mRNA levels increase. To characterize this regulatory circuitry further, 293T cells were transfected with an inducible vector expressing BCL6 with its 3’ UTR and a vector containing p53 promoter upstream of a luciferase reporter. When the expression of BCL6 was induced, the p53 promoter was repressed, resulting in a 60% reduction in luciferase activity. More interestingly, when we also over-expressed miR-34a at the same time, a 50% increase in luciferase activity was noticed, suggesting that miR-34a down-regulates BCL6, leading to de-repression of the p53 promoter.

**Conclusions:** While the initiating event during this germinal center B cell to plasma cell transition remains elusive, our data suggests that it is potentially regulated by a positive feedback loop involving p53, miR-34a, and BCL6, specifically p53>miR-34a>BCL6>p53. Future studies will be conducted to further examine this putative positive feedback loop and address its physiological relevance in the context of B-cell differentiation and malignancy.

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**ARTIFICIALLY LOW HEMOGLOBIN A1C MEASUREMENTS IN A MULTI-ETHNIC GROUP OF DIABETICS**

J. Parker, J.A. Tayek

Harbor-UCLA, Torrance, CA.

**Purpose of Study:** To identify artificially low A1C concentrations in a multi-ethnic group of diabetics.

**Methods Used:** Diabetic patients with a low A1C(<7.0%) measured using the Diamac assay were screened to identify how common and what types of hemoglobin abnormalities occur at an LA County Internal Medicine Clinic. A1c was corrected based on the amount of hemoglobin A on electrophoresis(Corrected A1c) and based on an accepted formula(Estimated A1c). Descriptive statistics were used for comparisons.

**Summary of Results:** The average A1c was 4.8 ± 0.4% (mean ± sem) in those patients with abnormal hemoglobins. The corrected A1c, based on the amount of hemoglobin A, averaged 7.8 ± 0.4% (< 0.05 vs measured A1c). The
estimated A1c (7.4 ± 0.4%) and the corrected A1c no significantly different. In our patient population approximately 80% (37 of 47) of those with a artificially low A1c had sickle trait. Sickle trait patients have approximately 70% hemoglobin A. Unfortunately, A1c assays do not correct for hemoglobinopathies. For example, in sickle trait, the A1c measurement does not correct for the 30% loss in hemoglobin A, your A1c results is approximately 30% falsely low. In our population, additional hemoglobin abnormalities included approximately 2% E hemoglobin, 2% C hemoglobin and a few other rare hemoglobin. The measured A1c in sickle trait patient should be adjusted upward by dividing the A1c by the amount of hemoglobin A corrected A1c. In those patients who also had multiple blood glucose concentrations an estimated A1c was also determined using the formula: mean blood glucose = 31.7xA1c-66.1. The corrected and estimated A1c were not significantly different. The plot below demonstrates the measured (squares), corrected (diamonds), and estimated A1c measurements (x-axis). There is significant correlation (r = 0.84, P < 0.05) between the corrected and estimated A1c.

**Conclusions:** When there is a mismatch between the blood glucose measurements and the reported A1c, a hemoglobin electrophoresis should be considered to identify those patients where the A1c is not an accurate reflection of glucose control. Since sickle trait occurs in 8% of African Americans and Hemoglobin E occurs in up to 25% of Cambodians, then A1c measurement in the lab can likley provide falsely low results. More attention should be paid to clinical blood glucose concentrations when the A1c looks “too good” to believe.

**Summary of Results:** At 24 hour exposure to 200 and 400 mM CoCl2 led to 35% and 45% decrease in CREB protein expression, respectively. To determine whether AKT was essential for CoCl2 mediated CREB degradation we exposed SMC to CoCl2 with and without AKT inhibitor. In cells exposed to 200 mM CoCl2, inhibition of AKT blocked CREB down-regulation at 24 and 48 hours. 400–600 mM CoCl2 were more toxic to the cells and AKT inhibitor did not block CREB degradation. CREB down-regulation induced by H2O2 was not blocked by AKT inhibition. In summary, cobalt chloride exposure leads to a dose dependent CREB down-regulation in SMCs that can be prevented by blocking AKT induction at low doses, but not at higher doses.

**Conclusions:** Cobalt is a resolvable model to study hypoxia mediated CREB degradation.

### Metabolism

**Concurrent Session**

8:30 AM

Friday, January 30, 2009

#### 94 COBALT MIMICS HYPOXIA MEDIATED CREB DOWN-REGULATION IN VASCULAR SMOOTH MUSCLE CELLS

M. Brar1,2, L. Knaub1,2, J.E. Reusch1,2 1Denver Veterans Affairs Medical Center, Denver, CO and 2University of Colorado Health Sciences Center, Aurora, CO

**Purpose of Study:** Vascular smooth muscle cell (SMC) proliferation plays a critical role in the pathogenesis of pulmonary hypertension and atherosclerosis. It is known that hypoxic damage induces SMC proliferation, but the cellular mechanism(s) responsible for this proliferation are incompletely understood. The transcription factor CREB (cAMP Response Element Binding Protein), is essential to normal SMC function by maintaining cellular quiescence. In animal models of pulmonary hypertension CREB expression is diminished in the pulmonary vasculature, we believe this loss contributes to excess SMC proliferation. In animal models of pulmonary hypertension CREB expression is diminished in the pulmonary vasculature, we believe this loss contributes to excess SMC proliferation.

**Methods Used:** Primary SMC were serum starved for 48 hrs, then exposed to CoCl2 (200,400,600 mM) and H2O2 (300 mM) for 6, 24 and 48 hrs with and without AKT inhibitor. Cells were harvested, and Western blots were performed and analyzed for the target protein - CREB.

**Results:** CoCl2, inhibition of AKT blocked CREB down-regulation at 24 and 48 hours. 35% and 45% decrease in CREB protein expression, respectively. To determine whether AKT was essential for CoCl2 mediated CREB degradation we exposed SMC to CoCl2 with and without AKT inhibitor. In cells exposed to 200 mM CoCl2, inhibition of AKT blocked CREB down-regulation at 24 and 48 hours. 400–600 mM CoCl2 were more toxic to the cells and AKT inhibitor did not block CREB degradation. CREB down-regulation induced by H2O2 was not blocked by AKT inhibition. In summary, cobalt chloride exposure leads to a dose dependent CREB down-regulation in SMCs that can be prevented by blocking AKT induction at low doses, but not at higher doses.

**Conclusions:** Cobalt is a resolvable model to study hypoxia mediated CREB degradation.

### 95 ORAL ETHANOL BEFORE SLEEP DELAYS RECOVERY FROM OVERNIGHT HYPOGLYCEMIA IN HEALTHY SUBJECTS

S. Mitchell, M. Eversole, T. Hammer, M.R. Burge University of New Mexico, Albuquerque, NM.

**Purpose of Study:** We have previously demonstrated that low dose intravenous ethanol delays recovery from daytime hypoglycemia in elderly patients with type 2 diabetes. We hypothesized that low dose oral ethanol before sleep would similarly delay glucose recovery from insulin-induced hypoglycemia overnight in sleeping, healthy, nondiabetic, elderly subjects.

**Methods Used:** Nine healthy subjects (age 63 ± 12 years, HbA1C = 5.3 ± 0.5%, BMI = 26 ± 5 kg/m2) were admitted to the UNM CTSC for two overnight studies in random order. At 2200, subjects ingested sugar free punch with or without 95% ethanol (ethanol vs. placebo) to achieve mean alcohol concentrations of 0.09 ± 0.02% (mild intoxication as determined by breath analyzer) by midnight during the ethanol arm of the study. After 0300, during stage 2 sleep, insulin was infused to slowly decrease plasma glucose to 40–50 mg/dl, at which time insulin was stopped. Plasma glucose was sampled at baseline and every 15 minutes for two hours following the glycemic nadir.

**Summary of Results:** Mean plasma glucose recovery from nadir is shown in the Table below.

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<tbody>
<tr>
<td>Mean Glucose Placebo</td>
<td>91.0</td>
<td>84.4</td>
<td>74.5</td>
<td>64.9</td>
<td>46.9</td>
</tr>
<tr>
<td>Mean Glucose Ethanol</td>
<td>91.0</td>
<td>84.4</td>
<td>74.5</td>
<td>64.9</td>
<td>46.9</td>
</tr>
<tr>
<td>P Value by Unpaired T-Test</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
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<td>0.12</td>
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</table>

**Conclusions:** We conclude that low dose oral alcohol, sufficient to induce low-level intoxication, delays recovery from insulin-induced hypoglycemia during sleep in healthy elderly subjects.

### 96 SITAGLIPTIN EFFECTS ON TRIGLYCERIDE AND FREE FATTY ACID METABOLISM

R.H. Nelson, J.M. Miles, A. Vella Mayo Clinic, Rochester, MN.

**Purpose of Study:** The effect of dipeptidyl peptidase-4 (DPP-4) inhibitors on lipid metabolism in type 2 diabetes is controversial, with conflicting reports in the literature. Individuals with impaired fasting glucose (IFG) are at increased risk of cardiovascular disease. As part of a study examining the effect of the DPP-4 inhibitor sitagliptin (SITA) on IFG, we determined the effect of SITA on triglyceride (TG) and free fatty acid (FFA) metabolism using a placebo-controlled, parallel-group design.

**Methods Used:** Subjects with IFG (n = 22) were randomized to SITA 125 mg/d or placebo (PL) and studied at baseline and after 8 weeks treatment. In a subset of subjects, spillover of FFA from dietary fat was studied during peak chylomicronemia after ingestion of a mixed breakfast (45% carbohydrate, 40% fat, 15% protein), using tracer infusions of [1-13C] oleate and a [oleyl-3H] triolein-labeled lipid emulsion. Plasma TG concentrations, 13C oleate enrichment, 3H oleate specific activity, 3HTG were measured. Plasma FFA concentrations were measured.

**Summary of Results:** In both SITA and PL, there was no change from baseline to week 8 in fasting (453 ± 39 vs. 411 ± 40 and 435 ± 31 vs. 414 ± 27, 123

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POSTNATAL OVERGROWTH AND CHANGES IN ADIPOKINES AFTER MATERNAL ZINC DEFICIENCY

Methods Used:
Zinc (Zn) is critical for maintaining structure and stability of insulin and the insulin receptor; however, the interaction between Zn, insulin, and glucose metabolism is complex. Mild to moderate maternal Zn deficiency affects maternal carbohydrate metabolism and fetal growth and development, but the mechanisms behind changes in offspring glucose homeostasis are not well understood.

Methods Used: Rats were fed Zn deficient diet (ZnD, 7 μg/g) or control diet (CON, 25 μg/g) ad libitum for 3 weeks, bred and kept on Zn deficient diet during pregnancy and lactation. Postnatally, rat pups were culled to 7 pups/dam and allowed to nurse their original mothers. After weaning, rat pups were separated by gender, and fed regular rat chow ad libitum. Insulin and glucose tolerance tests (ITT, GITT) were performed on the pups at 5 and 10 weeks of age. Rats were sacrificed at 3 and 15 weeks of age, and tissues were collected for further analyses. mRNA expression of adipokines were analyzed by quantitative real-time PCR.

Summary of Results: Although no differences in litter size and birth weight were noted between the two groups, pups from ZnD dams weighed significantly more than CON animals by postnatal day (PD) 10 (+15%) and PD 20 (+10%). There were no significant differences in serum Zn and insulin levels between the groups at 3 weeks, but glucose levels were significantly higher in ZnD pups than in CON pups. Expression of leptin and adiponectin in adipose tissue of ZnD rats was significantly lower than in controls at 3 weeks of age. There was no difference in body weight between groups after weaning, but both male and female pups from the CON group were more sensitive to insulin and glucose stimulation than ZnD pups at both 5 and 10 weeks of age without affecting serum glucose and insulin levels.

Conclusions: Maternal Zn deficiency results in decreased expression of adipokines which may be associated with the excessive postnatal weight gain in the offspring. Maternal Zn deficiency resulted in increased insulin resistance in the offspring, suggesting that maternal Zn status may affect insulin and glucose homeostasis postnatally through the insulin signaling pathway.

ADIPOKINES AFTER MATERNAL ZINC DEFICIENCY

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hypertension. We hypothesize that Carvedilol has more beneficial effects on markers of inflammation and endothelial function compared to Metoprolol.

Methods Used: This is an investigator initiated study of a sub study of the GEMINI study. Subjects were randomized to receive either Carvedilol or Metoprolol. Studies completed at baseline and 5 months included a fasting blood draw to measure inflammatory, thrombotic and insulin sensitivity parameters. Endothelial function was tested by measuring changes in brachial artery flow mediated vasodilation. An oral glucose tolerance test (OGTT) was administered. 2 hours later all studies were repeated. Data were analyzed using student’s t-tests and repeated measures ANOVA.

Summary of Results: Plasminogen Activator Inhibitor-1 (PAI-1), increased significantly from baseline in the Metoprolol group but not in the carvedilol group (Table 1). There were no differences in other inflammatory or thrombotic markers in either group (data not shown). There was a trend toward worsening insulin resistance in the Metoprolol group as demonstrated by increasing HbA1c and Homeostasis Model Assessment: Insulin resistance (HOMA-IR)[Table 1]. Flow mediated vasodilation increased in both groups following the OGTT at the baseline study. There was an increasing trend up in flow- mediated vasodilation under both fasting and post OGTT conditions in the carvedilol group compared to baseline. Metoprolol blunted the increase in flow mediated vasodilation following OGTT (P < 0.05).

Conclusions: Metoprolol was associated with adverse metabolic effects including increases in PAI-1 and trends toward worsening insulin resistance and endothelial dysfunction compared to Carvedilol.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coreg (b)</th>
<th>Metoprol (b)</th>
<th>Coreg (T)</th>
<th>Metoprol (T)</th>
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<tbody>
<tr>
<td>PAI-1 (mg/dL)</td>
<td>20±12±5</td>
<td>19.5±2.4</td>
<td>24±1±6</td>
<td>28.4±2±6</td>
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<td>HOMA-IR</td>
<td>6.6±0.6</td>
<td>6.8±0.8</td>
<td>6.5±0.9</td>
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<tr>
<td>Plasma glucose</td>
<td>94±8</td>
<td>94±8</td>
<td>93±7.6±5</td>
<td>150±8.4</td>
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B: Baseline; P: Post-treatment * P value < 0.05

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INHIBITION OF EARLY DIFFERENTIATION OF NIH3T3 PREADIPOCYTES BY STEAROYL-COA DESATURASE INHIBITORS

J.K. Ye1,2, M. Patterson1,2, S. Lim1, C. Mao1,2, W.P. Lee1,2 1Los Angeles BioMedical Research Institute at Harbor-UCLA, Torrance, CA and 2David Geffen School of Medicine at UCLA, Los Angeles, CA.

Purpose of Study: Stearoyl-CoA desaturase enzyme (SCD) converts stearate to oleate ([C18:0] to [C18:1]) and palmitoleate to palmitoleate ([C16:0] to [C16:1]) in liver and adipose tissue. The isoform SCD2 is constitutively expressed, while SCD1 expression is induced during adipocyte differentiation. Oleate, the product of stearoyl-CoA desaturation, is known to induce adipocyte differentiation and SCD1 expression independently. The role of SCD inhibition in adipocyte differentiation has not been clarified. The purpose of the study is to explore the effects of SCD inhibition on desaturation activity and differentiation of preadipocytes during early differentiation.

Methods Used: NIH3T3 preadipocytes were cultured with 1) DSMO or 2) methylisobutylxanthine, dexamethasone and insulin (MDI) or 3) MDI and inhibitor C8G290 or 4) MDI and (110,12 conjugated linoleic acid (CLA) for 72 hours. Medium with compounds was removed, and cells were grown with serum-containing medium containing 110,12 CLA-acetate for another 72 hours. Oil Red O staining was performed. Analysis of fatty acid mass isomers was performed by GC/MS and desaturation indices calculated.

Summary of Results: Cell counts were decreased in the CGX290 group by ~30% (P < 0.05) and by ~50% (P < 0.01) in the CLA group compared to the MDI only group. The oleate/steareate desaturation index was decreased by ~20% (P < 0.01) in the CGX290 group, and by ~40% (< 0.001) in the CLA group. There were changes in de novo lipogenesis in the CGX290 and CLA groups. Oil Red O staining showed decreased staining intensity in the in the CGX290 and CLA groups in comparison to the MDI differentiated control group.

Conclusions: CGX290 and CLA addition resulted in decreased oleate in cell culture and prevented early differentiation of NIH3T3 preadipocytes. CGX290 and CLA are known to inhibit both SCD1 and SCD2. Since oleate is a known inducer of adipocyte differentiation, SCD2 inhibition likely reduced the oleate needed to induce and sustain differentiation in NIH3T3 cells. SCD2 inhibition is a potential mechanism of inhibition of adipocyte differentiation. SCD inhibition during early differentiation may lead to programmed changes in adipocyte differentiation altering future development of obesity.

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Postprandial Serum Fructose Level in Patients Tested for Diabetes

F.N. Wahljadi, M.E. Patterson, S. Lim, J. Yee, C.S. Mao, W. Lee Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA.

Purpose of Study: The obesity epidemic in the United States and other developed countries has been linked to the increased consumption of fructose and sucrose. High consumption of fructose has been associated with insulin resistance, elevated plasma triglyceride levels, and hyperuricemia in experimental animals. The impact of the increased consumption on fructose metabolism is not known. Determination of fructose level in serum has been hindered due to low concentration of fructose and interference from glucose in the serum sample. Currently there are few assays that are suitable for clinical evaluation of serum fructose levels. The objectives of our study are 1) to develop a GC/MS assay for the simultaneous determination of plasma glucose and fructose level and 2) to perform a survey on post-prandial plasma samples from patients evaluated for diabetes.

Methods Used: We have developed an assay based on the common derivatization techniques of monosaccharide into its respective methoxyacetic acid derivatives (MOAs) and the unique fragmentation behavior of methoxyacetic acids for the GC/MS analysis. Plasma glucose-1,2-13C2 were used as internal standards. Left over plasma samples from patients evaluated for diabetes were obtained from the Clinical Laboratory without patient identifier with IRB approval.

Summary of Results: Plasma glucose ranged from 2.69 to 14.75 mM in 43 post-prandial samples. The mean and standard deviation of post-prandial plasma glucose values were 6.51 ± 3.52 mM. Plasma fructose values were two orders of magnitude less than that of glucose ranging from 9.75 to 112.86 µM, with mean and standard deviation value 35.30 ± 25.08 µM. There was no correlation between plasma glucose and fructose concentrations.
Conclusions: Our results were in general agreement with those of Kawasaki et al. (2004) except that the fructose levels were significantly higher than those in Japanese patients with type 2 diabetes. Our results suggest a higher level of fructose intake in the selected population. High levels of fructose consumption have been associated with retinopathy, nephropathy, in type 2 diabetes. Routine measurement of plasma fructose may be of value in monitoring fructose intake in patients with obesity and diabetes.

104 THE EFFECT OF BODY MASS INDEX ON FASTING BLOOD GLUCOSE AFTER INITIATION OF EXTENDED-RELEASE NICIN IN DYSPLASMIC PATIENTS

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Purpose of Study: Nicin increases blood glucose, but whether the degree of increase is associated with increasing body mass index (BMI) is unknown. We evaluated the effect of extended-release nicin initiation on fasting blood glucose (FBG) and the development of new-onset diabetes mellitus (DM) in relation to body mass index (kg/m2) in non-diabetic patients.

Methods Used: This retrospective observational study used data from six facilities within a geographical region of the Department of Veterans Affairs (VA). Patients included were 18 years or older and on a stable extended-release nicin dose (minimum 100 days) between 500 and 1500 mg between January 2001 and April 2007. Patients were excluded if they were new to VA, on corticosteroids or insulin, if medication adherence was <80%, or if they met criteria for DM.

Summary of Results: 857 patients with normal glucose tolerance at extended-release nicin initiation were studied. Average FBG post nicin initiation was stastically significantly correlated with increasing BMI (P < 0.001, R = 0.144 Pearson correlation coefficient). Factors independently associated with change in FBG using multiple linear regression were BMI (P = 0.007), baseline average glucose (P < 0.001), baseline average triglycerides (P = 0.003) and change in potassium (P = 0.037). 252 patients developed DM post nicin initiation. BMI, (P < 0.001) baseline average glucose (P < 0.001) and baseline triglycerides (P < 0.047) were independent predictors for the development of new-onset DM, (logistic regression analysis).

Conclusions: We found an association between increasing BMI and increasing FBG and diagnosis of new-onset DM after extended-release nicin initiation.

Neonatal – Pulmonary I

Concurrent Session

8:30 AM

Friday, January 30, 2009

105 URINE DESMOSINE EXCRETION IN PRETERM INFANTS WITH LUNG DISEASE

R.L. Keller1, B. Starcher2, P.L. Ballard1, R.A. Ballard1 UCSF, San Francisco, CA and 2Univ of TX, Tyler, TX.

Purpose of Study: Urinary desmosine (by-products of elastin metabolism) are variably elevated in experimental lung fibrosis and in acute and chronic lung disease of children and adults. In premature animals, lung elastin turnover is variably elevated in experimental lung fibrosis and in acute and chronic lung disease. In the first month of life, urine desmosine levels in preterm newborns surviving without BPD were higher than those in infants with BPD or death. This difference may represent decreased elastin turnover and alveolarization in more severe lung disease.

Methods Used: This retrospective observational study used data from six facilities within a geographical region of the Department of Veterans Affairs (VA). Patients included were 18 years or older and on a stable extended-release nicin dose (minimum 100 days) between 500 and 1500 mg between January 2001 and April 2007. Patients were excluded if they were new to VA, on corticosteroids or insulin, if medication adherence was <80%, or if they met criteria for DM.

Summary of Results: 857 patients with normal glucose tolerance at extended-release nicin initiation were studied. Average FBG post nicin initiation was stastically significantly correlated with increasing BMI (P < 0.001, R = 0.144 Pearson correlation coefficient). Factors independently associated with change in FBG using multiple linear regression were BMI (P = 0.007), baseline average glucose (P < 0.001), baseline average triglycerides (P = 0.003) and change in potassium (P = 0.037). 252 patients developed DM post nicin initiation. BMI, (P < 0.001) baseline average glucose (P < 0.001) and baseline triglycerides (P < 0.047) were independent predictors for the development of new-onset DM, (logistic regression analysis).

Conclusions: We found an association between increasing BMI and increasing FBG and diagnosis of new-onset DM after extended-release nicin initiation.

108 STAT5B PROTEIN ABUNDANCE IS INCREASED IN THE LUNG FOLLOWING PROLONGED MECHANICAL VENTILATION OF PRETERM LAMBS

M.J. Dahl, L. Dong, M.J. McCoy, D.B. Metcalf, R.A. McKnight, B. Yoder, D.M. Null, R.H. Lane, K.H. Albertine University of Utah, Salt Lake City, UT.

Purpose of Study: Prolonged ventilator support of preterm neonates is necessitated by hypoxia. Preterm neonates who require prolonged mechanical ventilation (MV) frequently develop bronchopulmonary dysplasia (BPD), which is characterized in part by thick, cellular mesenchyme in the distal airspace walls. Insulin-like growth factor 1 (IGF1), which is upregulated by hypoxia, is also upregulated in the lung of neonates with BPD. A consequence of upregulated IGF1 expression is increased cell proliferation. Hypoxia-induced gene expression of IGF1 is mediated through STAT (signal transducers and activators of transcription), especially STAT5b. Whether STAT5b is upregulated by prolonged MV in preterm neonates is not known. We hypothesized that STAT5b protein abundance will be greater in the lung of preterm lambs managed for 3d by MV compared to high-frequency nasal ventilation (HFNV; positive outcome control).

Methods Used: Preterm (PT) lambs, treated with antenatal steroids and postnatal surfactant, were managed by MV or HFNV(n = 4 each). At the end of 3d, peripheral lung tissue was analyzed by immunoblot for STAT5b. Gestation controls were fetal start (FS; ~132d gestation) and fetal end (FE; ~136d gestation).

Summary of Results: The MV group had significantly more normalized abundance of STAT5b protein (*P < 0.05) in lung tissue than the HFNV group (table).

Conclusions: We conclude that ventilation mode affects abundance of STAT5b in the lung. MV causes greater abundance of STAT5b than HFNV.

107 MECHANISM OF REDUCED LUNG INJURY BY HIGH FREQUENCY NASAL VENTILATION IN A PRETERM LAMB MODEL OF BRONCHOPULMONARY DYSPLASIA

J. Feng1, R. Lee1, R. Sakurai1, R. Lane1, K. Albertine1, J. Torday1, V. Rehan1 LA Biomed, Torrance, CA and 1University of Utah, Salt Lake City, UT.

Purpose of Study: Despite intense research, the pathogenesis of Bronchopulmonary Dysplasia (BPD), i.e., chronic lung disease of the premature infant, remains incompletely understood. Using in vitro and in vivo rat models, we have extensive data to support that disruption of alveolar Parathyroid Hormone-related Protein (PTHrP)-Peroxisome Proliferator-Activated Receptor γ (PPARγ) signaling is a central event in this process. However, whether the same paradigm is applicable to other species is unknown. We examined whether disruption of PTHrP-PPARγ-signaling will also be evident in a well-established preterm lamb model of BPD.

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Furthermore, mechanical support using high frequency nasal ventilation (HFNV), a known protective strategy against the development of BPD, will promote, and conventional mechanical ventilation (CMV) will inhibit PTHrP-PPAR signaling.

Methods Used: We compared preterm lambs managed by HFNV and by CMV up to three wks following preterm delivery at 132 days GA (term ∼ 150 days). The specific markers analyzed by Western hybridization included PTHrP and its receptor, PPARγ, Surfactant Protein-B (SP-B), SP-C, cholinophosphate cytidylyltransferase-α (CCF-α), and α-smooth muscle actin (α-SMA).

Summary of Results: In 3 wk old mechanically ventilated preterm sheep, the expression of key alveolar homeostatic epithelial-mesenchymal markers examined was significantly altered, suggesting the disruption of PTHrP-PPAR signaling in the BPD model of preterm sheep, as has been previously shown in the rat model of BPD. There was also clear evidence for increased homeostatic PTHrP-PPARγ signaling with HFNV, and decreased PTHrP-PPARγ signaling with CMV, suggesting a possible mechanism underlying reduced lung injury with HFNV.

Conclusions: Disrupted PTHrP-PPARγ signaling is the hallmark of BPD pathogenesis in the human since it has been documented in all species in which it has been examined so far. Enhanced PTHrP-PPARγ signaling may explain the molecular mechanism underlying reduced lung injury and therefore the reduced incidence of BPD with HFNV support vs CMV support (Grant Support: NIH-HL 75405).

108 LARYNGEAL MASK AIRWAY FOR SURFACTANT ADMINISTRATION IN AN ANIMAL MODEL OF RESPIRATORY DISTRESS SYNDROME

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Purpose of Study: The purpose of this study was to compare the physiologic impact of surfactant administered via a laryngeal mask airway with the standard approach of instillation through an endotracheal tube.

Methods Used: Randomized, controlled trial using a newborn piglet model. Lung injury was induced by lung surfactant washout and animals were randomized into one of the following groups: 1. LMA placed, no surfactant administered (control; n = 8) 2. Surfactant (lucinactant; Discovery Laboratories, Inc., Warrington, PA) via laryngeal mask airway (LMA; n = 8) 3. Surfactant via endotracheal tube (ETT; n = 8). Physiologic data were recorded throughout the 3.5 hr study and analyzed using ANOVA.

Summary of Results: PaO2 levels of the LMA and ETT groups were significantly increased compared to controls (P < 0.05). LMA and ETT groups were not statistically different. Heart rate, blood pressure and pH did not differ between groups.

Conclusions: Administration of surfactant via a laryngeal mask airway resulted in similar physiologic changes as instillation via an endotracheal tube. These data suggest that further study in human neonates is justified. If proven effective, some infants with respiratory distress may be able to receive surfactant via a laryngeal mask airway and mechanical ventilation.

Funding provided by the Neonatal Resuscitation Program Research Fund and Children’s Hospitals & Clinics of Minnesota Foundation. Surfactant provided by Discovery Laboratories, Inc.
matures only at 60% of control, \( P < 0.05 \). At D6, IUGR increased levels of RAR\(\gamma\) in both sexes to 50% of control \( (P < 0.05) \). At D21 IUGR increased expression of RAR\(\gamma\) by 125% of control \( (P < 0.05) \) and males to 150% of control \( (P < 0.05) \). At D21, male levels of RAR\(\gamma\) were increased to 140% of control \( (P < 0.05) \) but there was no effect in females. Finally, our IHC results show IUGR decreased RAR\(\alpha\) in both epithelium and mesenchyme without affecting localization.

**Conclusions:** We conclude that IUGR decreases expression of RAR\(\alpha\), RAR\(\gamma\) and RAR\(\gamma\) at critical times of rat lung development - D0, the saccular stage and D6, the alveolar stage. As hypothesized, affects of IUGR showed gender specificity, and males appear to be more adversely affected. Unexpectedly, we see that at D21, a time of waning lung development, IUGR increased expression of RAR\(\gamma\). We speculate that IUGR results in prenatatal reprogramming, the effects of which continue to be evident later in life.

111 \textbf{CHARACTERIZATION OF THE LUNG MESENCHYMAL-SPECIFIC DERMOCRINE CONDITIONAL PTHrP KNOCKOUT PHENOTYPE}

J. Torday1, W. Deng2, W. Shi2, R. Lee1, V. Rehan1 1Harbor-UCLA Medical Center, Torrance, CA and 2Children’s Hospital of Los Angeles, Los Angeles, CA.

**Purpose of Study:** Parathyroid Hormone-related Protein (PTHrP) is necessary for the epithelial-mesenchymal interactions that generate lung alveoli. Epithelia-derived PTHrP is necessary for the differentiation of adipherelial fibroblasts into lipofibroblasts; Mesenchymally-derived PTHrP is also necessary since there is resultant failed alveolarization, though this mechanism of PTHrP action has not been determined.

**Methods Used:** Heterozygous PTHrP floxed\(^{flx}\)/Dermo1-Cre mice were bred with homozygous PTHrP \(^{flx}\) mice to generate mesenchyme-specific PTHrP knockout offspring. Lungs from wild type and PTHrP knock out mice were collected from P3, 1.29; P6, 1.55) and vascularization (PECAM: P3, 0.67; P6, 1.26).

**Conclusions:** PTHrP signaling is central to alveolarization. Understanding its mechanisms of action is important to basic understanding of lung biology as well as to clinical applications. We will determine the nature of the mesenchymal PTHrP signaling mechanism at the cell, tissue and organ levels.

Supported by NIH Grant HL-055268 (JST/VKR); HL075405 to VKR.

112 \textbf{PHYSIOLOGIC VITAMIN D HORMONE 1a,25(OH)\(_2\)D\(_3\) HAS SPATIAL AND TEMPORAL-SPECIFIC ACTIONS DURING PERINATAL PULMONARY MATURATION}

S. Fonseca, R. Sakurai, E. Shin, J. Torday, V. Rehan Harbor-UCLA Medical Center, Torrance, CA.

**Purpose of Study:** The mechanisms leading to increased surfactant synthesis and septal thinning, the key features of perinatal lung maturation, remain incompletely understood. Using in vitro models, we have shown that the physiologic Vitamin D steroid hormone 1a,25(OH)\(_2\)D\(_3\) (1,25D) may be an important paracrine/autocrine effector of perinatal lung maturation. However, its role under in vivo conditions has not been examined. We hypothesize that 1,25D administered in vivo will promote alveolar maturation by increasing surfactant synthesis and septal thinning. In this study, we determined alveolar type II (ATII) and fibroblast differentiation and lung morphology following parenteral administration of 1,25D to rat pups.

**Methods Used:** Sprague Dawley rat pups were administered saline (control) or 1,25D (5 ng/kg) once daily up to 3 weeks. After sacrifice the lungs were harvested and stained for markers of ATII cell and fibroblast differentiation and morphometry on postnatal days 1, 7, 14, and 21. The markers of ATII cell and fibroblast differentiation examined by Western hybridization included Surfactant Protein (SP-B), SP-C, Cholinephosphate Cytidylyltransferase-\(\alpha\) (CCT-\(\alpha\)), Parathyroid Hormone-related Protein (PTHrP) and its receptor, Peroxisome Proliferator-Activated Receptor (PPAR\(\gamma\)), and Bcl-L/Bax ratio.

**Summary of Results:** 1,25D administration significantly increased the expression of key ATII cell and fibroblast differentiation markers as well as increased alveolar counts, but paradoxically, it increased septal thickness \( (P < 0.05 \) vs control for both). With 1,25D administration the Bcl-L/Bax ratio also increased significantly at all time points examined.

**Conclusions:** Vitamin D Administration to neonatal pups increased ATII cell and fibroblast differentiation and septal thickness by an increase in septal thickness. This increase along with increased Bcl-L/Bax ratio suggests increased fibroblast proliferation, likely due to inhibited apoptosis. We conclude that spatial and temporal-specific actions of Vitamin D play a critical role in perinatal pulmonary maturation by stimulating key alveolar epithelial-mesenchymal interactions and lipofibroblast proliferation/apoptosis.

113 \textbf{EFFECT OF INHALED NITRIC OXIDE ON PLASMA NITRITE CONCENTRATIONS IN INFANTS WITH PERSISTENT PULMONARY HYPERTENSION}

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**Purpose of Study:** The effects of inhaled nitric oxide gas (iNO), used clinically to treat persistent pulmonary hypertension of the newborn (PPHN), are not limited to the lung. However, because the half-life of NO in blood is only milliseconds, it is not clear how its effects reach the periphery. Recent evidence suggests that nitrite in blood, once thought to be an inactive metabolite of NO and an index of nitric oxide synthase activity, can actually be reduced back into NO, particularly under hypoxic conditions. We hypothesized that blood nitrite concentrations would be increased by iNO therapy in newborn infants, thereby implicating nitrite as a potential mediator of the systemic effects of INO.

**Methods Used:** One mL blood samples were collected from ten newborn infants with PPHN prior to initiation of iNO, 1 to 2 hr after initiation of iNO at 20 ppm, just prior to weaning from iNO, and 12 to 24 h later. Blood samples were also collected from six infants without PPHN and from twelve healthy adults.

**Summary of Results:** Nitrite levels were not elevated during administration of 20 ppm or 5 ppm iNO and then decreased 12 to 24 h following cessation of iNO \((0.093 \pm 0.017 \mu M, P < 0.05)\). Nitrite concentrations in infants without PPHN were lower than those of adults \((0.240 \pm 0.014 \mu M, P < 0.05)\).

**Conclusions:** Blood nitrite concentrations are elevated in infants with PPHN consistent with accelerated NO production as part of body defenses against pulmonary hypertension. Nitrite concentrations are significantly lower in newborn infants than in adults suggesting either decreased endogenous NO production from L-arginine or increased endogenous nitrite metabolism.
Methods Used: We conducted a retrospective chart review of all VLBW infants admitted to the LLUCH NICU from 01/01/2006-06/30/2008. Echocardiograms, 74 wk GA, atrioventricular defects, congenital anomalies, \( >10 \) DOL. Severe PPHN on DOL1 was defined by echo criteria (R to L shunt across PDA, tricuspid regurgitation jet velocity, significant RVH or RV septal flattening) and oxygen index (OI) \( >10 \). Sustained PPHN was defined as meeting echo and OI criteria for PPHN for \( >24 \) hours. Echocardiograms were reviewed by an independent pediatric cardiologist to confirm PPHN. Eight infants with PPHN who were failing medical management received iNO as a compassionate use. GA, BW, Apgar scores, surfactant use, pressors, postnatal steroids, OI, grade 3-4 IVH and survival to discharge were compared between infants with PPHN diagnosed on DOL 1 and infants with sustained PPHN.

Summary of Results: Of 429 infants admitted, 86 were admitted after 10 DOL, leaving 343 infants for the study. 44 infants had PPHN by echo but 5 were excluded for OI \( \leq 10 \). 39 infants (GA 27.6 \pm 2.6 wk; BW 1008 \pm 271 g; OI 18.7 \pm 6.3; 5 minute Apgar 5.7 \pm 2.3) met both echo and OI criteria for severe PPHN on DOL1 for an incidence of 11.3%. 13 of these 39 infants had sustained PPHN (GA 26.8 \pm 3.3 wk; BW 883 \pm 26 mm; OI 21.9 \pm 8.9; 5 minute Apgar 5.8 \pm 2.4) for an incidence of 3.8%. There were no significant differences in GA, BW, Apgars, surfactant use, pressors, postnatal steroids, OI, grade 3-4 IVH, and survival to discharge between the infants with PPHN on DOL1 and those with sustained PPHN. Grade 3-4 IVH occurred in 5/11 (head US not obtained in 2 infants) infants in the sustained PPHN group and was not increased in the infants treated with iNO.

Conclusions: Although moderate PPHN as part of RDS is common on DOL 1, there are some infants who develop sustained PPHN similar to that seen in older infants. Severe PPHN is uncommon in VLBW infants and was seen in 1.3% of infants in this cohort. When it occurs, PPHN in this group can be just as deadly leading to high morbidity and death. The best treatment for severe PPHN in the VLBW infants currently is unknown. Is there a role for iNO in this group?

## 115 LEPTIN STIMULATES TADPOLE LUNG DEVELOPMENT: IMPLICATIONS FOR UNDERSTANDING EVOLUTION OF VERTEBRATE PHYSIOLOGY

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Purpose of Study: The evolutionary principles surrounding vertebrate adaptation to land are fundamental to Neonatology. Leptin, a metabolic hormone produced by adipocytes, has been implicated in ontogeny and phylogeny of vertebrate respiration (Torday and Rehan, 2004), endothermy (Mezentseva and Newman, 2008) and locomotion (Crespi and Denver, 2004), the key elements for evolutionary adaptation of land vertebrates. Preterm mammals have immature lungs, and are adipocyte- and leptin-deficient, seeming to recapitulate evolutionary phylogenetic and developmental traits. To test the hypothetical role of leptin in physiologic frog lung adaptation, we have treated Xenopus laevis tadpole lung cultures with frog leptin.

Methods Used: Xenopus laevis tadpole lung (stage 55–57) was treated with frog leptin (10 ng/ml/48 h) in culture. Lung tissue surfactant protein-B,-C mRNA and saturated phosphatidylcholine synthesis were determined, and electron photomicrographs were examined morphometrically.

Summary of Results: Treatment of cultured tadpole lung with frog leptin (10 ng/ml/48 h) significantly increased faveolar diameter (30%), decreased epithelial cell height (37%) and basement membrane thickness (22%). Leptin (10 ng/ml/48 h) significantly increased faveolar diameter (30%), decreased epithelial cell height (37%) and basement membrane thickness (22%). Leptin treatment also increased the size of lamellar bodies (50%), consistent with electron photomicrographs that develop sustained PPHN similar to that seen in older infants. Severe PPHN is uncommon in VLBW infants and was seen in 1.3% of infants in this cohort. When it occurs, PPHN in this group can be just as deadly leading to high morbidity and death. The best treatment for severe PPHN in the VLBW infants currently is unknown. Is there a role for iNO in this group?

## 116 GROWTH OF CORPUS CALLOSUM IN VERY PRETERM NEONATES WITH AND WITHOUT A HEMODYNAMICALLY SIGNIFICANT PATENT DUCTUS ARTERIOSUS DURING THE FIRST POSTNATAL MONTH

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Purpose of Study: Decreased growth of the corpus callosum (CC) and history of a hemodynamically significant PDA (hsPDA) are associated with poor neurodevelopmental outcome. In this study, we sought to determine whether a decreased growth rate of the CC is associated with a hemodynamically significant PDA (hsPDA) in very preterm neonates.

Methods Used: Retrospective analysis of a prospectively collected data of preterm infants with a birth weight (BW) of \( <1250 \) g that had serial cranial ultrasound measurements of the length of the CC as part of our standard clinical care. Patients with congenital anomalies were excluded.

Summary of Results: Sixteen infants [BW = 931 \pm 178 g, gestational age (GA) = 27 \pm 2 weeks; OI = 245 \pm 265 g, GA = 27 \pm 1 weeks] without a hsPDA were included. Demographic and perinatal characteristics were not different between the two groups. Growth rate of CC was higher in patients without a hsPDA (Figure).

Conclusions: These preliminary data suggest that the growth rate of the CC may be different in very preterm neonates with a history of a hsPDA compared to patients without a hsPDA during the first postnatal month. Enrollment of more patients and appropriate statistical analysis to assess the association between hsPDA and CC growth rate are underway.

## 117 A NEW MOUSE MODEL OF NEONATAL BRAIN INJURY

Y. Knauer, R.J. Wong, H. Zhao, D.K. Stevenson Stanford University School of Medicine, Stanford, CA.

Purpose of Study: Ischemia-reperfusion (IR) or hypoxia (Hx) can cause cell growth and brain structure disruption, contributing to neonatal morbidity and mortality. The vulnerability of the brain and the pattern and extent of injury depend upon the severity of the hypoxic-ischemic insult, maturity, and other factors. Some infants experience in utero IR injury followed by postpartum Hx stress. To date, there has been no mouse model to study this “double-hit” effect of antenatal IR with ensuing post-natal Hx on brain injury. We have developed a mouse model for this purpose.

Methods Used: To cause in utero fetal IR injury, abdomens of pregnant FVB mice (E17) were exposed, uterine arteries identified, and transiently occluded on bilaterally for 10 min using microvascular clamps. Once blood flows were re-established, abdomens were closed and mice were returned to cages for recovery and spontaneous vaginal delivery. The degree of occlusion was confirmed by micro-ultrasound (VisualSonics) on a selected set of pups at surgery. After delivery, IR-injured mice (P4) were exposed to 12 h of Hx (8% O2). At P35, mice were sacrificed and brains harvested for histology.

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using H&E staining. Sham-operated age-matched pregnant mice and pups exposed to normoxia were used as controls.

Summary of Results: During ischemia, fetal heart rate and blood flow velocity decreased ~4X from pre-oclusion levels (180 ± 15 to 48 ± 6 bpm, and 108 ± 6 to 22 ± 2 mm/s, respectively). IR/Hx mice had significantly less gain in body (79% of controls, 18.3 ± 0.2 vs 23.1 ± 2.5 g) and brain (85% of controls, 411.2 ± 1.4 vs 484.3 ± 10.2 mg) weights. H&E brain sections showed enlarged ventricles due to tissue loss consistent with brain injury, and decreased hippocampal (by 64%) and corpus callosum (by 38%) size consistent with white matter injury (Fig.).

Conclusions: This “double-hit” mouse model can reproduce reliably gross and microscopic pathologic changes in the brain. Preventive or therapeutic approaches, including hypothermia or pharmacologic treatments, can be evaluated using this model.

118 CEREBRAL REGIONAL OXYGEN SATURATION AND CEREBRAL FRACTIONAL OXYGEN EXTRACTION IN PRETERM INFANTS WITH AND WITHOUT HEMODYNAMICALLY SIGNIFICANT PATENT DUCTUS ARTERIOSUS DURING THE FIRST FOUR POSTNATAL DAYS

R.G. Cayabyab, K. Barsegghyan, S. Sardesai, I. Seri

Purpose of Study: To compare cerebral regional oxygen saturation (rSO2) and cerebral fractional oxygen extraction (CFOE) in preterm neonates with and without a hemodynamically significant patent ducta (hsPDA) during the first 4 postnatal days.

Methods Used: Retrospective analysis of prospectively collected data of preterm infants ?3 weeks’ gestation. Starting within 12 hours after delivery, patients were continuously monitored with near infrared spectroscopy using INVOS 5100C Oximeter (Somanetics, Troy, MI) during the first 4 postnatal days. O2 saturation was measured by pulse oximetry and extracted from patient records. CFOE was calculated as the difference between O2 saturation and the corresponding rSO2. Hemodynamic significance of the PDA was defined by echocardiographic and clinical criteria.

Summary of Results: Six infants with a hsPDA (birth weight: 1099 ± 235 g; gestational age: 28 ± 1 weeks) and seven infants without a hsPDA (birth weight: 1318 ± 424 g; gestational age: 30 ± 2 weeks) comprise the study population. Cerebral rSO2 and CFOE tended to be higher and lower, respectively in preterm infants without a PDA with the difference reaching statistical significance for rSO2 at 24 (82 ± 6.67 vs 72 ± 7.64, P = 0.035), 30 (83 ± 5.76 vs 74 ± 6.42, P = 0.038), 48 (80 ± 4.66 vs 73 ± 3.43, P = 0.02) and 54 (81 ± 5.61 vs 73 ± 4.66, P = 0.016) hours of age and for CFOE at 24 (0.14 ± 0.02 vs 0.24 ± 0.09, P = 0.049) and 42 (0.14 ± 0.06 vs 0.42 ± 0.06 P = 0.049) hours of age. Arterial O2 saturation did not differ between the groups.

Conclusions: These preliminary findings suggest that patients with a hsPDA have decreased rSO2 and increased CFOE shortly after delivery. We speculate that the decreased rSO2 represents diminished cerebral perfusion and thus O2 delivery and that the increase in CFOE occurs in compensation for the decreased cerebral tissue O2 delivery in neonates with a hsPDA.

119 BRAIN INJURY AND AMPLITUDE-INTEGRATED ELECTROENCEPHALOGRAM IN PRETERM INFANTS


Purpose of Study: Preterm infants are at risk for brain injury and adverse neurodevelopmental outcome. Amplitude-integrated electroencephalogram (aEEG) measures brain function and shows maturation of the background pattern with increasing postmenstrual age. The impact of brain injury on aEEG maturation is not known. The aim of this study was to quantitatively describe the effect of postmenstrual age and brain injury on aEEG.

Methods Used: This was a prospective cohort study including infants born <34 weeks gestation with aEEG and magnetic resonance imaging (MRI) in the newborn period. Exclusion criteria were evidence of congenital malformation or TORCH infection. Infants were considered to have significant brain injury if any of the following were present on magnetic resonance imaging: white matter injury (greater than 3 areas of T1 hypointensity larger than 2 mm), intraventricular hemorrhage > grade II, ventriculomegaly (largest atrial ventricular diameter >8–10 mm). A neurological examination was performed within 24 hours of MRI using standard criteria. A single-channel Odyssey 6000 monitor was used to record aEEG within 48 hours of MRI. The total aEEG score was calculated using the system described by Burdjalov et al. The relationship between total aEEG score and postmenstrual age and brain injury was assessed using linear regression for repeated measures.

Summary of Results: Twenty-six infants with 33 aEEG tracings were included in this study. Eight (33%) had brain injury as defined above. Total aEEG score was significantly associated with postmenstrual age (P < 0.001). For infants without brain injury, total aEEG score rose by 0.9 points (95% confidence interval: 0.6–2 points) with each week increase in postmenstrual age. Infants with brain injury had a trend toward lower scores that was not significant (P > 0.06). The effect of brain injury did not depend on postmenstrual age.

Conclusions: There were quantifiable changes in aEEG recordings with increasing postmenstrual age. The lower scores on aEEG in infants with brain injury were not statistically significant in this small cohort.

120 DEVELOPMENTAL ASSESSMENT, MAGNETOENCEPHALOGRAPHY (MEG), AND MAGNETIC RESONANCE IMAGING (MRI) IN PRETERM INFANTS: A PILOT STUDY


Purpose of Study: Although a variety of neuroprotective strategies have been evaluated, no specific treatment has been identified to reduce or prevent brain injury in preterm infants. One potential new therapy is the use of human recombinant erythropoietin (Epo), which has been shown to be protective in the developing brain. To assess the impact of Epo treatment on developmental outcomes, we performed developmental assessment, MEG and MRI in preterm infants who received Epo during their hospitalization, compared to those who did not.

Methods Used: As an initial pilot study to collect normative data, preterm infants ≤1500 grams birth weight were compared with healthy term infants. Follow-up data included Bayley III scales of cognitive and language development. For MEG, frequent auditory stimuli (800Hz tone) interspersed with infrequent (20%) higher frequency (1000 Hz) tones were presented, and brain responses measured using a prototype pediatric MEG system (babySQUID). For MRI, in addition to volumetric, DTI and MRS data to be presented, perfusion was determined on a 3T Trio Tim Siemens scanner, measured by the standard FAIR-QUIPSS1 (1) arterial spin labeling (ASL) sequence. All data were collected at 18-22 months by certified examiners masked to the treatment group.

Summary of Results: Data for 6 infants was available for analysis thus far. BSID III cognitive scores for preterm infants were 95.0 (range 85–100), while scores for term infants were 103.3 (95–120). Composite language scores were 82.7 (74–97) for preterm and 103.0 (97–112) for term infants. MEG analysis revealed that term infants showed a larger difference in response (mismatch response) early (~100 ms), reflecting increased ability to identify novel stimuli, whereas preterm infants showed a delay in mismatch response (maximal response peaking 200-300 ms). Differences in perfusion in frontal cortical areas was substantial between preterm and term infants (69 versus 91 mL/100 gram tissue/minute).

Conclusions: Initial results in this small number of infants show a trend in term infants towards improved cognitive and language scores, improved
ability to identify novel stimuli, and increased perfusion of critical areas of the brain responsible for executive function.

121 TIMING OF THE MEDICAL TREATMENT FOR PATENT DUCTUS ARTERIOSUS IN PRETERM INFANTS

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Purpose of Study: Prostaglandin inhibitors (e.g., non-steroidal anti-inflammatory drugs, NSAIDs) are used to close the ductus arteriosus. Both indomethacin (Indo) and ibuprofen (Ibu) have been used with reported equal effectiveness. However, it is not clear whether early versus late treatment with either drug at different birth weights (BW) is similar. The purpose of this study is to compare the efficacy of early (<4 days of age) versus late (>5 days) treatment with both drugs in the treatment of patent ductus arteriosus (PDA).

Methods Used: We retrospectively reviewed 65 infants who had a PDA that was confirmed by clinical exam and by echocardiogram from 2007-2008 at University NICU.

Summary of Results: There were 35 infants <800 g BW and 30 infants with BW 800-1200 g. In the <800 g group, 3 PDA closed spontaneously (>5%) and 9 PDA (30%) closed without treatment in infants >800 g birth weight, early treatment averaged 11 days of age. In the <800 g group, there were 12 infants treated early (8 Ibu, 4 Indo) and 20 infants treated late (8 Ibu, 12 Indo). PDA closure rate was higher in the early treatment (54%) than late treatment (5%), P = 0.003. In the 800 - 1200 g group, there were 7 infants treated early (4 Indo, 3 Ibu) and 11 infants treated late (4 Indo, 7 Ibu). PDA closure rate was similar between the early and late group (22% versus 21%). After receiving treatment, 2 PDAs eventually closed but 7 infants underwent surgical ligation in the <800 g. In the 800 - 1200 g group, 5 PDAs eventually closed while 3 underwent surgical ligation after treatment. There was no difference between the use of Ibu or Indo in closing the PDA in either BW group (38% vs 12% vs 33% or 25%).

Conclusions: Spontaneous closure of the PDA occurs more often in the 800-1200 g group than in the <800 g group. In the <800 g birth weight, early treatment with NSAIDs has higher closure rate than late treatment. For infants 800 - 1200 g birth weight, there was no difference in PDA closure in early or late treatment. There was no difference in efficacy of closure of the PDA between Indo and Ibu.

122 NITRITE CONCENTRATION IN SALIVA AND DIET OF TERM AND PRETERM INFANTS

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Purpose of Study: Necrotizing enterocolitis (NEC), an acute, idiopathic disease characterized by infection and necrosis of the bowel wall occurs in approximately 12% of premature infants. 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 nitrite in the stomach by the non-enzymatic reduction. Nitrite, in turn, is derived from diet and the conversion of nitrate to nitrite by commensal bacteria in the mouth. The role of ingested nitrite in the etiology of NEC has not been studied. We hypothesized that premature infants have decreased ingestion of dietary and salivary nitrate, which may contribute to the pathogenesis of NEC.

Methods Used: To quantify dietary intake of nitrate of preterm and term infants we measured nitrite concentration [NO3-] in fresh and frozen-stored human breast milk and infant formula. To assess oral bacterial production of nitrate from nitrate, we measured salivary nitrate and nitrite concentrations (by chemiluminescence) from preterm and term infants and adults.

Summary of Results: [NO3-] was significantly lower in freeze-thawed breast milk (0.092 ± 0.475 μM) than in freshly pumped breast milk (0.026 ± 0.007 μM, P < 0.05). [NO3-] did not differ in milk from mothers of term vs preterm infants. [NO3-] was higher in the infant formula (0.58 ± 0.10 μM) than either fresh (0.092 ± 0.011 μM) or frozen breast milk (0.026 ± 0.007 μM, P < 0.01). Nitrite concentrations in the saliva of preterm (15.9 ± 1.149 μM) and term infants (9.35 ± 0.475 μM) were similar, but both were significantly lower than adult saliva (52.03 ± 14.85 μM, P < 0.05 infants vs adult). The ratio of nitrite to nitrate concentrations in saliva, an index of the rate of bacterial nitrate conversion to nitrite, was higher in adults (0.153 ± 0.3143) than both term (0.021 ± 0.002) and preterm infants (0.031 ± 0.002, P < 0.01).

Conclusions: Freeze-thawing milk results in significant depletion of nitrite. Oral nitrate reductase activity is less in infants than in adults, yet there is no significant difference between preterm and term infants. Thus, the hypothesis that dietary nitrite deficiency may contribute to the etiology of NEC in preterm infants is not supported by our findings.

123 EXPERT MODELING IMPROVES ACQUISITION OF TECHNICAL SKILLS IN NEONATAL RESUSCITATION TRAINING

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Purpose of Study: Evidence suggests current training in neonatal resuscitation is not transferring to the real environment. Video analysis of resuscitations shows that Neonatal Resuscitation Program (NRP) guidelines are not followed more than 50% of the time. Decreased skill retention during the 2 year interval recommended for re-certification has also been shown. Validated technical skills scoring sheets have been introduced as a way for instructors to standardize the way technical performance is evaluated. Current literature on medical expertise suggests that modeling may facilitate the acquisition of expert technical skills. By observing, learners selectively take in information about performing to create a mental image that provides a cognitive reference for the learner. This image then becomes a reference for future performance. We instituted the addition of an “expert model” video to simulated NRP training to test the hypothesis that learners will better acquire and retain technical skills needed to successfully manage newborn emergencies.

Methods Used: An expert model video was created using a Delphi process to demonstrate expert skills, behaviors, and thought processes during newborn resuscitation. 31 incoming interns in a simulated NRP course were studied via a post-test only control group design. Baseline demographics, NRP cognitive test scores, and a subjective measure of confidence were collected. Both groups underwent comprehensive NRP training. The groups were randomized by a table of random numbers: the intervention group reviewed the expert model video while the control group practiced megacodes with instructor feedback. All participants then individually underwent a videotaped megacode in the simulator. The videos were scored by a blinded reviewer using a validated megacode skill checklist. 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, NRP experience, cognitive knowledge, or confidence. The intervention group scored significantly higher in technical skills than the control group (P < 0.001).

Conclusions: The addition of expert modeling to simulation-based neonatal resuscitation training improves acquisition of technical skills.

124 EXPERT MODELING IMPROVES THE ACQUISITION OF BEHAVIORAL SKILLS IN SIMULATION-BASED TRAINING

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Purpose of Study: In 2004 the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) published a report of 71 newborns with poor outcomes. It identified three major areas that may have led to these outcomes: problems with effective communication and teamwork, problems with staff competency, and problems with the training process. JCAHO recommended team training, mock emergency drills, and debriefings aimed at evaluating team performance to address these problems. Many educators have added simulation-based training to NRP to address these areas and focus on the principles of Crew Resource Management (CRM). Scholars argue that for learners to develop expert behavioral skills, the expert’s thought process needs to be demonstrated or modeled. This study was done to determine whether expert modeling enhances behavioral skill acquisition in simulation-based training.

Methods Used: An expert model video was created by a Delphi process to demonstrate expert skills, behaviors, and thought processes during newborn
resuscitation. 31 incoming interns in a simulated NRP course were studied via a post-test only control group design. Baseline demographics, NRP cognitive test scores, and a subjective measure of confidence were collected and both groups underwent comprehensive NRP training. The groups were randomized to an intervention group that viewed the expert model video while the control group practiced megacodes with an instructor. All participants individually underwent a videotaped megacode in the simulator. Three blinded reviewers then scored the videos with a validated delivery room behavioral skills assessment tool. 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, NRP experience, cognitive knowledge, or confidence. The intervention group scored significantly higher in behavioral skills than the control group ($P < 0.001$). The Cronbach’s alpha was 0.97 and the inter-rater reliability was 0.8.

**Conclusions:** The addition of an expert model video to a simulated NRP course improved the acquisition of behavioral skills. Expert modeling allows the educator to teach the behavioral component of crisis management (CRM) more effectively.

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### 125 THE EFFECTS OF PRENATAL METHAMPHETAMINE USE ON NEWBORN HEALTH: RESULTS FROM THE INFANT DEVELOPMENT, ENVIRONMENT AND LIFESTYLE (IDEAL) STUDY


**Purpose of Study:** Methamphetamine use among women is an increasing problem. The purpose of this study is to evaluate the medical outcomes of newborns exposed to methamphetamine in utero.

**Methods Used:** IDEAL screened 34,833 subjects at 4 clinical centers. Of the 3708 newborns eligible and consented, mother and newborn chart reviews were conducted on 204 exposed subjects (EXP) and 208 comparison subjects (COM). Exposure was identified by self-report and/or GC/MS confirmation of amphetamine and metabolites in infant meconium. The COM group was matched by race, birthweight, maternal education and type of insurance, and denied amphetamine use with a negative meconium screen.

**Summary of Results:** Women in the EXP group were more likely to be without a partner (56 vs. 34%; $P < 0.001$), be low SES (33 vs. 12%; $P < 0.001$), have fewer prenatal care visits (11 vs. 7 vs. 14; $P < 0.001$) and gain less weight during pregnancy (42 vs. 20 vs. 34; 16 lb; $P < 0.001$). Women in the EXP group used more alcohol (39 vs. 14%; $P < 0.001$), tobacco (80 vs. 27%; $P < 0.001$), marijuana (34% vs. 4%; $P < 0.001$) during pregnancy. There were no differences in the incidence of congenital anomalies or intraventricular hemorrhage and/or other abnormal head sonograms between the EXP and COM groups. EXP infants showed more “soft signs” including hypertonia ($P < 0.002$) sweating ($P < 0.001$), poor suck ($P < 0.001$), excessive suck ($P < 0.003$), and jitteriness and tremors ($P < 0.001$), but no increase in drug withdrawal. EXP infants were less likely to be breastfed ($P < 0.001$), have more child protective service (CPS) involvement ($P < 0.001$) and out-of-home placement at discharge (31 vs. 1%; $P < 0.001$). EXP had more CPS referrals (61 vs. 4%) and supervision at discharge (54 vs. 2%).

**Conclusions:** Exposed newborns had an increased incidence of symptoms associated with drug exposure but did not have symptoms requiring pharmacologic intervention. Though incidence of congenital abnormalities was not increased, the frequency of polydrug use, poverty and out of home placement increases concern for the future neurodevelopment of these methamphetamine-exposed children.

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### 126 BLADDER PRESSURE MEASUREMENT IN SICK NEONATES

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**Purpose of Study:** As a surrogate for intra abdominal pressure, we sought to define the range of bladder pressure in neonates ill enough to require an indwelling urinary catheter.

**Methods Used:** Informed consent was obtained for NICU patients at Primary Children’s Medical Center, Salt Lake City, UT, who required an indwelling urinary catheter. A pressure monitoring system (Adviser, Wolfe Tory Medical, Inc, Salt Lake City, UT) was attached to the catheter and periodic q2-4 h static pressure measurements were made until the catheter was discontinued.

**Summary of Results:** 32 neonates were enrolled in the study and data were collected on 30. Median birth weight, GA were 2580 g and 37 wk. Median duration of study was 5.5d. 18 neonates (60%) required staged abdominal surgery for gastroesophageal reflux (9), CDH (7), or bowel perforation (2). Other patients were being treated for PHH/N/EUMO (7), sepsis (3), or hydrops (1). 1219 bladder pressure measurements were obtained. The median bladder pressure (interquartile range) for all measurements was 10.9 cmH2O (4.1–13.6 cmH2O) with a mean (sd) of 9.7 (7.8) cmH2O. The 90th %tile was 17.7 cmH2O; 5 measurements were noted >34 cmH2O. 85% of values >90th %tile occurred in patients post operatively, compared to 15% in patients pre-operatively or who did not have abdominal surgery ($P < 0.001$, Fisher’s Exact). 13 of 18 post operative patients (72%) had bladder pressure measurements >90th %tile, compared to 2 of 12 non surgical patients (18%). ($P = 0.008$, Fisher’s Exact)

**Conclusions:** (1) Bladder pressure measurements are feasible and can be done easily as part of neonatal intensive care. (2) In this series, nominal bladder pressure values (<75th %tile) were ≤13.6 cmH2O. (3) The time of highest risk for intra abdominal hypertension (bladder pressure >90th %tile) was in the post-operative period. (4) The majority of bladder pressure measurements exceeded the range of normal CVP (4–8 cmH2O).

Speculation: Intra abdominal pressure which exceeds CVP could potentially complicate post operative healing and recovery. Even with the current surgical techniques which staged abdominal closures in our patients, approximately 58% of the measured bladder pressure values exceeded the upper limit of normal CVP (8 cmH2O). Whether surgical recovery could be enhanced by maintaining abdominal (bladder) pressure less than 8–10 cmH2O should be a topic for further study.

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### 127 ALPHA DEFENSINS AS A POTENTIAL BIOMARKER IN SCHIZOPHRENIC SWEAT

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**Purpose of Study:** Schizophrenia (SZ) is a debilitating psychiatric disorder characterized by a variety of symptoms, such as delusions and hallucinations. The diagnosis of SZ relies on subjective interviews and clinical observations. A laboratory measurement for diagnosis does not exist. Therefore, much effort is devoted to finding a biological marker for SZ.

A recent study found that alpha defensins, which are antimicrobial and nonspecific cytotoxic peptides, are significantly increased in the blood of SZ patients. Our study attempts to determine if alpha defensins are detectable in human sweat, and whether their concentrations differ between SZ and control groups.

**Methods Used:** Subjects were identified by licensed psychiatrists. Diagnosis of SZ was established by clinical interviews, which included the use of the DSM-SCID and the Birchwood Social Functioning Scale. Controls were screened to exclude individuals with current or past history of other psychiatric disorders. A total of 9 SZ patients and 15 controls were included. Sweat was collected from the volar forearm with the Macroaduct® Sweat Stimulation and Collection System. Samples were immediately frozen and then stored in a –80°C freezer. Samples were analyzed by ELISA at a 1:10 dilution.

**Summary of Results:** Although alpha defensins were detected in the sweat of both patients and controls, a significant difference in concentration between the two groups was not found ($t = -0.622$, df = 22, $P = 0.540$). Mean concentration in the control group was 126.5 pg/ml (SD = 80.05); mean concentration in the patient group was 145.54 pg/ml (SD = 57.07). A laboratory measurement for diagnosis does not exist. Therefore, much effort is devoted to finding a biological marker for SZ.
Thus, future studies should make efforts to gather ample sweat from all subjects, thereby allowing for less dilute samples. A larger volume of sweat gathered from each participant would also allow the researcher to run duplicate wells when performing the ELISA.

While there does not appear to be a significant difference between the sweat of SZ patients and controls, it is nevertheless important to note that detectable levels of alpha defensins were found in the sweat of both groups.

128 PREGNANCY-RELATED REDUCTION IN CONNECTIONS FROM THE CERVIX TO THE HYPOTHALAMIC PARAVENTRICULAR NUCLEUS

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Purpose of Study: In non-pregnant rodents, nerve fibers in the cervix make synaptic connections with neurons in the paraventricular nucleus of the hypothalamus (PVN; J Comp Neurol 418:484, 2000; J Neurosci Res 64:53, 2001; JSGI 12 (Suppl): 134 #153, 2005). In pregnant mice, a dramatic reduction in fibers that innervate the cervix from sensory portions of the thoraco-lumbar spinal cord, and to a lesser extent, autonomic and motor subdivisions has been found (Soc Neurosci #789,14, 2007). The present study tested the hypothesis that connections between the cervix and PVN are decreased in mice with pregnancy.

Methods Used: The retrograde transynaptic tracer pseudorabies virus (PRV; 3X ~1-2 µl of 1 x 10^6/µl Bartha K strain herpes virus 1.5 µl saline over 15 min) was injected into the cervix of C3H/HeN mice that were nonpregnant (NP) or pregnant on day 15 or 18 post-breeding (D15 or D18). After 5 days, mice were euthanized and perfused with 4% paraformaldehyde; cervix and brain were removed, sectioned, and processed by immunohistochemistry (primary antibody gift of Dr. Enquist, Curr Protocols Neurosci Suppl 9,1, 1999). Image analysis of the area of PVN with PRV stain with ImageProPlus (Media Cybernnetics, Bethesda, MD) provided a consistent and reproducible estimation of area of PRV stain in brain regions of interest.

Summary of Results: PRV-infected cells and fibers were distributed throughout the rostral-caudal expanse of the PVN. In the PVN from pregnant mice, total area of PRV stain was significantly reduced compared to that in NP mice (P < 0.05). In rostral and middle portions of the PVN, area of PRV stain significantly decreased relative to that in NP mice; ventromedially in NP mice, total area of PRV in the caudal PVN precluded statistical differences.

Conclusions: These findings indicate that there are fewer synaptic connections between the cervix and PVN during pregnancy and raise the possibility that diminished sensory information is conveyed to higher brain centers near term. Whether remaining neural connections to the cervix may be important for inflammatory processes that are associated with parturition remains to be determined.

129 INTERACTION OF METABOTROPIC GLUTAMATE 1A RECEPTORS(MGLUR1A) WITH MEMBRANE ESTROGEN RECEPTORS(MER) IN HYPOTHALAMIC ASTROCYTES INDUCES THE SYNTHESIS OF PROGESTERONE

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Purpose of Study: Estradiol of ovarian origin induces progesterone synthesis in hypothalamic astrocytes that are involved in estrogen positive feedback responsible for the LH surge. We have demonstrated that mGlur1a mediate mER initiated intracellular signaling to induce [Ca2+]i flux and progesterone synthesis.

Methods Used: The potential interaction was established using co-immunoprecipitation of mER and mGlur1a. [Ca2+]i flux in astrocytes was monitored with the calcium indicator, Fluo-4, and imaging performed on a Zeiss-510 Meta laser scanning confocal microscope.

Radioimmunoassay (RIA) was used to measure progesterone levels.

Summary of Results: 17β-estradiol at 1 nM, 10 nM, and 100 nM induced a similarly robust [Ca2+]i flux of 612 ± 42 relative fluorescent units (RFU) (n = 15), 641 ± 47 RFU (n = 18), and 629 ± 34 RFU (n = 16), respectively. These responses were all significantly greater than estradiol at 100 pM with [Ca2+]i flux of 282 ± 18 RFU (n = 25, P < 0.001). However, even estradiol at concentration as low as 100 pM induced a greater [Ca2+]i flux than controls at 134 ± 16 RFU (n = 14, P < 0.001). Blockade of mGlur1a with the selective antagonist, LY367385 (20 nM), attenuated the estradiol (1 nM)-induced [Ca2+]i flux from 639 ± 63 RFU to 186 ± 56 RFU (n = 5, P < 0.002). Conversely, the mGlur1a agonist, (S)-3,5-dihydroxyxypalicyglycine hydrate (DHPG) enhanced the estradiol effect. Estradiol (1 nM) in combination with DHPG (100 nM) induced a significantly greater [Ca2+]i flux (790 ± 42 RFU, n = 19) than 1 nM of estradiol (615 ± 36 RFU, n = 23, P < 0.05) or 100 nM of DHPG alone (346 ± 25 RFU, n=19, P < 0.05). Also, progesterone synthesis was greater with estradiol (1 nM) plus DHPG (100 nM) (20.2 ± 3.7 pg/ml, n = 4) than 1 nM of estradiol (57.3 ± 6.3 pg/ml, n = 4, P < 0.05). Therefore, progesterone synthesis is induced by estradiol in the presence of mGlur1a.

Conclusions: The mER interaction with mGlur1a is necessary to mediate cytoplasmic calcium signaling in hypothalamic astrocytes. The increase in [Ca2+]i is critical to induce progesterone synthesis in the brain.

130 ESTROGEN RAPIDLY ATTENUATES GLUTAMATERGIC NEUROTRANSMISSION AT PRO-OPIOMELANOCORTIN SYNAPSES

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Purpose of Study: It has long been known that cannabinoids increase feeding, and do so partly by decreasing the excitability of anorexigenic proopiomelanocortin (POMC) neurons of the hypothalamic arcuate nucleus (ARC). Conversely, the gonadal steroid hormone 17β-estradiol suppresses appetite, due in part to increased POMC neuronal activity as well as an attenuation of the cannabinoid-induced decrease in glutamatergic synaptic input onto these cells. Considerable evidence now indicates that estradiol can activate a cell membrane-bound estrogen receptor and powerfully alter cell physiology within minutes. We thus tested the hypothesis that the estrogen-mediated attenuation of the cannabinoid inhibition of glutamatergic synaptic input takes place on a rapid time scale.

Methods Used: Whole-cell patch clamp recordings were performed using hypothalamic slices prepared from ovariectomized female guinea pigs. We evaluated glutamatergic synaptic input in ARC neurons by monitoring the frequency and amplitude of miniature excitatory postsynaptic currents (mEPSCs). Slices were perfused for 10–15 minutes with either 100 nM estradiol benzoate (EB) or its ethanol vehicle. Baseline data was obtained over 3–4 minutes, after which both steroid- and vehicle-treated slices were subsequently exposed to varying concentrations of the cannabinoid CB1 receptor agonist WIN 55,212-2, yielding 3–4 minutes worth of additional data upon equilibration of the drug in the slice in order to evaluate the change in mEPSC frequency and amplitude. The recorded neurons were subsequently identified via immunohistochemical fluorescence using phenotype markers for POMC neurons.

Summary of Results: In cells from vehicle-treated slices, WIN 55,212-2 elicited a dose-dependent decrease in mEPSC frequency but not amplitude. EB treatment rendered the cannabinoid less effective in reducing mEPSC frequency, manifest by a rightward-shift in the agonist dose-response curve. These effects were observed in identified POMC neurons from both vehicle- and EB-treated slices.

Conclusions: This study demonstrates that estrogen rapidly diminishes the cannabinoid-mediated inhibition of glutamatergic input onto ARC POMC neurons. Such findings may be applied to feeding behavior regulation as well as elucidation of a membrane-bound estrogen receptor signal transduction pathway.

131 SEX STEROID HORMONE INFLUENCES ON THE CANNABINOID REGULATION OF ENERGY HOMEOSTASIS

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Purpose of Study: Gonadal steroids and cannabinoids modulate energy homeostasis in similar yet distinct fashions. Estrogen induces hypophagia and hypothermia, and cannabinoids elicit hyperphagia and hypothermia. Testosterone promotes weight gain, increases lean muscle mass, and serves as a useful adjunct to cannabinoid pharmacotherapy for cachexia due to cancer.
or HIV/AIDS. The purpose of this study was to elucidate any interactive effects of steroids and cannabinoids on the microstructural elements of feeding behavior. We tested the hypothesis that gonadal steroid hormones will alter cannabinoid modulation of appetite by influencing effects on daily and hourly intake, meal frequency, duration, and size, and body temperature.

**Methods Used:** Under ketamine/xylazine anesthesia, gonadectomies on female and male guinea pigs were performed alongside abdominal implantation of data loggers used to monitor core body temperature. After 4 days recovery, animals were acclimated to daily weighing, handling and living in an automated feeding chamber for 3 days, after which the five above-referenced indices of feeding behavior were monitored under ad libitum conditions around the clock for 7 days. The animals were subject to injection regimens consisting of one s.c. injection given at 8 a.m. every other day of ipsisexual sex hormone (estradiol benzoate; EB;10 μg), testosterone propionate (TP; 400 μg) or sesame oil vehicle in addition to concomitant daily injections of the cannabinoid agonist WIN 55,212-2 (0.1–1.0 mg/kg; s.c.) or its cremophor/ethanol/saline vehicle.

**Summary of Results:** EB-treated females had significantly decreased daily and hourly intake, meal frequency, weight gain body temperature but increased meal duration and size. Conversely, TP-treated male guinea pigs had significantly higher daily and hourly intake, meal duration and size, and weight gain. WIN 55,212-2 produced dose- and time-related increases in food intake and decreases in body temperature, the former of which was markedly diminished by EB co-treatment in females, and potentiated by TP manifest by a prolonged duration of action.

**Conclusions:** Gonadal steroids can clearly influence the cannabinoid regulation of energy homeostasis.

### 132 LOCATION OF POSTTRANSLATIONALLY MODIFIED P53 IN AXONS AND GROWTH CONES: IMPLICATION FOR A NOVEL FUNCTION?

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**Purpose of Study:** P53 is a tumor-suppressing protein that has different forms in cells due to post-translational modifications and various mutations. P53 has long been considered to function as a regulator of the cell cycle and DNA repair in the nucleus. However, the possibility of P53 being present in neuronal processes and contributing to axonal growth has not yet been explored. This study had three goals. First, it was to determine the amount of different forms of P53 in dendrites, the axon, and the axonal growth cone (GC) of neurons. Specifically, the different forms of P53 observed in the study were acetylated (Ac-P53), a conformational mutant (Mu-P53) and phosphorylated (P-P53). Second, it was to determine how the concentration of those forms changed as the neurons developed. Third, it was to test for possible P53 involvement in axonal growth by correlating P53 found in the axonal GC with GC size.

**Methods Used:** Rat embryonic hippocampal neurons were cultured, immunostained with anti Ac-P53, Mu-P53 and P-P53 in combination with the Executive Maze Task (EMT) were used to quantify executive function.

**Summary of Results:** The concentration of Ac-p53 was highest in the axon, followed by the dendrite, then the GC (P < 0.05). Mu-P53 was highest in the axon, followed by the dendrite, then the GC (P < 0.05). P-P53 was highest in the GC, then the axon, then the dendrite (P < 0.05). As neurons developed, all forms of P53 decreased in neuronal processes (P = 0.05) with the exception of Mu-P53, which insignificantly increased (P = 0.83) in the GC. For days 3 and 5, the amount of P-P53 and growth cone size had a positive correlation (R value = .73 and .86, respectively).

**Conclusions:** In the neuronal processes, the concentration of P53 was highest in axons and GCs. As the neurons matured, the concentration of the various forms decreased. Concomitantly, a positive correlation existed between P-P53 and growth cone size, suggesting that P53 may have a novel role in axonal development.

### 133 PEDIATRIC PATIENTS WITH POOR NEUROLOGICAL STATUS AND ARTERIOVENOUS MALFORMATION HEMORRHAGE: AN OUTCOME ANALYSIS

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**Purpose of Study:** In general, patients who present with low Glasgow Coma Scale (GCS) scores and/or fixed and dilated pupils are not expected to do well following arteriovenous malformation (AVM) hemorrhage. However, there is a sense amongst neurosurgeons that pediatric patients may make a better recovery than adults following such an event. There have been few studies focusing on the outcome of pediatric patients with poor neurological status following AVM hemorrhage.

**Methods Used:** This is a retrospective analysis of clinical presentation and outcome of 15 patients seen at our pediatric hospital presenting with low GCS scores (defined as GCS ≤6) and/or fixed and dilated pupils following AVM hemorrhage.

**Summary of Results:** Initial GCS scores ranged from 3 to 6, and 79% of the patients in this series presented with fixed pupils. Fifty-three percent of patients (8/15) suffered primarily a lobar hemorrhage, 20% (3/15) suffered primarily an infratentorial bleed, 13% (2/15) suffered primarily bleeds of the basal ganglia, and 13% (2/15) suffered exclusively intraventricular hemorrhage (IVH). Overall mortality was 20% (3/15) patients. All survivors (12/12) made a meaningful recovery and went on to live independent lives.

**Conclusions:** Pediatric patients suffering AVM hemorrhage have a good outcome and are able to function independently despite poor initial neurological state.

### 134 NOT SO MILD HEAD INJURY: MR DIFFUSION TENSOR IMAGING IMPLICATES PREFRONTAL INJURY IN EXECUTIVE FUNCTION IMPAIRMENT FOLLOWING VERY MILD TRAUMATIC BRAIN INJURY

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**Purpose of Study:** Diffusion tensor imaging (DTI) can detect brain abnormalities after traumatic brain injury (TBI), but it is not clear whether those abnormalities are truly responsible for cognitive impairments. We sought to identify fronto lobe substrates of executive dysfunction within two weeks after mild TBI (mTBI).

**Methods Used:** The study had IRB approval and informed consent. DTI and standardized neuropsychological assessments were performed on 20 mTBI patients with within two weeks of injury and 20 matched controls. Fractional anisotropy (FA) and mean diffusivity (MD) images (3.0T; 25 directions; b = 1000), were compared using whole brain voxelwise analysis at a false discovery rate <0.01. The Continuous Performance Task (CPT) and the Executive Maze Task (EMT) were used to quantify executive function. Spearman’s rank correlation analyses evaluated associations between diffusion measures and executive function, while accounting for potential confounders in multivariable analyses.

**Summary of Results:** Five frontal lobe white matter clusters of lower FA, including the dorsolateral prefrontal cortex (DLPFC), were present in patients (P < 0.005), with several clusters also demonstrating higher MD (P < 0.005), representing axonal alterations to white matter tracts. Patients performed worse on the (CPT) (P = 0.03) and the EMT (P = 0.008), indicating impaired executive function. In correlation analyses, lower DLPFC FA predicted worse executive function in patients (P < 0.05), independent of age, gender, education, stress, anxiety and depression.

**Conclusions:** FA indexes DLPFC axonal injury after mild TBI and predicts deficient executive function. Correlation of DTI with an important mTBI outcome (executive function impairment) at a location essential for that outcome, suggests that DTI is a meaningful indicator of brain injury and merits further investigation.
135 EFFECTS OF NICOTINE ON DEFAULT BRAIN MODE
FUNCTIONAL CONNECTIVITY

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Purpose of Study: Default brain mode (DBM) functional connectivity in the brain has been identified as a network of regions demonstrating concurrent functional activity when an individual is resting in a conscious, but inactive, state. The exact functions of the default mode network are not fully understood, but it is believed to be involved in a variety of tasks, including self-reflective activity (Garcia et al. 2003). Recent evidence has demonstrated that nicotine deactivates portions of the DBM network and enhances visuospatial attention when individuals are engaged in tasks requiring visual activity (Hahn et al. 2007). The purpose of this study is to identify effects that nicotine may have on the DBM network of individuals in a resting, inactive, state.

Methods Used: Fifteen individuals who reported themselves as non-smokers without a diagnosis of a psychiatric disorder participated in this study. Each participant was studied using functional magnetic resonance imaging (fMRI) and was scanned pre- and post-administration of a placebo patch or nicotine. Data was acquired during a period where the individual was presented with no stimuli and asked to remain awake but lay still and quiet. Data was analyzed using spatial independent component analysis and the DBM signal was identified via spatial correlation with a mask. Spatial differences between default mode components in pre- and post-placebo and pre-and post-nicotine groups were examined.

Summary of Results: Nicotine administration resulted in decreased activity of the DBM. Functional activity was most markedly diminished bilaterally in the posterior cingulate cortex, specifically the retrosplenium (BA29 and BA30).

Conclusions: The decrease in DBM activity as a result of nicotine deactivates the resting state of the brain even without the presence of an attention demanding task or salient stimulus. The retrosplenium is involved in episodic memory (Maguire 2001), thus nicotine may interfere with this process. Default mode connectivity has been demonstrated to be aberrant in schizophrenic patients (Garrity et al. 2007). As a large percentage of schizophrenic individuals smoke, our study to observe the effects of nicotine on the default mode in this population is currently ongoing.

136 RARE NERVE LESIONS OF NON-NERVE SHEATH ORIGIN: A 17-YEAR RETROSPECTIVE SERIES

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Purpose of Study: Peripheral nerve masses are frequently encountered in surgical pathology practice. However, once a peripheral nerve mass is determined not to be a nerve sheath neoplasm, differential diagnostic considerations drop off sharply. It was the goal of this study to review our experience with nerve and nerve root masses.

Methods Used: Computer-based, 17-year retrospective search of our pathology database from 1991-2008, including only cases where symptoms/signs were referable to a nerve lesion, necessitating surgical resection. Rare neoplasms were further studied by cytogenetic analysis or gene microarray to compare findings with similar tumors arising in more common anatomical sites.

Summary of Results: 458 cases of nerve lesions/masses were identified. After elimination of common lesions (nerve sheath tumors, ganglion cysts, traumatic or Morton neuromas, malignant peripheral nerve sheath tumors and paragangliomas), 37 cases (8%) remained, almost all of which were of non-nerve sheath origin. Notable rare nerve lesions included cavernous angiomia, massive capillary hemangioma, proximal traumatic neurona devoid of collagen, metastatic neuroendocrine pancreatic carcinoma, meningiomas invading nerve fascicles, and primary Ewing sarcoma, extraregional rhabdoid tumor (RT), and undifferentiated sarcoma. The latter presented in a child with diffuse, rope-like nerve enlargement several years before evolving into a more typical MPNST. Ewing sarcoma showed a rearrangement of the EWSR1 locus at 22q12 and the RT manifested loss of INI-1 protein expression. The undifferentiated sarcoma was found to have a gene expression pattern that clustered with other malignant peripheral nerve sheath neoplasms, but not Ewing sarcomas or rhabdomyosarcomas.

Conclusions: Pathologists and clinicians should be aware of the wide diversity of benign, metastatic, and primary diseases that can rarely affect peripheral nerve, often mimicking nerve sheath tumors.

137 THYROIDINE RAPIDLY ACTIVATES NAV1.6 SODIUM CURRENT VIA INTEGRIN ALPHAV/BETA3 DURING EMBRYONIC DEVELOPMENT

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Purpose of Study: Normal embryonic neuromodulation requires thyroid hormone, yet the mechanisms and targets of thyroid hormone during embryonic stages are ill-defined. The discovery of a nongenomic thyroid hormone pathway preferential for thyroxine (T4) and requiring integrin receptors allows for a new line of study into thyroid hormone mechanisms during development. Previous work showed T4 rapidly increases voltage-gated sodium current in zebrafish Rohon-Beard (RB) neurons. We aimed to identify the receptor and ion channel targets for T4’s rapid modulation of sodium current.

Methods Used: We isolated sodium current in zebrafish RBs and motoneurons with modified extracellular solutions and assayed for changes in sodium current peak amplitude via whole cell voltage-clamp recordings. Integrin αβ3 location was imaged by fluorescent immunocytochemistry with the αβ3 specific LIM09 antibody. Sodium channel α-subunits expressed by RBs (either nav1.6 or nav1.1α) were knocked-down by injection of antisense morpholinos at the one-cell stage targeted to isotype specific α-subunit RNA.

Summary of Results: Immunofluorescent stains in wildtype zebrafish showed no specific integrin αβ3 stain at 24 hours post fertilization (hpf), but 48 hpf embryos expressed integrin αβ3 in dorsal and ventral spinal cord cells. Acute application of 30 nM T4 did not alter RB sodium current at 24 hpf, yet T4 application at 48 hpf significantly increased peak sodium current 1.4-fold versus controls (P < 0.001), coinciding with the appearance of integrin αβ3 on RBs. Embryos displaying selective knockdown of nav1.1α or embryos injected with control morpholino increased peak RB sodium current (1.4-fold and 1.3-fold, respectively; P < 0.001) in response to T4 application. However, knockdown of nav1.6 occluded T4’s acute effects (P < 0.005). Caudal primary motoneurons, expressing both αβ3 and nav1.6, acutely increased peak sodium current 1.3-fold versus controls (P < 0.005) in response to T4.

Conclusions: Our results show T4’s rapid regulation of sodium current requires both integrin αβ3 and nav1.6, and can affect multiple neuronal populations. These in vivo experiments show T4’s rapid mechanism targeting nav1.6 is an important regulator of sodium current during embryonic stages.

138 SPINAL CORD ATROPHY AFTER CHRONIC INJURY CORRELATES WITH CLINICAL DEFICITS AND WORSENS OVER TIME

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Purpose of Study: Atrophy follows injury to the CNS and impedes behavioral recovery. Pathologic studies have shown cord atrophy after spinal cord injury (SCI), but this relationship has not been explored in living subjects. This study explores if degree of cord atrophy in subjects with chronic SCI correlates with degree of behavior deficits normally mediated by the spinal cord (SC). The relationship between atrophy and time post-injury is also examined.

Methods Used: In 23 subjects with SCI and 13 age-matched controls, neurological assessment was followed by an axial T2-weighted MRI scan of cervical SC. Cross-sectional area (CSA) was measured and averaged in 3 contiguous slices at C2-C3 (above injury level). SC rotation on MRI scan was measured and corrected. To normalize for biological variation in SC size, cervical CSA values were corrected for brain volume.

Summary of Results: Subject groups didn’t differ in age (34.0 ± 3.0 vs. 33.7 ± 3.3 yrs, SCI vs. controls, mean ± SEM, P > 0.9) or gender distribution (20 M/3 F vs. 10 M/3 F, P = 0.6). The SCI occurred 4.5 ± 0.7 yrs (range 0.7–10.9) prior, was traumatic in all cases, and at thoracic (T5-T11, n = 5) or cervical (C4-C7, n = 18) levels. Cervical spine CSA was significantly smaller in subjects with SCI (43 ± 2 mm^2) as compared to controls (75 ± 2 mm^2; P < 0.0001). There was no overlap in CSA values (28–60 for SCI vs. 65–85
for controls). Among subjects with SCI, extent of SC atrophy correlated with time since SCI ($r = 0.47, P = 0.02$), sensory status (ASIA bilateral pinprick score, $r = 0.69, P = 0.0003$), and motor status (ASIA bilateral motor score, $r = 0.40, P = 0.0556$). However, extent of SC atrophy was not related to ASIA bilateral light touch score or self-reports of bowel and bladder control; nor to age, AIS, disability measures, or neurological functions not mediated via the SC such as depression.

Conclusions: After chronic SCI, cord atrophy is present and strongly related to degree of deficit for most behaviors normally mediated through the cord. Correlation with motor and pinprick, but not light touch, scores might reflect features of normal tract anatomy or injury. Worsening cord atrophy with greater time post-injury suggests that loss of CNS tissue continues during the chronic phase of SCI.

139 RELATIONSHIP BETWEEN EXCESSIVE DAYTIME SLEEPINESS AND FATIGUE IN PATIENTS WITH MULTIPLE SCLEROSIS

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Purpose of Study: To investigate whether there is a relationship between excessive daytime sleepiness (EDS) and fatigue in patients with multiple sclerosis (MS).

Methods Used: The relationship between EDS and fatigue was examined prospectively in a group of unselected patients with MS seen in the setting of a MS Center. The study included 85 consecutive consenting patients with MS that were willing to complete the Epworth Sleepiness Scale (ESS) and Fatigue Severity Scale (FSS).

Summary of Results: Analysis identified that the ESS score was significantly correlated with the FSS score ($r = 0.278$) ($P < 0.05$). When comparing the mean ESS scores of the MS patients with a FSS score of greater than four versus the MS patients with a FSS score of less than or equal to four, we found that the mean ESS score of MS patients with a FSS score greater than four was significantly greater than the mean ESS score of MS patients with a FSS score less than or equal to four ($P < 0.05$). Analysis of the subgroup of patients with the relapsing remitting type of MS, found that their average ESS score, when coexisting with a FSS score greater than four, was significantly greater than the average ESS score of other MS patients diagnosed with relapsing remitting disease that have a FSS score less than or equal to four ($P < 0.01$).

Conclusions: Although higher scores in one scale were generally predictive of higher scores in the other, divergent results occurred in some patients, suggesting that EDS and fatigue are related but pathophysiologically distinct entities. In patients taking modafinil, improvement was reported in both sleepiness as well as fatigue. Our observed correlation of EDS with fatigue suggests that strategies which improve daytime hypersomnolence may also improve fatigue in patients with MS.

Pulmonary and Critical Care I

Concurrent Session

8:30 AM

Friday, January 30, 2009

140 YELLOW NAIL SYNDROME FOLLOWING THORACIC SURGERY: A CASE REPORT

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Case Report: Purpose of Study: Yellow nail syndrome (YNS) presents as a triad of yellow nails, lymphedema and chronic respiratory symptoms. The exact etiology of YNS is unknown but generally attributed to an underlying anatomical or functional lymphatic abnormality. Several associated conditions include endocrine and autoimmune diseases, infections and malignancy. This is the first reported association of this syndrome with thoracic surgery.

Methods Used: Case Report. Summary of Results: An 80-year-old man presented with dyspnea for several months, recurrent pleural effusions, and pneumonias occurring shortly after coronary artery bypass surgery. On examination, the nails of his fingers and toes were yellow and thickened, and lower extremity pitting edema extended up to his knees. A chest radiograph revealed a right pleural effusion that produced an exudative fluid on thoracentesis. After treatment with mechanical pleurodesis and an oral regimen of vitamin E, his condition resolved. Conclusion: YNS is a rare syndrome with a unique presentation. Early recognition of YNS may avoid extraneous diagnostic studies and therapies. Thoracic surgery may be associated with the development of YNS.

141 COBINAMIDE AND DOS MONITORING-A POTENTIAL NEW TREATMENT APPROACH FOR MASS CASUALTY CYANIDE POISONING

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Purpose of Study: To determine the ability of inhaled cobinamide to rapidly reverse cyanide (CN) toxicity using diffuse optical spectroscopy (DOS).

Methods Used: Cyanide toxicity was induced in New Zealand white rabbits using a standard 10 mg intravenous CN infusion model developed in our laboratory. Quantitative DOS monitoring of physiologic effects of cyanide toxicity were performed continuously during cyanide toxicity and treatment concurrently with standard arterial and venous blood gas sampling, and cyanide levels. Animals were treated with aerosolized cobinamide (83.5 mg or 240.6 mg), or controls; and response to therapy measured.

Summary of Results: DOS was able to detect increases in oxyhemoglobin, decreases in deoxyhemoglobin, and reductions in oxidized cytochrome C-oxidase during cyanide poisoning. Aerosolized cobinamide groups showed rapid reversal of cyanide toxicity (within less than 10 minutes) in contrast to control animals as measured by DOS, and confirmed by standard blood gas and cyanide levels.

Conclusions: 1) Cobinamide is capable of rapid and complete reversal of cyanide toxicity. 2) The rapid reversal of cyanide toxicity with aerosolized cobinamide suggests that a compact portable inhaler method could be developed. 3) DOS is able to noninvasively detect and monitor the development and reversal of cyanide toxicity. These findings suggest that cobinamide may represent a novel treatment potentially capable of rapid
reversal of cyanide toxicity deliverable in readily available forms for mass casualty cyanide exposures.

**Methods Used:** We studied the effect of IL-6 on intestinal TJ permeability by using an in vitro epithelial system consisting of filter-grown Caco-2 monolayers. Electrical resistance was measured across the Caco-2 monolayer with and without treatment with IL-6 using an EVOM voltmetor. TJ protein expression was analyzed by Western blotting.

**Summary of Results:** Treatment of Caco-2 monolayers with IL-6 (20 ng/ml) caused a 35% (P < 0.001) reduction in electrical resistance. The drop in resistance was maximal after 48 h of IL-6 incubation. IL-6 supplementation between 1-10 ng/ml caused significant reductions in electrical resistance at 48 h (10% to 35%) in permeability. Treatment of Caco-2 monolayers with IL-6 did not significantly alter the expression of the TJ regulatory proteins Myosin Light Chain Kinase or Zonula Occludens-1. Further studies will assess the effect of IL-6 on expression of trans-membrane TJ proteins Occludin and the Claudins. We will also assess the effect of IL-6 on junctional localization of TJ proteins by immunofluorescence.

**Conclusions:** IL-6 causes a significant decrease in electrical resistance in intestinal epithelium.

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**142 CONTRIBUTION OF BIRTH ASPHYXIA TO PERINATAL AND CHILD MORTALITY IN RURAL TIBET**

J. Norris 1, B. Fassl 2, F. Nkoy 2

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

**Purpose of Study:** Unattended delivery and limited access to health care are common in rural Tibet. However, little consolidated and standardized data on contributors to child mortality exists. Measuring mortality within standard cause of death categories would allow to quantify the burden of individual contributors and guide future public health interventions. The purpose of this study was to describe child mortality during perinatal, neonatal and infancy periods in Tibetan children under 5 years of age over a 9 year period and to determine important contributors to child mortality.

**Methods Used:** We calculated mortality rates from death records collected by the Tibet Health Bureau (THB) in Medro Gonggar County from 1998 to 2006. For 1998 to 2001, the analysis utilized abstracts of death certificate information. For 2002–2006, we directly reviewed all available death certificates. Listed causes of death were assigned standardized death categories. Analysis is descriptive.

**Summary of Results:** Overall, 462 child deaths and 70 stillbirths were reported during the study period. 52% of deaths (251/462) occurred in the neonatal period, 83% (385/462) in infancy. Perinatal deaths accounted for 52% (277/532) of all reported deaths. Birth asphyxia was the single most predominant cause of death accounting for 34% (155/462) of child deaths, 51% (277/532) of neonatal deaths and 48% (132/277) of perinatal deaths. Other major causes of child mortality were respiratory problems 30% (132/462), diarrhea 11% (51/462) and prematurity 8% (36/462).

**Conclusions:** Birth asphyxia is the single most predominant cause of child death in rural Tibet. Public health interventions targeting management of birth and newborn resuscitation are urgently needed. More studies are needed to examine the contribution of other factors such as high altitude to the increased birth asphyxia rate.

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**143 INTERLEUKIN-6 INCREASES INTESTINAL EPITHELIAL TIGHT JUNCTION PERMEABILITY**

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UNM, Albuquerque, NM.

**Purpose of Study:** Septic shock causes a significant defect in intestinal tight junction (TJ) permeability. An important consequence of intestinal barrier dysfunction is systemic exposure to gut flora, causing further release of cytokines and a perpetuation of the pro-inflammatory state. Interleukin-6 (IL-6) is a major cytokine mediator of the prolonged inflammatory state of sepsis, the time course of increased IL-6 levels in septic shock mirrors the prolonged intestinal barrier disturbance. We propose that IL-6 modulates intestinal permeability and regulates the expression and junctional localization of tight junction proteins.

**Methods Used:** A total of 969 screened participants had post bronchodilator spirometry were used so that asthmatic subjects with significant airway reactivity were excluded. The ndd spirometers (Zurich, Switzerland) measured FEV6 values from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria: FEV1/FVC ratios <70%. Severity is classified from percent predicted FEV1 (%PreFEV1). Using lower limits of normal (LLN) calculated from the NHANES III normal data set for both the FEV1/FVC and the FEV1/FEV6 ratios, we compared the GOLD classification on each subject to the ATS recommended criteria (FEV1/FVC ratio < LLN) and also the FEV1/FEV6 to its NHANES III lower limit of normal.

**Methods Used:** Only results from post bronchodilator spirometry were used so that asthmatic subjects with significant airway reactivity were excluded. The ndd spirometers (Zurich, Switzerland) measured FEV6 values from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria: FEV1/FVC ratios <70%. Severity is classified from percent predicted FEV1 (%PreFEV1). Using lower limits of normal (LLN) calculated from the NHANES III normal data set for both the FEV1/FVC and the FEV1/FEV6 ratios, we compared the GOLD classification on each subject to the ATS recommended criteria (FEV1/FVC ratio < LLN) and also the FEV1/FEV6 to its NHANES III lower limit of normal.

**Conclusions:** IL-6 causes a significant decrease in electrical resistance in intestinal epithelium.
15.3% of the subjects change classification when using other classification criteria. Using the GOLD criteria classifies more participants as having COPD than either the FEV1/FVC or FEV1/FEV6.

145 USE OF CUFFED OR UNCUFFED ENDOTRACHEAL TUBES IN PEDIATRIC BURN PATIENTS: A 10-YEAR REVIEW
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University of Washington School of Medicine, Seattle, WA. 2University of Arkansas for Medical Sciences, Little Rock, AR and 3Harborview Medical Center, Seattle, WA.

Purpose of Study: Uncuffed endotracheal tubes (UETTs) have been traditionally preferred over cuffed endotracheal tubes (CETTs) in pediatric patients to prevent subglottic tracheal injury. However, UETTs may complicate airway management and ventilation in burn-injured children due to risks of difficult reintubation (e.g., presence of face/neck burns) and hypoventilation (e.g., inhalation injury requiring high ventilation pressures) if too small a tube is chosen. To quantify their relative risks, we reviewed and compared adverse event rates associated with the perioperative use of UETTs and CETTs in a large sample of pediatric burn patients.

Methods Used: We retrospectively reviewed 329 cases of operating room endotracheal intubation of children 0-10 years of age admitted to our regional burn center over a 10-year period. Patient demographics, injury characteristics, and clinical information were abstracted from medical records, including adverse events of clinically significant air leak, need for endotracheal reintubation, post-extubation stridor, and failed extubation. We compared outcomes using multivariable logistic regression, controlling for age, sex, face/neck burns, and burn severity.

Summary of Results: CETTs were used for 105 intubations and UETTs were used for 93 intubations (131 were indeterminate). Comparing CETTs and UETTs, respectively, there were no significant differences in the rates of stridor (7.6% v. 4.3%) or failed extubation (1.9% v. 3.2%). Controlling for demographic and clinical characteristics, patients receiving UETTs were significantly more likely to experience clinically significant air leaks than those with CETTs (OR 29.2, 95% CI 6.0, 141.6), and immediate reintubation was required much more frequently with UETTs (OR 12.0, 95% CI 4.4, 32.4).

Conclusions: Our data suggest that perioperative use of UETTs in pediatric burn patients is associated with substantially increased rates of unacceptable air leak and reintubation. Due to the frequent challenge of airway and ventilation management in these children, this practice should be reconsidered to allow this population access to the potential benefits of modern high-volume, low-pressure CETTs.

146 MESenchymAL STEM CELLS ENHANCE BACTERIAL CLEARANCE AND REDUCE MORTALITY AND LUNG INJURY FROM E. COLI PNEUMONIA
N. Gupta, M.A. Matthay University of California, San Francisco, San Francisco, CA.

Purpose of Study: We have previously demonstrated that mesenchymal stem cells (MSC) have a protective effect in the endotoxin model of acute lung injury (ALI) in mice that is related to their immunosuppressive properties (Gupta et al, J Immunology, 2007). Here we test the effects of MSC in a live bacterial model of ALI since bacterial infection is the most common cause of clinical ALI.

Methods Used: 27BL/6 male mice (Jackson Labs, 25-30 grams) were used for all experiments. Mice were first injured with E. coli (106 cfu/mouse) given intratracheally (IT) and then allowed to recover. Four hours later, mice were given treatment with either MSC (750,000 cells/30 μl of PBS) or PBS (30 μl). Mice were then followed over 24-48 hours before collection of samples for determination of lung injury as measured by excess lung water and bacterial colony counts. Survival over this time period was also noted in each group.

Summary of Results: MSC treated mice had a significant improvement in survival at 48 hours compared to PBS treated mice (55% vs 0%, n = 11-13 per group, P = 0.01). Also, at 48 hours, MSC treated mice had a significant reduction in the severity of lung injury as measured by excess lung water (156 ± 63 vs 204 ± 41 μl, n = 10-12 per group, P = 0.05). This protection was associated with enhanced bacterial clearance from the lung at 24 hours, in MSC treated mice (1.3 × 106 ± 0.6 × 106 vs 3.5 × 106 ± 1.6 × 106 cfu/ml, n = 5-6 per group, P = 0.01).

Conclusions: MSC protect against E. coli pneumonia induced ALI by reducing the severity of lung injury and improving survival at 48 hours. This protection is associated with enhanced bacterial clearance from the lung in the MSC treated mice. These results suggest a novel role of MSC in the immune response against bacterial infection.

147 DETECTION OF PLEURAL MALIGNANCIES USING GRIN LENS BASED 3D SWEPT SOURCE OPTICAL COHERENCE TOMOGRAPHY
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Purpose of Study: To determine the feasibility of rapid thoracoscopic GRIN lens based 3D swept source (SS) optical coherence tomography (OCT) for real time in-vivo high resolution (10 μm) imaging of pleural based malignancies in an animal model. The dynamic focusing range and ability to rapidly capture images, along with the static design of the probe, makes it an ideal diagnostic tool.

Methods Used: Rabbits weighing 3-4 kg were using in this study. VX2 carcinoma cells were implanted using a thoracoscopic technique. Approximately 12 x 106 cells were applied to an abraded area of the pleura. 15-18 days after implantation, the animals underwent a second thoracoscopic surgery and OCT was performed using the prototype GRIN lens based 3D SS system we developed in our laboratory on any tumors or abnormalities that were seen. Upon sacrifice, the imaged areas were excised for histological sectioning and H&E staining.

Summary of Results: The GRIN lens based 3D SS system at 30 frames per second with 512 A-lines per frame was able to capture images of and detect airway abnormalities during thoracoscopy in numerous areas, including the pleura, chest wall, pericardium, and the lungs. The abnormalities were confirmed by histological evaluation and compared to the OCT findings.

Conclusions: The dynamic focusing range and rapid speed of this prototype system allowed for near histologic resolution imaging of pleural based malignancies. The imaging probe of the system was found to be easily adaptable to various sites within the thoracic cavity. The ability of OCT to detect abnormalities and optically and noninvasively guide biopsies may provide an increased yield in early detection of cancer in the pleura and can be readily adapted to other sites including rigid airway examinations.

148 PRIMARY AORTOBRONCHIAL FISTULA
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Case Report: Purpose of Study: The purpose of this study is to present a unique case of primary aortobronchial fistula diagnosed after the discovery of air within the false lumen of a thoracic aortic aneurysm on chest computed tomography in a patient who presented with fever and hemothorax.

Methods Used: Case Report.

Summary of Results: A 49-year-old male with a DeBakey III thoracic aortic aneurysm presented to the emergency department with fever and hemothorax for three weeks. He denied any epistaxis, hematemesis, melena, or tuberculosis risk factors. Laboratory results demonstrated anemia and leukocytosis. Chest computed tomography performed two months prior to

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149 FLUCTUATIONS IN BLOOD GLUCOSE LEVELS DURING HYPERBARIC OXYGEN THERAPY
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Purpose of Study: To observe the fluctuations in blood sugar levels in subjects undergoing hyperbaric oxygen (HBO) therapy.

Methods Used: Blood glucose monitoring was performed using a finger prick test before and after each HBO treatment. Patients underwent hyperbaric oxygen therapy for a variety of indications: compromised graft, diabetic foot ulcer, refractory osteomyelitis, and soft tissue radionecrosis. Both diabetics and non-diabetics were included in the study.

Summary of Results: 110 treatments were conducted on 14 patients (13 males and 1 female) with an average age of 60. [see table].

Conclusions: There were significant differences in pre- and post-treatment blood glucose levels of patients undergoing hyperbaric oxygen therapy when calculated overall as well as in diabetics and non-diabetics considered separately. Continued investigation with a larger patient population is in progress.

Blood Glucose Levels (mg/dL) Before and After HBO Therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>135.53</td>
<td>120.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetics</td>
<td>186.63</td>
<td>165.60</td>
<td>0.007</td>
</tr>
<tr>
<td>Non-diabetics</td>
<td>116.09</td>
<td>103.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2.5 atm</td>
<td>115.32</td>
<td>106.12</td>
<td>0.068</td>
</tr>
<tr>
<td>2.0 atm</td>
<td>141.21</td>
<td>125.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean in last hour</td>
<td>119.77</td>
<td>100.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No meal</td>
<td>140.60</td>
<td>128.13</td>
<td>0.001</td>
</tr>
<tr>
<td>No juice or water only</td>
<td>144.64</td>
<td>126.55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cranberry juice</td>
<td>133.52</td>
<td>118.22</td>
<td>0.012</td>
</tr>
<tr>
<td>Orange juice</td>
<td>126.90</td>
<td>110.65</td>
<td>0.056</td>
</tr>
<tr>
<td>Apple juice</td>
<td>116.10</td>
<td>118.80</td>
<td>0.780</td>
</tr>
</tbody>
</table>

*p-values calculated using paired t-tests for pooled means.

150 OP-1 ENHANCES OSTEOGENESIS IN OSTEOPROGENITOR CELLS CHALLENGED WITH POLYMETHYL METHACRYLATE PARTICLES
R. Chiu, S. Kann, T. Ma, S. Goodman Stanford University School of Medicine, Stanford, CA.

Purpose of Study: Periprosthetic osteolysis results in part from the biologic reactions of bone cells and osteoprogenitors to orthopedic wear debris. Previous studies have shown that polymethylmethacrylate (PMMA) particles inhibit the differentiation, proliferation, and mineralization of osteoprogenitor cells in vitro. OP-1 (BMP-7), a growth factor that induces bone formation, may potentially stimulate osteogenesis in osteoprogenitor cells inhibited by PMMA particles. In this study, we exposed MC3T3-E1 osteoprogenitor cells challenged with PMMA particles to OP-1, and analyzed the time-dependent effects of this growth factor on the osteogenesis of these cells.

Methods Used: Confluent cultures of MC3T3-E1 osteoprogenitor cells (ATCC) were challenged with PMMA particles (10 μm, Polysciences) at doses of 0.000, 0.075, 0.150, and 0.300% v/v for 20 days, starting from the first day (Day 1) of differentiation in osteogenic medium. These cells were treated with OP-1 (200 ng/ml) during the following days of osteogenic culture/particle treatment: (1) days 1-20, (2) days 4-20, and (3) days 1-4. Control cells were challenged with PMMA particles throughout this 20-day period but were not exposed to OP-1. Mineralization was measured by von Kossa staining with NIH Imaging quantification of the total area of stained matrix after the 20-day culture period.

Summary of Results: MC3T3-E1 cells challenged with PMMA particles showed a dose-dependent decrease in mineralization. The exposure of these cells to OP-1 during days 1-20, 4-20, and 1-4 of culture/particle treatment resulted in significant increases in mineralization. At each particle dose, cells treated with OP-1 at these different time periods showed similar levels of increased mineralization, which signifies that the first four days of osteogenic differentiation (days 1-4) was a sufficient time window for osteoprogenitor cells to respond to the stimulatory effects of OP-1.

Conclusions: This study has shown that OP-1 stimulates the osteogenesis of MC3T3-E1 osteoprogenitor cells that have been inhibited by PMMA particles in vitro. Clinically, the administration of OP-1 to the site of osteolysis in total joint replacement may increase bone formation by stimulating the osteogenic differentiation of osteoprogenitor cells.

151 PROLONGING CARDIAC ALLOGRAFT SURVIVAL WITH DONOR MHC I ALPHA-1 HELICAL PEPTIDES
J. Nguyen1, N. Semiletova2, J. Kapucic-Weglinski2 1David Geffen School of Medicine at UCLA, Los Angeles, CA and 2The Dumont-UCLA Transplant Center, Los Angeles, CA.

Purpose of Study: Chronic rejection of cardiac allografts is dependent on the active recognition of donor antigens by the recipient’s immune system. Alloreactive antibodies produced by the host recognize the MHC I molecules expressed on the graft endothelial cells. We hypothesized that altering recipient humoral immunity by introducing donor MHC I alpha-1 helical peptides would attenuate chronic cardiac allograft rejection.

Methods Used: Transplanted cardiac allografts were harvested from inbred BUF, WF, LEW, and PVG rats and transplanted into ACI rats. In the experimental group, donor peptides were administered by portal vein at day 0 and subtherapeutic levels of Cyclosporine (CsA) (10 mg/kg/day) was administered over days 0-2 (n = 37). A control group included ACI rats that did not receive a transplant (n = 3). A second control group included ACI recipients that received syngeneic grafts (n = 3). A third control group included allograft recipients that were only treated with CsA (10 mg/kg/day) over days 0-7 (n = 3). Allografts were harvested and examined on day 120.

Summary of Results: Donor peptides induce donor specific tolerance and prolonging transplant survival (P < 0.05). Peptide therapy downregulates expression of the pro-apoptotic proteins BAX and caspase-3, thus promoting allograft survival (P < 0.07). We observed that donor peptides significantly upregulated the anti-inflammatory cytokine IL-10 (P < 0.01) while down-regulating IL-4 (P < 0.08).

Conclusions: Our present findings suggest that the attenuation of vasoactive amine release and the local immune response may explain how donor peptides prolong allograft survival. This novel immunotherapeutic approach...
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BENEFICIAL EFFECTS OF EXERCISE ON PROGRESSION OF ABDOMINAL AORTIC ANEURYSM

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Purpose of Study: Abdominal aortic aneurysm (AAA) is a pathological thickening of the infrarenal aorta often accompanied by atherosclerosis, inflammation, and thrombosis. Chronic physical exercise may be beneficial in the pathobiology of AAA due to its effects on local blood flow and inflammatory gene expression. The objective of this study was to determine whether an exercise regimen protects against AAA expansion by modulation of gene expression.

Methods Used: C57Bl6 ApoE-/- mice (8 wks) were subcutaneously implanted with mini-osmotic pumps containing angiotensin II at a constant infusion rate of 1000 ng kg-1 min-1. Exercising mice ran 12 m/min on motorized treadmill for 30 minutes per day, 5 days a week for one week before pump implantation and then for the study duration. Nonexercising mice were implanted with angiotensin II pumps and placed on a non-moving treadmill. Ultrasound was used to measure in vivo aortic diameter at 0, 7, 14, 21, and 28 days using transverse short-axis views. Mice were sacrificed at 28 days for RT-PCR or histological analysis by H&E stain. Statistical significance was determined by unpaired t-test, with results reported as significant when P < 0.05.

Summary of Results: AAA growth was significantly decreased in the exercise versus control group at 7 [1.29±1.12 mm (n = 20) vs. 1.51±0.37 mm (n = 16)], 14 [1.33±1.12 mm (n = 13) vs. 1.74±0.54 mm (n = 10)] and 21 [1.5±2.25 mm (n = 13) vs. 1.80±0.59 mm (n = 10)] days. Histological analysis revealed reduced intimal thickening in the exercise group compared to control group, which ranged from marked intimal thickening to dissection and humatoma. RT-PCR analysis showed a significant 5.74±3.08 fold change in eNOS, 20±0.9 fold change in MCP-1, and 42±23 fold change in VCAM-1 for exercise (n = 5) vs. control group (n = 8) at 28 days.

Conclusions: Exercise is beneficial in attenuating the rate of AAA expansion with less severe and extensive pathology in the aortic wall. While eNOS is increased with exercise, there is evident down-regulation of inflammatory genes on a chronic basis. Further studies will elucidate the mechanism by which exercise mediates anti-inflammatory effects.

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SMALL INTESTINAL LENGTHENING BY MECHANICAL EXPANDER IN RATS WITH SHORT BOWEL

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Purpose of Study: Small intestinal lengthening may be achieved by the application of a mechanical expander in the setting of short bowel, while maintaining intestinal enzymatic activity in lengthened segments.

Methods Used: Seventeen female Sprague Dawley rats underwent 76% small bowel resection and were allowed to adapt for 6 weeks. The animals underwent the placement of a mechanical expander device with or without gradual mechanical lengthening. After 3 weeks, the intestinal segments were retrieved for analysis of enzymatic activities and histological parameters.

Summary of Results: Intestinal segments were lengthened 2.5-fold (P < 0.05). Specific alkaline phosphatase activity was 0.18 ± 0.07 μmol/mg-min in isolated intestinal segments without mechanical lengthening and 0.21 ± 0.05 μmol/mg-min in the mechanically lengthened segments (P < 0.05). Specific lactase activity was 0.0003 ± 0.0003 μmol/mg-min in isolated intestinal segments and 0.0002 ± 0.0002 μmol/mg-min in the mechanically lengthened segments (P < 0.05). The total lactase activity was 2.4 ± 0.5 μmol/min in the isolated intestinal segments and 4.9 ± 2.3 μmol/min in the mechanically lengthened segments (P > 0.05). The total lactase activity was 0.005 ± 0.005 μmol/min in the isolated intestinal segments without mechanical lengthening and 0.007 ± 0.007 μmol/min in the mechanically lengthened segments (P > 0.05). Smooth muscle thickness was 372 ± 137 μm in the isolated intestinal segments and 526 (212 μm in the mechanically lengthened segments (P < 0.05).

Conclusions: Mechanical small bowel lengthening may be completed in rats with short bowel. Results also indicate a concomitant sustained specific enzyme activity and an increase in the total enzymatic activity in the lengthened segments, indicating preservation of enzymatic activity and a potential for increased function.

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POLYMETHYL METHACRYLATE PARTICLE-INDUCED SUPPRESSION OF OSTEOPROGENITOR DIFFERENTIATION INVOLVES IMPAIRMENT OF OSTEOPROGENITOR VIABILITY BY NECROSIS

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

Purpose of Study: Osteolysis in total joint replacement is mediated in part by biologic reactions of bone cells to orthopedic wear debris. Recently, particles of polymethylmethacrylate (PMMA) bone cement have been shown to inhibit the osteogenic differentiation of osteoprogenitor cells. However, the mechanism of this inhibitory effect has not been investigated. The purpose of this study was to determine whether the inhibition of osteoprogenitor differentiation by PMMA particles involves impairment of cell viability by necrosis or apoptosis.

Methods Used: Confluent cultures of MC3T3-E1 osteoprogenitor cells (ATCC) in non-osteogenic (ascorbic acid-free) medium were treated with PMMA particles (1-10 μm, Polysciences) at doses of 0.006, 0.038, 0.075, 0.150, 0.300, and 0.600% v/v for 72 hrs. Culture supernatant levels of lactate dehydrogenase (LDH), an intracellular enzyme released from dead cells, were measured at 24-hr intervals. The number of viable adherent cells was determined at similar time intervals by hemocytometer cell count with trypan blue staining. Particle effects on proliferation were assessed by incubating cells in BrdU for 24 hrs following particle pre-treatment for 24, 48, and 72 hrs, with subsequent measurement of BrdU uptake. A TUNEL assay was performed to detect apoptotic cells in MC3T3-E1 cultures at each time interval.

Summary of Results: MC3T3-E1 cells challenged with PMMA particles showed a significant dose- and time-dependent increase in LDH release and significant dose-dependent decreases in cell number and BrdU uptake. MC3T3-E1 cells showed evidence of particle phagocytosis, swelling, and lysis, as observed under the microscope. TUNEL assay revealed no apoptotic cells in particle-treated cultures.

Conclusions: This study has shown that PMMA particles induce osteoprogenitor cell death, as evidenced by the increase in LDH release and the decreases in cell number and BrdU uptake. Evidence of cell swelling and lysis, a characteristic of necrosis, and the absence of apoptotic cells in the TUNEL assay indicate that cell death occurs by necrosis, not apoptosis. Osteolysis induced by implant wear debris therefore involves not only inflammation and bone destruction, but also decreased osteoblast production by particle-induced osteoprogenitor necrosis.

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ARTHRODESIS OF THE FIRST METATARSOPHALANGEAL JOINT: A ROBOTIC CADVERIC STUDY OF DORSIFLEXION ANGLE

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Purpose of Study: Arthrodesis of the first metatarsophalangeal joint (MTPJ) is indicated for severe osteoarthritis or as a revision of failed surgeries. Studies have suggested an optimum dorsiflexion angle (DA) between 20 and 25 degrees. The goal of our study was to investigate a correlation between angle and plantar pressure in postoperative gait. We hypothesized that there exists a fused DA at which pressures are minimized under the hallux and the head of the first metatarsal (MTH).

Methods Used: Six cadaveric foot specimens underwent incremental dorsiflexion by angle. The specimens were imaged and then for the study duration. Nonexercising mice were implanted with angiotensin II pumps and placed on a non-moving treadmill. Ultrasound was used to measure in vivo aortic diameter at 0, 7, 14, 21, and 28 days using transverse short-axis views. Mice were sacrificed at 28 days for RT-PCR or histological analysis by H&E stain. Statistical significance was determined by unpaired t-test, with results reported as significant when P < 0.05.

Summary of Results: Intestinal segments were lengthened 2.5-fold (P < 0.05). Specific alkaline phosphatase activity was 0.18 ± 0.07 μmol/mg-min in isolated intestinal segments without mechanical lengthening and 0.21 ± 0.05 μmol/mg-min in the mechanically lengthened segments (P < 0.05). Specific lactase activity was 0.0003 ± 0.0003 μmol/mg-min in isolated intestinal segments and 0.0002 ± 0.0002 μmol/mg-min in the mechanically lengthened segments (P < 0.05). The total alkaline phosphatase activity was 2.4 ± 0.5 μmol/min in the isolated intestinal segments and 4.9 ± 2.3 μmol/min in the mechanically lengthened segments (P > 0.05). The total lactase activity was 0.005 ± 0.005 μmol/min in the isolated intestinal segments without mechanical lengthening and 0.007 ± 0.007 μmol/min in the mechanically lengthened segment (P > 0.05). Smooth muscle thickness was 372 ± 137 μm in the isolated intestinal segments and 526 (212 μm in the mechanically lengthened segments (P < 0.05).

Conclusions: Mechanical small bowel lengthening may be completed in rats with short bowel. Results also indicate a concomitant sustained specific
Conclusions: An understanding of the optimum fused DA may prevent abnormal plantar pressures following arthrodesis. Our findings support the hypothesis that an angle-pressure relationship exists, and the regressions indicate that it is inversely related for the hallux and the MTH. The suggested range of 20 to 25 degrees encompasses our results.

Methods Used: We used 16 skeletally mature, female sheep to reproduce a chronic, RC injury. The infraspinatus tendon was identified and resected along its attachment to the humerus and covered with Gore-Tex to minimize reattachment. We reoperated on the sheep 6 weeks later and reattached the infraspinatus using coated suture. Fiberwire was coated with PDGF using the dip-coating process. The sheep were confined and euthanized at 6 weeks to excise the infraspinatus. We quantified the structural properties in the repaired tendons while loading to failure. Failure was defined as catastrophic failure of the repaired specimens resulting in separation of the tendon/suture interface resulting in the suture pulling through the tendon. Two specimens failed within the substance of the scar tissue distal to the repair site. The stiffness and ultimate load of the coated sutures were 622 ± 117.66 N and 1726.45 N, respectively. The stiffness and ultimate load of the uncoated control sutures were 37.94 ± 4.37 N and 1581.37 ± 70.19 N, respectively. The moduli and ultimate stress of the PDGF specimens were 37.94 ± 5.10 and 2.37 ± 0.20 MPa, respectively. Controls resulted in failure of the suture in 2-3 weeks, with both the tissue distal to the repair. The stiffness and ultimate load of the standard sutures were 305.19 ± 0.9324 and 1.74 ± 2.25 MPa, respectively. The stiffness and ultimate stress were 1.74 and 2.25 MPa, respectively. The modulus and ultimate stress of the PDGF specimens were 37.94 ± 5.10 and 2.37 ± 0.20 MPa, respectively.

Conclusions: Compared to conventional non-outflow cannulae, fenestrated outflow cannulae allow for procedures of longer duration and more arthroscopic irrigation fluid to be used without the associated weight gain seen with traditional cannulae. We recommend routine use of fenestrated outflow cannulae.

Purpose of Study: Soft tissue fluid retention is a relatively common problem following arthroscopy, with 2% of patients developing severe problems, such as soft tissue edema to skin necrosis, neuropathy, and intraoperative loss of airway. Recently, a fenestrated outflow cannula has been introduced (Cannuflow, San Jose, CA), intended to reduce interstitial swelling seen during arthroscopic procedures. We aim to test the effectiveness of this fenestrated outflow cannula design in minimizing fluid weight gain seen after shoulder arthroscopy.

Methods Used: After obtaining IRB approval, we enrolled 28 consecutive patients undergoing shoulder arthroscopy and randomized them into two groups using two different types of cannulae: Fenestrated and Conventional. The weight gain attributable to arthroscopy was obtained by calculating input/output differences. Patient data collected included age, sex, BMI, shoulder diagnosis, and type of procedure. Surgical factors included patient positioning, case duration, and arthroscopy irrigation fluid volume used. Patient and surgical factors of the two groups were compared using Student’s t-test and chi-squared analysis. Linear regression was performed for both the Fenestrated and Conventional groups to assess the fluid weight gained based on duration of procedure and irrigation fluid used, with slope comparisons based on t-distributions.

Summary of Results: Both groups of patients were comparable by patient and surgical factors (P > 0.05, all variables). For weight gain as a function of fluid volume, the Conventional group showed a significantly greater slope than the Fenestrated (slope = 0.0216 ± 0.0378 vs. 0.0021 ± 0.3405, P = 0.041). For weight gain as a function of procedure duration, the Conventional group showed a significantly greater slope than the Fenestrated (slope = 0.5416 ± 0.1599 vs. 0.0144 ± 0.9324, P = 0.049).

Conclusions: Compared to conventional non-outflow cannulae, fenestrated outflow cannulae provide procedures of longer duration and more arthroscopic irrigation fluid to be used without the associated weight gain seen with traditional cannulae. We recommend routine use of fenestrated outflow cannulae.

Purpose of Study: Endoscopic Third Ventriculostomy (ETV) has been introduced (Cannuflow, San Jose, CA), intended to reduce interstitial swelling seen during arthroscopic procedures. We aim to test the effectiveness of this fenestrated outflow cannula design in minimizing fluid weight gain seen after shoulder arthroscopy.

Methods Used: After obtaining IRB approval, we enrolled 28 consecutive patients undergoing shoulder arthroscopy and randomized them into two groups using two different types of cannulae: Fenestrated and Conventional. The weight gain attributable to arthroscopy was obtained by calculating input/output differences. Patient data collected included age, sex, BMI, shoulder diagnosis, and type of procedure. Surgical factors included patient positioning, case duration, and arthroscopy irrigation fluid volume used. Patient and surgical factors of the two groups were compared using Student’s t-test and chi-squared analysis. Linear regression was performed for both the Fenestrated and Conventional groups to assess the fluid weight gained based on duration of procedure and irrigation fluid used, with slope comparisons based on t-distributions.

Summary of Results: Both groups of patients were comparable by patient and surgical factors (P > 0.05, all variables). For weight gain as a function of fluid volume, the Conventional group showed a significantly greater slope than the Fenestrated (slope = 0.0216 ± 0.0378 vs. 0.0021 ± 0.3405, P = 0.041). For weight gain as a function of procedure duration, the Conventional group showed a significantly greater slope than the Fenestrated (slope = 0.5416 ± 0.1599 vs. 0.0144 ± 0.9324, P = 0.049).

Conclusions: Compared to conventional non-outflow cannulae, fenestrated outflow cannulae allow for procedures of longer duration and more arthroscopic irrigation fluid to be used without the associated weight gain seen with traditional cannulae. We recommend routine use of fenestrated outflow cannulae.
159 OCULAR COMPLICATIONS FOLLOWING MINIMALLY INVASIVE UROLOGIC SURGERY

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Purpose of Study: Ocular complications (OC) including optic irritation and corneal abrasion (CA) have been sporadically reported after open surgery. The incidence of OC following minimally invasive surgical procedures has not been well documented. Minimally invasive surgery such as robotic prostatectomy for prostate cancer and laparoscopic kidney procurement may result in an increased risk of OC due to head-down (Trendelenburg) positioning and aggressive hydration, respectively. The purpose of this study was to evaluate the incidence of OC and CA following robotic prostatectomy (RP), hand-assisted laparoscopic donor nephrectomy (HALDN), and hand-assisted laparoscopic nephrectomy (HALN).

Methods Used: A chart review was conducted of 387 consecutive patients (191 RP, 141 HALDN, and 55 HALN) over a 3-year period. Ocular complications were strictly defined as any oculomotor complaint requiring treatment orophthalmologic consultation. Corneal abrasions were diagnosed by ophthalmologic consultation. Binary logistic regression and chi-square tests compared the incidence of OC and CA by group with P < 0.05 considered significant.

Summary of Results: OC were observed in 5.2% of RP patients (OR 1.46; P = 0.63), 6.4% of HALDN patients (OR 1.81; P = 0.46) and in 3.6% of HALN patients (reference). All documented OC in HALDN patients involved the dependent eye (P < 0.001) suggesting fluid overload and chemosis as potential contributing mechanisms to OC. CA occurred in 3 RP (1.6%) and 2 HALDN (1.4%) patients compared to no HALN patients (P = 0.65). No patients suffered long-term ophthalmologic sequelae.

Conclusions: A small but significant number of patients treated with minimally invasive urologic surgery developed OC. Although not statistically different, RP with its prolonged Trendelenburg position, and HALDN with the aggressive hydration (given to maximize kidney function) resulted in higher incidence of OC compared to HALN. All OC following HALDN involved the dependent eye, further supporting conjunctival edema as a potential etiology. The relatively high incidence of OC in minimally invasive urologic surgery highlights the importance of further study to determine the precise mechanisms of injury and techniques to prevent these complications.

160 EVALUATING OUTCOMES OF CRANIAL VAULT REMODELING SURGERY FOR CRANIOSYNOSTOSIS: USING 3D PHOTOGRAMMETRY FOR QUANTITATIVE ANALYSIS

N. Jourabchi, J. Bradley David Geffen School of Medicine at UCLA, Los Angeles, CA.

Purpose of Study: Craniosynostosis affects infants, causing cranial sutures to close early and restrict brain and skull growth. This results in skull deformity and increased intracranial pressure, causing blindness, mental retardation, and other anomalies. Treatment is cranial vault surgery and post-operative helmet molding therapy. To date, computed tomography (CT) has been the primary mode of obtaining accurate quantitative data for the assessment and evaluation of craniosynostosis, although it is associated with potentially harmful radiation and need for sedation. Since craniosynostosis can be effectively diagnosed with an initial plain x-ray, we aim to replace the use of CT with noninvasive 3D surface imaging for pre- and post-operative evaluations.

Methods Used: We used the 3DM photoangular imaging system to perform 3D surface imaging that is precise and noninvasive. 3D photogrammetry uses two digital cameras in triangulation configuration to acquire 3D surface geometry and texture. The system then integrates the images obtained through algorithms to produce a 180 degree 3D image. Using a lifelike doll, we utilized the 3DiMD camera and PC based software to create the 3D images and develop a protocol for 3D cranial image acquisition, measurement, and analysis.

Summary of Results: 3D Cranial landmarks, measurements, and image-acquisition for 3D photogrammetry had not yet been described. We have described ten anthropometric cranial landmarks, as well as linear, surface, and volume measurements, and four 3D image capture views for 3D cranial analysis. We have also developed a standard protocol for 3D cranial image acquisition, measurement, and analysis.

Conclusions: We have developed a standard protocol for 3D cranial image acquisition, measurement, and analysis and will use this protocol to: 1) assess craniofacial shape and volume in craniosynosostis patients before and after surgery, 2) determine the best treatment and evaluate the outcome of the treatment, and 3) develop a standard protocol for providing the best and least invasive treatment for craniosynosostis. Previous studies have used CT to evaluate quantitative outcomes of treatment for craniosynosostis. Our study uses 3D photogrammetry as a safer alternative because CT is associated with harmful radiation exposure and need for sedation in infants.

Western Student Medical Research Forum
Student Scientific Session I
8:30 AM
Friday, January 30, 2009

161 DECREASING INTIMATE PARTNER VIOLENCE IN ALASKA’S KENAI PENINSULA THROUGH AWARENESS AND RESOURCE EDUCATION

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Purpose of Study: Intimate partner violence is a significant problem in Alaska, where rates of domestic violence and rape are substantially higher than the US as whole. Discussions with Kenai Peninsula health care providers revealed a deficit in comprehensive knowledge of local intimate partner violence resources, which created a barrier in patient screening and treatment. A resource guide and information session was designed to increase provider awareness and improve intimate partner violence screening, safety planning and knowledge of local resources.

Methods Used: A literature review was performed to investigate the efficacy of intimate partner violence screening methods and determine how best to improve screening rates by physicians and staff. Meetings were held with local domestic violence and sexual assault assistance programs to gather first hand data about available resources. Additionally, inquiries were made with clinic staff regarding specific needs for effectively aiding and referring victims of intimate partner violence.

Summary of Results: Identifying local resources for victims of domestic violence and sexual assault was recognized as a high priority for the Kenai Peninsula. Resource guides were prepared which addressed screening, safety planning, local referrals and numerous hotlines for victims. These single sheet, easily concealable guides were stocked in bathrooms and exam rooms for use by patients. The resource guide also served as a reference tool for providers. An information session was provided for clinic staff regarding the resource guide contents and its practical uses. Feedback from staff was positive, enthusiastic and thankful.

Conclusions: Intimate partner violence screening and education are successful tools in combating domestic violence and sexual assault. Educating providers on screening methods and safety planning, as well as equipping them with referral information has been shown to be effective in helping victims break free from violent relationships. Health care providers in the Kenai Peninsula look forward to incorporating the resource guide into daily use, and anticipate more success in combating domestic violence and sexual assault.

162 Hepatitis B Provider Protocols and Patient Education

E.D. Prince University of Washington School of Medicine, Seattle, WA.

Purpose of Study: Hepatitis B is the most common serious liver disease in the world, affecting 1 out of 20 people. The Asian American and Pacific Islander population served by the International Community Health Centers (ICHS) clinics of Seattle has a higher than average rate of chronic hepatitis B infection, up to 1 in 10 patients. This community stands to benefit from health interventions, both through evidence-based provider practices and improved patient education.

Methods Used: Hepatitis B was identified as an important health issue in the ICHS patient population through discussion with clinic practitioners. A literature review was conducted, and evidence based practices were condensed into two projects for two target populations. A revised assessment and treatment protocol was developed for physicians summarizing clinical guidelines for managing hepatitis B patients, depending on patient risk factors and disease
state. For patients and their families, a brochure was created which summarized basic facts about hepatitis B in an easily-accessible manner.

Methods: Our results are unique because we were able to review the revised hepatitis B protocol, which, after further work will be incorporated into the clinic’s operational guidelines. The brochure was also sent for further review and, with approval, may be translated into multiple languages for the diverse patient population of ICHS.

Conclusions: Hepatitis B infection is disproportionately high among Asian American and Pacific Islander populations. These populations stand to benefit from greater education on this issue. With increased use of evidence-based practices by providers and improved patient education services it is hoped that the morbidity, mortality and future incidence of this disease can be decreased.

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A COLLABORATIVE COMMUNITY HEALTH PROJECT AIMED AT REDUCING THE PREVALENCE OF DENTAL DISEASE

University of British Columbia, Vancouver, BC, Canada.

Purpose of Study: The Spiti Valley is an isolated region located in the Indian Himalayas with poor access to sustainable health care. In collaboration with local leaders, Global Health Initiative (GHI) from the University of British Columbia (UBC), conducted general health screens at a boarding school for children. Our aim was to identify the contributing factors of dental caries and develop a sustainable program to improve dental health.

Methods Used: General health screen stations were established to assess all 377 students. During the physical exam, students were assessed and triaged by UBC medical students and treated by Australian dentists from a non-governmental organization. A survey was conducted to evaluate the contributing factors of dental caries and oral hygiene habits. Subsequently, toothbrushes and fluoridated toothpaste were distributed, and storage units were built. In collaboration with school staff and caregivers, dental hygiene lesson plans were created for 3 age groups. Education sessions included rationale, technique, and consequences of not brushing. Visual aids and student volunteers were used to demonstrate brushing technique and to engage the class. To establish a routine and reinforce proper technique, GHI supplied toothbrushes daily with the children.

Summary of Results: Poor technique and lack of regular dental hygiene were contributing factors to dental caries. A survey of 198 children showed the following: 39% brushed once per day; 18% brushed several times per week; 9% brushed several times per month; and 39% never brushed. Other factors included increased candy intake, lack of brushes, and use of non-fluoridated toothpaste. The effectiveness of the educational component was measured using DMFS (decayed/moving filled teeth) assessments. The effectiveness of the program was evaluated next year when the GHI team returns to Spiti Valley. In light of the visible benefits, the dental health program will be implemented into the school curriculum and the administration will continue to finance all necessary supplies.

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COMMUNITY BUY-IN TO GLOBAL DENTAL HEALTH VOLUNTEER FIELD TRIPS

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University of British Columbia, Vancouver, BC, Canada.

Purpose of Study: In 2008, two dental students from University of British Columbia and a BC licensed dentist traveled to a rural Ugandan community to create a collaborative dental health program in an orphanage. Dental health questionnaires, height and weight, caries assessment/treatment, and oral health education were carried out. Involvement of community members expanded project implementation and goal achievements.

Methods Used: The orphanage director, school principal, teachers, local dentists and local dental therapists were active in the program. Participation included: 1) clinical director/school principal/teachers 2) measurements (Ht/Wt), questionnaires/dmfs (decayed missing filled teeth) assessments 3) teachers/ interview children in local language 4) educators: local dental therapists/teachers 5) local dental therapists for treatment. In 2 weeks, 94 children were surveyed and assessed. A brush-in program was created by teachers. Urgent dental needs (extractions/ART- traumatic restorative technique restorations) were addressed. Supplies were purchased locally. Canadian dentist and dental students, and a Ugandan dentist completed DMFS surveys in 3 days. 1) Ugandan children seen will continue to improve as teachers, local dentists and the community become actively involved in their children’s health.

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IMPROVING AVAILABILITY OF HEALTH CARE TO WORKERS ABOARD FISHING VESSELS BY PROMOTING A BOAT VISIT PROGRAM

T. Kelly
University of Washington, Seattle, WA.

Purpose of Study: Dutch Harbor lies 800 air miles from Anchorage on Alaska’s Aleutian chain and has been the largest fisheries port in the United States since 1981. Large fishing vessels employing hundreds of workers from all over the world spend an average of 24 hours in port between 14-30 day voyages. Very limited health care is available to the workers while at sea and it can be difficult for them to seek care while in port. A program was designed to improve access to health care while in port for the workers aboard fishing vessels.

Methods Used: A literature review was completed to investigate barriers to health care for migrant workers. Discussions with boat captains, pursers, and fishers aboard in Dutch Harbor revealed lack of time as a major reason for not seeking medical care. An outreach program was designed to promote Ililiuk Clinic’s under-used boat visit program which saves time by bringing clinicians directly to the vessels. Contacts were made at the private port facilities and the city harbor to educate land-based liaisons regarding the boat visit program. Brochures were designed to familiarize pursers, captains, and fishing vessels administrators with the medical boat visit program. Posters with boat visit contact information were created to be displayed in strategic locations aboard the fishing vessels and in port offices.

Summary of Results: Pursers, captains, vessels agents, and port administrators were found to be well informed of the availability of medical boat visits. They were enthusiastic about the program and were enthusiastic about the potential savings of time and money the program could provide. Brochures and posters were retained by clinicians to be distributed to captains and pursers who were not in port during the initial outreach effort.

Conclusions: During their short stays in port fishermen have little time to seek medical care. By bringing clinicians directly to the fishing vessels a boat visit program can increase access to health care. Educating boat captains, pursers, vessels agents, harbor masters, and fishing company administrators about the time and money to be saved by taking advantage of the program may be an effective way to improve the rates of usage.

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REDUCING POSTPARTUM DEPRESSION RISK IN LATINA WOMEN WITH ANTEPARTUM INTERVENTION

N. Fox
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Purpose of Study: CDFMC has many 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. Latine 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 staffed by a provider. The 4 stations were: calming baby, adjusting to life with a newborn, family planning and infant care. Primagravida 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% 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.

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NOSOCOMIAL INFECTION PREVENTION IN CUSCO, PERU

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Purpose of Study: For overworked staff and impoverished patients requiring prohibitively expensive treatment, nosocomial infections constitute a significant drain on resources that increase morbidity and mortality. Available data suggests there are increased rates of intra-hospital transmission in low-resource settings due to a combination of substandard infrastructure, inadequate resources, rigid health care hierarchies and lack of education on appropriate preventative measures. This project attempted to decrease the incidence of nosocomial infections in the burn unit of the Hospital Regional in Cusco, Peru through education and resource acquisition.

Methods Used: Over US$600 was raised to acquire medicine, gloves, masks, toys, and other supplies. A digital camcorder was purchased to make health education videos for regional community health centers and to document ward conditions for future fundraising efforts. An information session for patients, parents and staff covered germ theory, disease prevention, basic hygiene and hand-washing techniques. Soap and laminated copies of illustrated hand washing instruction sheets were placed near every sink in the ward; laundry detergent was purchased for general use. The unit psychologist assumed responsibility for continuing education and supply distribution because of her close contact with patients and families.

Summary of Results: Participation of patients and parents was over 90%, but only one staff member was in attendance.

Conclusions: Since staff members constitute an important disease vector, their lack of attendance was a detriment to the effectiveness of the intervention.

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DIABETES PREVENTION AND HEART HEALTH EDUCATION FOR CHILDREN OF THE YAKAMA INDIAN RESERVATION

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Purpose of Study: To educate 6-8 year old children about the causes and risks of diabetes and heart disease and to highlight the importance of diabetes prevention through interactive learning and “hands-on” demonstrations during summer camp classes.

Methods Used: An extensive literature search was performed on the topic of juvenile and adult onset diabetes in Native American populations, as well as effective teaching strategies for long-term outcome benefits. An Indian Health Services Diabetes Educator was consulted to further discuss effective teaching methods, and various teaching materials from the “Shake That Sugar” community education program were obtained. A Yakama tribal elder donated a buffalo heart, liver and tongue for use in hands-on demonstrations with the children. Classroom presentations included a didactic component consisting of powerpoint presentation and an interactive component consisting of trivia competitions, demonstrations of “living anatomy,” diabetic pathology simulation modules, nutritional examples, cardiac function simulation of the heart, and handouts for at home glucose monitoring.

Summary of Results: 96 children and 20 adults participated in the classroom demonstrations. Many participants returned after their sessions to further explore the materials. The presentations received positive feedback from both staff and campers alike. The campers showed most interest in actively exploring the diabetic pathology simulation modules and the buffalo organs.

Conclusions: Childhood obesity directly correlates to increased risk for type 2 diabetes mellitus, and Native American children are at greater than a 55% risk of being obese or at risk for becoming obese. Native American children suffer from diabetes at greater than 190% the rate of non-Native American children. Age-appropriate education about the causes and risks of diabetes from an early age is essential to the prevention of diabetes. Although evidence suggests that one-time information sessions do not greatly affect outcomes, the process of first becoming aware of the disease and its causes is an important step towards reducing lifetime risk.

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THE RUPERT FREE HEALTH CLINIC: A COLLABORATION BETWEEN PHYSICIANS AND THE COMMUNITY

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Purpose of Study: Free clinics continue to spring up all over the country to serve the uninsured, homeless, and their communities. Free clinics not only help to promote good health, but the convey a sense of community volunteerism. Rupert, ID is a small rural area of some 5,645 citizens of which an estimated 24% are lacking health insurance coverage. Since it is a farming community, there is a large Hispanic and Caucasian population, the main users of free clinics throughout the country.2,3 Although there are a number of physicians in the area, there is only one sliding fee clinic, so options and opportunities are scarce for the poor. A free health clinic could provide basic acute health services to the uninsured in the Rupert area and help with community health education.

Methods Used: Physicians and community organizations were contacted to verify interest in collaborating to jumpstart a free health clinic. Using the input from area physicians, other free clinics in the area, and the literature, a business plan was established and presented to community organizations and physicians.

Summary of Results: Physicians and community organizations were receptive to the idea and felt a free clinic would be beneficial to the area. Area physicians and the local community organizations were mailed a brochure containing contact numbers and a basic operating plan in order to get the idea off the ground. The plan outlined how a clinic would be started, the cost of operating a clinic, how it would be managed, the services that would be provided, how financing would be obtained, and insurance and liability coverage.

Conclusions: The clinic would be an excellent resource to the community and Rupert, ID is an ideal setting with ample resources to sustain a free health clinic. The clinic is not intended to provide comprehensive, long-term care, but would provide acute treatment to the uninsured and underinsured.4,5 The free clinic will not be a solution to the greater problem, but is only a temporary solution to a growing problem.2 Nonetheless, it is a viable and feasible option that may reap great rewards to the city of Rupert and its citizens. Not only does a free clinic in the area have the potential to serve the uninsured, but it can also help educate the community and alleviate the burdens placed on local hospitals.
ABCD(E) and the UK’s Cancer Research Campaign’s seven-point checklist criteria for recognizing lesions of concern. Residents and caregivers were then shown pictures of pigmented lesions of no concern, some concern and serious concern with discussion about their classification by the seven-point checklist. Techniques for preventing intense skin damage due to sunlight were discussed. A business-card sized tool was created with the seven-point checklist.

**Summary of Results:** Risk factors for developing skin cancers, methods for preventing further skin damage as a result of sun exposure, simple ways to recognize concerning pigmented skin lesions and techniques used by physicians to remove skin cancers were explained to caregivers and residents of Rock Cove Assisted Living. Informational cards were provided to attendees and additional cards were provided to staff for dispersal to additional staff and residents not in attendance as well as future residents.

**Conclusions:** Increased education of patients regarding pigmented lesions elevates the likelihood of seeking consultation of a physician. With the tools and information provided, frequent skin self-checks performed by patients and examination by caregivers at Rock Cover Assisted Living will lead to an increased identification of pigmented skin lesions of concern.

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**DIABETES EDUCATION AND MANAGEMENT IN THE POLYNESIAN COMMUNITY OF ANCHORAGE, ALASKA**

T. Griffin

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**Purpose of Study:** The Pacific Islander community is the fastest growing ethnic community in Alaska. The Providence Family Medical Center is an urban underserved primary care clinic staffed by medical residents that sees a significant population of Polynesian patients with chronic diabetes. The purpose of this project was to improve the quality of care for Polynesians in the Anchorage community by addressing the need for culturally appropriate diabetic prevention and management.

**Methods Used:** The diabetic Polynesian population was identified as the focus of a community project by polling clinicians and observing clinical challenges. A multi-systems approach was taken to improve patient care. Efforts were combined with the working group of the Diabetic Prevention Committee and the State of Alaska to develop diabetic prevention awareness. Tasks included spearheading the Polynesian subset of their Diabetes prevention campaign and creating an educational poster for a Polynesian audience. Discussions with Polynesian community members were conducted to identify health concerns, social hubs in the Anchorage Polynesian community, and the effectiveness of created educational materials. A literature review was performed for validation of methods used to create educational materials. Research of health community programs in Anchorage designed for Polynesians was conducted and findings were presented to clinic providers to raise cultural awareness. Plans to develop a health fair hosted by Polynesians in spring 2009 were made by pairing Samoan community leaders and the Alaska Health Fair, Inc.

**Summary of Results:** A Polynesian diabetes prevention poster was developed and will be disseminated throughout Alaska. Clinic providers were educated about available programs for Polynesian patients and provided diabetic resources in the Samoan language. Polynesian community leaders were connected with public health organizations to develop their own health fair in a medically underserved Polynesian neighborhood. Discussions with Polynesian community members were conducted to identify health concerns, social hubs in the Anchorage Polynesian community, and the effectiveness of created educational materials. A literature review was performed for validation of methods used to create educational materials. Research of health community programs in Anchorage designed for Polynesians was conducted and findings were presented to clinic providers to raise cultural awareness. Plans to develop a health fair hosted by Polynesians in spring 2009 were made by pairing Samoan community leaders and the Alaska Health Fair, Inc.

**Conclusions:** In order to best engage people in healthy behaviors patient interventions and providers must be culturally sensitive. A multi-systems approach to improve trust between providers and the Polynesian community assists physicians and patients leading to improve the management of diabetes.

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**NEIGHBORHOOD WALKING GROUP PARTICIPANTS AND THEIR WALKING BEHAVIOR IN AN URBAN, LOW-INCOME LATINO COMMUNITY IN LOS ANGELES, CA**

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**Purpose of Study:** This study was conducted to describe the walking program participants and assess their walking behavior over time.

**Methods Used:** N = 961

10 walking groups at 5 different locations
Each group walks for at least 45 minutes and is led by 2 compañeras.
Basic demographic information on participants was collected
A daily attendance log was kept. Results for the first 6 months have been tabulated and presented.

**Summary of Results:** The top two effective recruitment approaches are speaking with a program representative and receiving a flyer. 81% of adult participants are female. On average, adult participants with at least 60 days of data walked for at least 45 minutes 2.25 days a week. The attrition rate from the 1st to the 2nd week of the program was 24.5%; however, the attrition rate declined from the 2nd to the 3rd week to 9.2% and from 3rd to 4th week to 5%. From the 8th week on, the attrition rate had stabilized to 1.9%. Participants who walk beyond week #1 greatly increase their chances of continuing to participate in the walking group program. Sun Valley Saludable, an inexpensive, community-based walking group program, is demonstrating sustained success over time.

**Western Student Medical Research Forum**

**Student Scientific Session II**

**Friday, January 30, 2009**

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**EVALUATION OF THE LEARNING CURVE OF THE REVERSE TOTAL SHOULDER: A RETROSPECTIVE REVIEW**

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**Purpose of Study:** The development of the reverse total shoulder design in total shoulder arthroplasty has shown to be a challenging procedure although yielding substantially positive outcomes. The learning curve of this procedure is often quoted as a confounding factor in the literature, yet no one has quantified at what rate surgeons become adept at this procedure. The aim of our study was to establish the number of cases needed to reach the plateau of the learning curve.

**Methods Used:** After gaining IRB approval, one orthopedic surgeon was followed through the first 62 consecutive cases implanting the reverse total shoulder prosthesis. The independent variable in our study was the chronological case number. Case length, inferior screw length, and sum of screw length were our continuous dependent variables, whereas if 4 screws were placed, and position (if any) of missing screw(s) comprised our categorical data. For continuous variables, consecutive cases were added until the linear regression slope included 0 within its 95% CI. At the break point determined by the value obtained from linear regression, contingency tables were created for the categorical data.

**Summary of Results:** For case length, a significantly negative slope was seen with the first 18 cases. Thereafter, the slope leveled (showing no significant difference from a slope of 0). Sum of screw length and inferior screw length were both found to have significantly positive slopes throughout the entire range of consecutive cases. Using the break point derived from case length analysis, categorical data evaluation revealed that the first 18 cases were significantly different from the subsequent 44 cases in both (1) if 4 screws were placed (P = 0.02) and (2) the position of the missing screw(s) (P = 0.001), with the posterior screw being missed more often in the first.
series, contrasting with the anterior screw being absent more frequently in the last cases.

Conclusions: Gaining proficiency in this procedure takes approximately 18 cases, which is relatively consistent with previous literature concerning the learning curve of other orthopedic procedures. However, because of the continuing upward trend in both the sum of screw length and inferior screw, fully mastering the implantation of the total reverse shoulder may exceed 62 cases.

174 MIDFACE RECONSTRUCTION WITH A SINGLE LATISSIMUS DORSIS/SERRATUS ANTERIOR-RIB/SCAPULA OSTEOMYCUTANEOUS MEGA FLAP

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Case Report: Objectives: The development of microvascular free tissue transfer techniques have provided the reconstructive surgeon a broad range of tissues to select from in order to appropriately fit composite defects of the head and neck. The subcapular vascular pedicle provides one the largest ranges of possible composite free flaps. The objective of this report is to present a technique of using a single combined latissimus dorsi, serratus anterior-rib/scapula (LD/SA-R/S) osteomyocutaneous flap for reconstruction of an extensive midface defect.

Methods: This case report is of a 74-year-old female, who underwent surgical ablative of a recurrent facial naso lacrimal carcinoma, which had invaded the maxillary and frontal sinuses, with metastasis to the neck. The patient then underwent maxillofacial reconstruction using the combined LDSA-R/S osteomyocutaneous mega flap, based upon the subcapular vascular pedicle.

Summary of Results: Following the extensive facial and skull base tumor extirpation, the patient underwent immediate midface reconstruction. As a result of the extensive defect present, we decided to use a flap composed of the latissimus dorsi, serratus anterior, rib, and scapula in order to simultaneously reconstruct the patient’s midface. The 6th rib was selected to reconstruct the maxillary alveolar ridge, while the vascularized scapula was used to reconstruct the orbital rim and mid-face. The thoracodorsal and subscapular vessels were then tunneled and placed into the left face at the border of the mandible. Microvascular anastomoses were performed, connecting the thoracodorsal and subscapular vessels to the facial artery and common facial vein. The patient did well postoperatively.

Conclusions: The use of the LDSA-R/S free flap in reconstruction of the face should be recognized as a possible free flap for cases of extreme facial defects, which require a large flap with both bone and soft tissue. The subscapular vascular pedicle provides a robust blood supply, allowing for the single flap to be adequately vascularized, while reducing the risks associated with multiple flaps and surgeries.

175 THE EFFECT OF LOW-DOSE RADIATION CT PROTOCOLS UPON URETERAL STONE DETECTION

J.L. Koning, F. Jellison, J. Smith, J. Heldt, N. Spengler, L. Nicolay, W. UPON URETERAL STONE DETECTION THE EFFECT OF LOW-DOSE RADIATION CT PROTOCOLS

UPON URETERAL STONE DETECTION THE EFFECT OF LOW-DOSE RADIATION CT PROTOCOLS

Methods Used: This cadaver model simulated the most difficult clinical calciﬁcation conditions. Calcium oxalate stones ranging in size from 3-7 mm. Stones were placed into a cadaver and scanned using MDCT at 140, 100, 60, 30, 15, and 7.5 mAs with other imaging parameters constant. Images were reconstructed at 2.5 mm section width, randomized, and reviewed independently by two blinded radiologists.

Summary of Results: Overall sensitivity and speciﬁcity of distal ureteral calciﬁcation detection were 96.4% and 87.0%, respectively. Calculus detection rates for 140, 100, 60, 30, 15, and 7.5 mAs settings had sensitivities of 98%, 97%, 96%, 95%, 95% and 95% and speciﬁcities of 87%, 88%, 87%, 90%, 83%, and 87%, respectively. Negative predictive values were similar at all settings, ranging from 0.98 to 0.99. Interobserver agreement was excellent with $k = 0.96$. There was no signiﬁcant difference in sensitivity or speciﬁcity at any mAs settings. The 7.5 mAs setting resulted in a 90% reduction in radiation exposure compared to the 140 mAs.

Conclusions: Detection of distal ureteral stones in the absence of hydronephrosis represents one of the most challenging clinical scenarios. In this study radiation exposure was reduced by as much as 96% with no effect upon sensitivity or speciﬁcity in the detection of distal ureteral stones. Low-dose protocols may signiﬁcantly lower the risk of secondary malignancies due to reduced radiation exposure.

176 AESTHETIC MICROVASCULAR RECONSTRUCTION OF THE LOWER EXTREMITY: AN ALGORITHM PRIORITIZING DONOR SITE APPEARANCE AND FUNCTION

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Purpose of Study: To retrospectively review the outcomes of a group of patients treated according to an algorithm of lower extremity reconstruction that focuses on a new paradigm of interrelated goals: maximizing aesthetic outcome while minimizing loss of function. Three principles inform the algorithm: 1) All efforts to achieve a primary closure of the flap donor site while replacing lost skin with new skin (instead of traditional muscle with grafted skin), 2) Use flap donors as close to the wound as possible to minimize the iatrogenic extension of morbidity, 3) If skin grafting of a surgical site was necessary strongly prefer the original site of trauma over uninjured donor site.

Methods Used: A retrospective review of all below-knee microvascular reconstructions performed by a single surgeon following a new reconstructive algorithm at two Level 1 trauma centers. PATIENTS: From September 2005 to August 2008, forty-one patients who ranged between 13 and 75 years of age underwent lower extremity free flap reconstruction. The mean age was 40.7 years (SD = 16.4). The majority of patients were male (75%), and trauma was the most common indication for free flaps reconstruction (65%).

Summary of Results: Primary closure of the donor site was achieved in 35 of 40 cases (87.5%). Reconstructive success rate was 97.5%, there was one flap failure. Flap preference was related strongly to wound size: small wounds (<4 cm), peroneal perforator flaps for medium wounds (<6 cm), anterolateral thigh perforator flap for large size wounds (6-12 cm), and latissimus dorsi for massive wounds (>12 cm).

Conclusions: A new algorithm which emphasizes recent advances in microsurgery through use of perforator (muscle sparing) and super-microsurgery (anastomoses of vessels less than 1 mm) was implemented. This review demonstrated excellent success rates while avoiding traditional muscle transplants which at the same time are unaesthetic and cause loss of function through muscle sacrifice. By choosing donor sites that can be closed primarily iatrogenic morbidity is minimized. By keeping the donor site as close to the traumatic wound as possible, the overall morbidity of treatment is contained to the smallest area possible. Drawbacks include a need for advanced microsurgical skill; however we feel the benefit to the patient far outweighs this concern.

177 GIANT OSTEOMA OF THE MANDIBLE CAUSING CEREBROVASCULAR ACCIDENTS

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Case Report: Osteomas are benign bony growths that are typically asymptomatic and usually do not require treatment except in the case of secondary coexistence. Incidence of osteoma is rare but in the maxillofacial region, osteomas often present on the mandible. Mandibular osteomas have been recognized to cause pain, mechanical or aesthetic deviations secondary to excessive growth. Neurovascular disease has not yet been a recognized complication of enlarged osteomas.

A 59-year-old Caucasian male was referred for an evaluation of a mass on his left mandible. This patient had a history of cerebrovascular accidents with two strokes and seven reported transient ischemic attacks. First noticing the
growing mass about three years prior, he developed pain and saw his dentist who discovered the growth on x-ray. Also, complications from a repaired right mandible fracture in 1993, cross-bite and limited jaw opening, were reported as exacerbated. He had no history or indications of hypertension, diabetes or any heart and artery disease.

On physical examination, the patient was well nourished and interacted normally except a noticeable expressive aphasia from previous stroke. The head and neck exam revealed significant findings with a palpable mass of the left mandibular angle and ramus measuring about 4 cm on palpation. Computed tomography revealed a medially growing left mandibular mass with a length of 7 cm that was compressing the left internal carotid artery.

The patient underwent a left mandible resection with reconstruction using a fibular free flap with temporomandibular joint arthroplasty. In surgery, the patient was found to have a massive left mandibular ramus osteoma measuring 5.0 × 5.0 × 7.0 cm, encroaching on the left internal carotid artery. The diagnosis of osteoma was confirmed on histopathological examination.

The literature shows no previous cases of mandibular osteomas causing stroke or transient ischemic attack. This is the first report of an osteoma causing anatomical obstruction of the internal carotid artery and ischemia to the brain. Carotid artery impingement should be considered a possible complication of osteoma outgrowth in the maxillofacial region and likewise carotid narrowing secondary to an osteoma should be considered as a possibly etiology in neurovascular attacks.

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BASAL COMPONENT OF DISTORTION PRODUCT OTOACOUSTIC EMISSIONS REVEALED USING THREE DIFFERENT EMISSION PROPERTIES

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Purpose of Study:
Distortion Product Otoacoustic Emissions (DPOAEs) are sounds in response to two pure tone stimuli that come back out of ears and can be measured in the ear canal by a sensitive microphone. These measures have proved useful in objectively assessing hearing in both animals and humans. A more complete understanding of the source of emissions is of considerable clinical importance for more specifically locating cochlear lesions of damaged outer hair cells involved with hearing loss. DPOAEs are currently thought to arise from a combination of “wave-fixed” components, which map to the generation site near the frequencies of the stimuli used to elicit the emission, and an indirect DPOAE “place-fixed” component, where the emission initially travels to the apex and then is reflected back out to the ear canal from its’ own frequency place. There is however recent evidence for a third type of emission sources. The overlapping high frequency tails of the traveling wave excitations produced by the stimulus tones on the basilar membrane may also affect emission characteristics significantly by generating “basal” components, which interact with the aforementioned components to produce the overall emission.

Methods Used:
As part of a general effort to characterize and understand these different components, DPOAEs were collected from three rabbits with normal hearing in both ears; and their phase, tuning and latency properties were explored at different stimulus levels thought to either maximize or minimize basal source contribution to the emission.

Summary of Results:
The overall results confirm the contribution of basal components to the DPOAE sources and point to methods of removing these components from the DPOAE measurement.

Conclusions:
The contribution of this study to clinical hearing diagnosis and treatment methods is potentially very significant. Eliminating “basal components” will allow DPOAEs to much more specifically locate the frequency place of cochlear lesions, and thus will provide the necessary information to tailor treatments to characteristics of a patient’s hearing loss.

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COMPARISON OF DPOAE ONSET TO ABR FIRST WAVE LATENCIES SUPPORTS COMPRESSION WAVE HYPOTHESIS FOR DPOAE REVERSE PROPAGATION

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Purpose of Study:
Auditory brain stem response (ABR), a clinical tool that can measure excitement of brain stem auditory centers, has been extensively used in testing of neural hearing loss and can be used to estimate the delay between stimulus input and excitation of auditory centers. Distortion Product Otoacoustic Emissions (DPOAEs) are sounds in response to two pure tone stimuli that come back out of ears and can be measured by microphone. These measures have proved useful in objectively assessing hearing in both animals and humans.

Currently there is some confusion regarding the mechanism by which DPOAEs are transmitted to the ear canal. One theory suggests backwards transmission of a traveling (slow) wave along the basilar membrane from the DP source. In this case we could expect the latency of DPOAEs to be twice the distance from DP generation site to the oval window divided by the velocity of the traveling wave. Essentially, the latency of the DPOAE should be roughly twice the time necessary to reach the DP generation site and twice that of the ABR first wave latency.

An alternative hypothesis is the compression (fast) wave model in which DPs travel by longitudinal compression waves of the cochlear fluid. Due to near instantaneous propagation of liquid compression waves, this theory proposes the DPOAE latency to be the approximately the distance from DP generation site to oval window divided by the velocity of the forward traveling wave. That is, on the order of one half the time of required of the basilar membrane traveling wave model or roughly the same as ABR first wave latency.

Methods Used:
In an effort to determine which model predominates within the cochlea we have collected ABRs and DPOAEs from six normal hearing rabbit ears at different stimulus levels and frequencies.

Summary of Results:
Obtained DPOAE latencies have been roughly equivalent to ABR latencies for lower level stimuli. These comprehensive results support the existence of the compression wave mechanism.

Conclusions:
A better understanding of the mechanisms by which DPOAEs propagate back out of the cochlea could lead to clinical tests utilizing these measures to quantify various hearing losses.

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COMPARISON OF THE RADIAL FOREARM FLAP VS. ANTEROLATERAL THIGH FLAP IN PHARYNGOESOPHAGEAL RECONSTRUCTION

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Purpose of Study:
The radial forearm free flap (RFFF) and the anterolateral thigh free flap (ALTFF) have become two of the most common and reliable flaps used for pharyngoesophageal (PE) reconstructions. While both provide adequate coverage of PE defects there remains ambiguity regarding the clinical and functional differences between these two flaps. The purpose of this study was to evaluate the pre-operative, peri-operative, and post-operative factors related to PE reconstruction in order to elucidate the benefits of one flap to another.

Methods Used:
After obtaining Institutional Review Board approval, a case review was performed on thirty-four consecutive patients who underwent PE reconstruction using either the ALTFF (16 patients), or RFFF (18 patients), between May of 2005 and June of 2008 at a tertiary care medical center. A comprehensive examination of patient history, sequelae of disease, and follow-up care, in addition to a comprehensive review of literature was performed.

Summary of Results:
The thirty-four patients who were included in the study there were no flap failures. There were no perioperative mortalities and one post-operative death (2.9%). The size of the ALTFF ranged from 6 to 9 cm in width and 11 to 20 cm in length, and the size of the RFFF ranged from 7 to 9 cm in width and 11 to 18 cm in length. Both donor sites provided adequate tissue for PE reconstruction, and both donor sites provided comparable functional outcomes of speech and swallowing success. Saliary fistula rates were increased in the ALTFF group, while infection rates were increased in the RFFF. Patients who had a RFFF complained of donor site morbidities including hand numbness and scarring more often than patients with the ALTFF flaps.

Conclusions:
This study has demonstrated that low morbidity and high success rates can be achieved with either the ALTFF or the RFFF for circumferential and partial PE reconstruction. The ALTFF provides an advantage over the radial forearm flap due to its availability of large amounts of skin for larger PE defects, lower donor site morbidity and superior aesthetic outcomes.
181 ABERRANT SKIN PERFORATORS IN OSTEOCUTANEOUS FIBULAR FREE FLAPS

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Purpose of Study: The fibular free flap is the preferred flap for oromandibular reconstructions. This is largely due to the course of the peroneal artery that serves the fibula as well as supplying perforating septocutaneous branches to the overlying skin. This allows the surgeon to take one composite osteocutaneous flap, rather than two separate flaps, greatly decreasing morbidity.

Perforators from the peroneal artery are reliable in most patients, but the literature shows a significant minority (10-20%) with anomalies such as musculocutaneous perforators from the soleus muscle, perforators from the posterior tibial artery or rarely the absence of perforators. Knowledge of the incidence and nature of these aberrations is important before harvesting the fibula. Our purpose was to evaluate the occurrence of anomalous cutaneous vasculature of the fibular skin paddle.

Methods Used: Internal Review Board approval was obtained for a retrospective chart review of all patients undergoing a fibular free flap at a tertiary care referral center over the last 4 years. 74 patients' charts were available and were included in the data collection. The operative reports were evaluated for age, sex, tourniquet time, aberrant arterial anatomy on preoperative angiography, number of perforators, their location and vessel of origin.

Summary of Results: The average age was 60.9 with 47 males and 27 females with no age (P = 0.84) or gender correlation with aberrations. The average tourniquet time was 68.5 minutes, with no correlation with aberrant perforators (P = 0.71). The average number of perforators per flap was 1.8. Four of 74 flaps (5.4%) had the skin paddle supplied by the peroneal artery with an aberrant course through the soleus muscle (musculocutaneous). Two of 74 flaps (2.7%) had perforators supplied by the posterior tibial artery. One of 74 flaps (1.4%) had no identifiable perforator to the skin.

Conclusions: Of 74 osteocutaneous fibular free flaps reviewed, a total of 9.5% of the fibular flaps had aberrant skin perforators. When musculocutaneous perforators are identified, care must be taken to preserve the perforator as it is traced through the soleus muscle. When the perforators originate from the posterior tibial artery or are not available, other methods for reconstruction must be taken into consideration such as harvesting additional muscle with the fibula or harvesting another flap.

182 THE HEMOSTATIC SANDWICH: A TAMPOONADE METHOD FOR CONTROLLING SEVERE BLEEDING IN PERCUTANEOUS KIDNEY STONE SURGERY

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Purpose of Study: A potential significant complication of percutaneous kidney stone removal surgery (PCNL) is surgical tract bleeding. The ideal method to control this bleeding would be to stop the bleeding without compromising kidney function. Current techniques to control tract bleeding including vessel embolization and nephrectomy both result in a loss of kidney function. The purpose of this study is to describe a novel hemostatic sandwich technique, which controls severe hemorrhage from the percutaneous tract by creating a tamponade effect between two catheter balloons.

Methods Used: A retrospective review was performed on four PCNL patients that experienced severe tract bleeding and were treated using the hemostatic sandwich technique. Two balloon catheters were used in conjunction with gelatin matrix to form a hemostatic non-occlusive sandwich. A large balloon catheter was placed into the renal pelvis, inflated, and gently pulled against the inner wall of the kidney to occlude the inner surface of the nephrostomy tract. This prevented blood or gelatin matrix (FloSeal®) from entering the renal pelvis or the collecting system while simultaneously preventing urine from leaking out of the kidney. The outer surface of the tract was occluded with an additional balloon catheter which was placed just below the skin. Five milliliters of gelatin matrix was injected into the tract between the two balloons prior to inflation of the second balloon catheter thereby completing the hemostatic sandwich.

Summary of Results: Mean estimated blood loss was 562 milliliters and the post-operative hemorrhoglobin stabilized by day two in all patients. The mean length of hospital stay was 7 days. No patients required further invasive procedures or further renal exploration to control bleeding. There were no major complications following use of this technique and the only minor complication was a single case necessitating blood transfusion.

Conclusions: The hemostatic sandwich successfully controlled bleeding in all four patients. The hemostasis achieved without renal damage suggests that this procedure should be considered in all patients with severe bleeding following percutaneous kidney surgery.

183 OUTCOMES OF RECTOVAGINAL FISTULA SURGERY: RECTOVAGINAL FISTULA PLUG VERSUS FLAP ADVANCEMENT

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Purpose of Study: Fistulas between the rectum and vagina are a problem manifested by the passage of intestinal contents and gas through the vagina. Our aim is to compare outcomes of the new bioprosthetic rectovaginal fistula plug to the current gold standard of conventional flap closure in the treatment of rectovaginal fistulas. Long-term success rates of 60% with conventional rectovaginal fistula repair have been reported previously.

Methods Used: This is a retrospective cohort study of all patients treated for rectovaginal fistulas by a single colorectal surgeon at the University of British Columbia from 1997 to 2008. The primary outcome was full healing (fistula opening closed with no drainage or infection) at 12 weeks postoperatively. Patients with postoperative follow-up prior to 12 weeks were excluded from this study.

Summary of Results: There were 29 females with a median age of 37 (range, 20-57). Twenty-four patients were treated by flap closure and 5 had insertion of a rectovaginal fistula plug. The mean follow-up was 12 weeks (range, 4-16). Two patients were excluded from the plug group because their postoperative course was less than 12 weeks. Full healing rates were 56% for flap closure and 67% for plug insertion.

Conclusions: The use of bioprosthetics for the management of rectovaginal fistulas is a new technique, which, based on early experience, seems to yield results comparable to that of conventional advancement flap repair. Given the low morbidity and relative simplicity of the procedure, the rectovaginal fistula plug should be considered an alternative effective treatment for patients with rectovaginal fistulas.

184 RADIOSURGERY INDUCED MALIGNANT JUGULAR FORAMEN SCHWANNOMA

A. Tu, R. Akagami UBC, Vancouver, BC, Canada.

Purpose of Study: Case Report

Methods Used: Chart review

Summary of Results: Our patient initially presented with a Vernet’s syndrome. Investigations subsequently found a jugular foramen schwannoma which was then treated with stereotactic radiosurgery. A recurrent lesion developed 9 years later and on surgical debulking was found to be a schwannoma containing both benign and malignant elements. This report reviews current literature on jugular foramen lesions and radiosurgery induced cranial nerve malignancies.

Conclusions: CNS radiosurgery induced malignancy is a rare event; malignant transformation of previously benign lesions are uncommonly described. This report is the first ever documented case of radiosurgery induced malignancy in a benign jugular foramen schwannoma.

185 DEVELOPMENT OF LENTIVIRAL VECTORS FOR EX VIVO REGIONAL GENE THERAPY FOR SPINAL FUSION

P.S. Ge1, B.J. Van Handel1, H.K. Mikkola2, J.C. Wang1,3 1David Geffen School of Medicine at UCLA, Los Angeles, CA; 2Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA, Los Angeles, CA and 3UCLA Comprehensive Spine Center, Santa Monica, CA.

Purpose of Study: Spinal arthrodesis is a fundamental treatment for a variety of spinal pathologies. Bone morphogenetic proteins (BMPs) are growth factors in the TGF-beta superfamily. In particular, BMP2 and BMP7 are involved in osteoblast differentiation and have been shown to have osteoinductive potential. Recombinant human BMP2 and BMP7 are used in a
variety of orthopaedic procedures including spinal arthrodesis to facilitate bone repair, however the treatments are costly and require long durations. This study aims to develop lentiviral vectors encoding BMP2 or BMP7 for the purpose of ex vivo regional gene delivery to enhance spinal fusion.

**Methods Used:** An existing lentiviral vector expressing eGFP downstream of a cytomegalovirus (CMV) promoter was modified by the addition of a human elongation factor 1-alpha (EF1a) promoter to generate Lenti-eGFP. The vector was further modified by inserting the coding sequences for human BMP2 and BMP7 downstream of the EF1a promoter to generate Lenti-eGFP-BMP2 and Lenti-eGFP-BMP7, respectively. The constructs were transfected into 293FT cells and eGFP expression was evaluated by flow cytometry. BMP2 and BMP7 expression were evaluated by quantitative RT-PCR. Lentiviruses were packaged by Lipofectamine-mediated transfection of 293FT cells, and viral titers were determined by flow cytometry and quantitative RT-PCR.

**Summary of Results:** We constructed and packaged lentiviral vectors encoding eGFP, BMP2, and BMP7. In vitro transfection of 293FT cells demonstrated high levels of eGFP expression from all three vectors, with concomitant BMP2 and BMP7 overexpression from the Lenti-eGFP-BMP2 and Lenti-eGFP-BMP7 vectors, respectively. Viral infection in 293FT cells resulted in stable expression of eGFP, BMP2, and BMP7.

**Conclusions:** We have developed lentiviral vectors expressing the osteoinductive proteins BMP2 and BMP7 for use in regional gene therapy. Future studies include lentiviral infection of human adipose-derived mesenchymal stem cells, maintenance of stable gene expression within these cells, and in vivo implantation of these cells into our rat spinal fusion model to assess their ability to enhance spinal fusion.

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**Western Student Medical Research Forum**

**Student Scientific Session III**

8:30 AM  
Friday, January 30, 2009

**186 PARENTAL EDUCATION ON ALTERNATIVE FLUORIDE SOURCES FOR PREVENTION OF DENTAL CAVITIES WITHIN CHILDREN RESIDING IN JUNEAU, ALASKA**

E.S. Spencer  
University of Washington School of Medicine, Seattle, WA.

**Purpose of Study:** In October of 2006 the community of Juneau, Alaska voted to remove fluoride from the community water source. Since the passing of the bill there has been no progress in the provision of free fluoride alternatives for the children. Professional literature and local health providers agree that removal of such a historically successful preventative public health measure puts the youth of Juneau at significantly increased risk for tooth decay and dental caries. A parental education program for families residing in communities with sub-optimally fluoridated water was designed to increase parental awareness of alternative sources of fluoride for protection of their children’s teeth.

**Methods Used:** A literature search was conducted regarding fluoride and prevention of dental caries and enamel fluorosis. The review supported the use of topical and systemic fluoride in the prevention of dental decay in infants and children. Interviews were conducted with the Water Utility Superintendent, the Public Health Center Manager, the State Dental Officer and local physicians. A brochure, outlining alternative fluoride sources, was developed from information derived from the professional literature and guidelines set by the CDC, ADA, AAP, and AAPD. Two presentations were prepared for local parenting groups offered by the Family Birthing Center and Bartlett Regional Hospital.

**Summary of Results:** Brochures were distributed to local family practice clinics, parenting groups, and the Juneau Family Birth Center. The presentation at the Juneau Family Birth Center was well received by the ten mothers present and was followed by an extensive question and answer session.

**Conclusions:** Education is key when there is a significant change in local public health measures. Many children residing in Juneau will receive insufficient levels of fluoride due to a lack of access to health or dental care or simply because their parents are unaware of the health implications. This will result in elevated levels of tooth decay and dental caries within Juneau’s youth. The State Dental Health Officer is currently working to provide fluoride varnishes for children within the Juneau school system. This, in conjunction with increased parental awareness, seems the best option for guaranteeing all of Juneau’s children receive proper fluoride protection.

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**187 COMMUNITY HEALTH ROUNDUP: A LOOK AT WEIGHT LOSS SOLUTIONS IN DILLON, MT**

M. Turner  
UWSOM, Seattle, WA.

**Purpose of Study:** Obesity is a common problem in any part of the US, even a town which has access to numerous outdoor activities. Physicians in Dillon, MT, estimate that they spend a significant amount of their clinic time counseling on weight loss. Despite availability of local exercise resources, many are under-utilized. This prompted the need for a project to assist facilities to join forces in designing strategies to assist citizens with the goal of becoming healthier.

**Methods Used:** The community hospital and YMCA administrators were brought together to describe current programs and to develop new community weight loss strategies. Local resources were cataloged and a literature review of successful national weight loss programs was performed. An article was published in the local paper and flyers were distributed in the community to alert citizens of the new plan and the upcoming meeting.

Community members were provided an opportunity to describe their preferred methods of weight loss. They were introduced to the program offered jointly by the YMCA and the hospital. Educational materials about resources in the community were given to the participants and ideas of future community needs were collected.

**Summary of Results:** The YMCA and hospital staff produced a one year collaboration that would include joint community and individual education to meet identified needs. Planning was also initiated for the possibility of a future diabetes centered program and funding options.

About 20 community members participated and indicated a desire to be involved with the weight loss program. During the meeting, several citizens expressed ideas to help improve Dillon’s health and future actions were discussed.

Community networking resulted in other local groups requesting collaboration in future plans including the University of Montana Western, the Dillon schools, and Senator Baucus’s Rural Health Initiative Group. A follow-up community meeting was held in late September to discuss further planning and funding options.

**Conclusions:** Community organizing to fight the obesity epidemic in Dillon, MT can be successful. Community input is essential to effective weight loss and healthy habits. Facilitating local agencies to work together using multiple strategies to encourage healthy lifestyle behaviors improves social support among the community and may improve successful outcomes.

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**188 REDUCING CHILD OBESITY THROUGH EDUCATION OF PRIMARY CARE PROVIDERS IN OTHELLO, WASHINGTON**

A.K. Farrar  
University of Washington School of Medicine, Seattle, WA.

**Purpose of Study:** Othello is a rural town in Washington. Project specialists in the health clinics in Othello agreed that child obesity is a concern. To address this issue, an informational session imparting the latest research and community data was presented to health care providers in an effort to reduce the levels of child obesity in Othello and surrounding communities.

**Methods Used:** An assessment for the project was performed by a specialist in the electronic practice management system using specifications created by the project designer. The analysis found that 35% of the children, between ages 2 and 8, had a BMI above 19 (consistent with obesity) and 46% had a BMI above 18 (consistent with overweight). Extensive research was done regarding the provider’s role in reducing the levels of overweight children. This role involves proper screening of overweight children, informing parents and patients of the consequences of excess weight, using motivational interviewing techniques, providing nutritional and activity information, and working with the greater population. This data and research was then presented to a group of primary care providers in a thirty-minute presentation followed by a ten-minute discussion. Hard copies of the presentation and helpful handouts for parents were given to each attendee. One week later, an evaluation was distributed to assess the usefulness of the information.

**Summary of Results:** Fifteen health care providers, comprising three quarters of the providers in Othello, attended the presentation. These providers serve several thousands of children in the area. Three providers did the survey and their averaged responses were as follows: the utility of the presentation was rated at 8.67 (1 being not at all useful and 10 being extremely useful), and the average number of times per day that they used information from the presentation in the clinic was two. Within the first week,
several providers referred to the nutritionist overweight children ready to make lifestyle changes.

**Conclusion:** Child obesity is a major problem in Othello. The providers were exposed to this knowledge, as well as key steps in motivational interviewing techniques, for the first time through this presentation. Educating providers about their roles in reducing child obesity was an important step in increasing healthy living in Othello.

**189 ENCOURAGING AN ACTIVE LIFESTYLE IN KIDS: THE “FITNESS FUN” ACTIVITIES PACKET**

J. Cunningham University of Washington School of Medicine, Seattle, WA.

**Purpose of Study:** Obesity and diabetes are significant health issues in Chelan, WA, where about 61.1% of the adult population is diabetic and about 59% obese as estimated in 2007. The likelihood of both being obese and developing diabetes as an adult is well correlated with childhood obesity. Therefore, this project targets the pediatric population in Chelan to try and help foster a more active and healthy lifestyle by providing a “Fitness Fun” activities packet for kids.

**Methods Used:** The “Fitness Fun” activities packet was completed with the help of professional literature, the guidance of a local nutritionist, and the influence of conversations with parents in the clinic. The idea was to find some way to motivate kids to increase their daily activity levels, but in a fun—and more realistic—way. The project consisted of a poster for kids to hang up and mark off a box for each day they spend at least a half hour playing some active game. Once the children fill the squares on the poster their parents can reward them. To accompany this, I included a list of suggested activities (e.g. hula hoops, swimming, soccer, biking, tag) and a list of recommended healthy snacks. This packet was completed in both English and Spanish versions due to the large Latino population in Chelan County.

**Summary of Results:** The implementation of this project is still in the preliminary stages where it is being printed and distributed to children who come to the Columbia Valley Community Health Clinic (CVCHC) and the Women, Infants, and Children (WIC) Center in Chelan. The WIC center is currently planning to introduce a semiannual raffle for a prize using the filled out forms.

**Conclusions:** The “Fitness Fun” activities packet will remain with the CVCHC and WIC centers as a useful tool for motivating kids to increase their activity. The need for a list of suggested games and snacks came about from conversations with parents in the clinic who needed recommendations for such activities and snacks. The positive reinforcement for the kids and involvement of the parents will hopefully encourage a longer-lasting lifestyle change and help reduce the development of obesity and diabetes in adulthood.

**190 AUTOMATED EXTERNAL DEFIBRILLATOR AWARENESS AT THE SWINOMISH INDIAN TRIBAL COMMUNITY**

K.D. George University of Washington, Seattle, WA.

**Purpose of Study:** The patient population observed at the Swinomish Indian Health Clinic demonstrated risk factors for sudden cardiac arrest such as hypertension, hyperlipidemia and diabetes. The tribal community has five automated external defibrillators (AEDs), part of a nationwide public access defibrillation (PAD) program, located on the reservation. The goal of this project is to increase public awareness about the use of AEDs and to increase confidence in the lay rescuer so that if needed, they will know where the AED is, how to operate it and most importantly to remember to activate 911.

**Methods Used:** Three separate one hour classes were taught at different locations on the reservation during the employees work day. The focus was on dispelling myths about the AED and reinforcing proper use. Because the instructor was not a licensed instructor, it was an informational course. Because of the low level of average education among the tribal members, the information was kept basic and the themes were repeated. The hope was to encourage the participants that they cannot do further harm to a person experiencing cardiac arrest unless no aid is attempted and 911 is not called. CPR was refreshed by teaching hands-only CPR as an alternative to the traditional 30:2 CPR. The AED was brought to the classes so the participants could become familiar with it.

**Summary of Results:** Thirty-four people attended the classes. In the beginning of each class, the question was asked “who feels they would help someone by doing CPR and using the AED?” At the beginning of class, approximately 15% agreed but by the end, 90% felt confident when asked the same question. Understanding the relative safety and the algorithm of the AEDs made the most impact on these statistics.
Summary of Results: The presentation for residents and staff of QHAL focused on portion sizes, carbohydrate counting (CC), and meal planning (MP). The presentation was interactive and designed to allow residents to practice MP with the models and ask questions. The residents were enthusiastic to learn about the changes they could make to their meals to ensure better glycemic control. The staff was very open to hearing about simple changes they could make to the meal plan to provide better nutrition for their diabetic residents. The teaching materials were left for the future use of the residents and the staff made plans to visit a dietician for additional education about nutrition and MP. In the week following the presentation, three residents had improved blood glucose levels enough to require reduction in their daily insulin dosages. The staff stated how motivated the residents were about CC at meal times.

Conclusions: Diabetes self-management nutrition education is an effective tool in empowering diabetics into balancing their carbohydrate intake and thereby enabling better glycemetic control. As the residents of QHAL began CC and MP they were able to reduce their blood sugar levels enough to require reduced insulin treatment. The residents and staff seemed very receptive to future education in their plans to visit the local dietician for more information.

193 IMPROVING TREATMENT CONTINUITY FOR PEDIATRIC IRON DEFICIENCY ANEMIA IN JUNEAU, ALASKA

E.B. Ashbaugh University of Washington School of Medicine, Seattle, WA.

Purpose of Study: Alaskan Natives suffer a higher rate of Iron Deficiency Anemia (IDA) than the general population. Pediatric iron deficiency is proven to have lifelong effects on cognitive, motor and behavioral development. A project was designed to both educate the southeast Alaska Native community about IDA and also coordinate the efforts of community providers to screen and treat the affected patients.

Methods Used: Literature review was conducted regarding the epidemiology of IDA in pediatric Alaskan Natives, and the effective screening and treatment methods. A database of patients with current anemia diagnoses at the Southeast Alaska Native Health Consortium (SEARHC) was created using chart review to track screening, treatment, follow-up and current status. Protocols followed by community providers were then compiled into a comprehensive summary. An educational presentation to local providers included a discussion about better ways to screen, track and treat patients within the multi-layered health care system. Following this, the brochure was tailored to Alaskan Native patients were created for disbursement. Mailers were designed to explain lab results and treatment protocol to anemic patients. Notifications were devised to alert pertinent providers of patients screened outside the clinic. A project summary and related material was distributed among SEARHC providers to facilitate a standard treatment protocol.

Summary of Results: The project highlighted both the prevalence of IDA and the difficulty SEARHC has had in effectively treating affected patients. The patient database and lab report mailers were used to notify all patients of their current status and treatment needs; informational brochures were included. The round table discussion allowed local pediatricians, SEARHC providers and administration, public health nurses, and Women, Infants and Children (WIC) providers to compare and evaluate the combined screening and intervention opportunities.

Conclusions: Tools customized to Southeast Alaska Native communities for improved patient awareness and education can help emphasize the importance of iron replacement therapy and improve patient compliance. Cooperative efforts to screen and track anemic children creates a stronger net to catch the patients who have before slipped through untreated, and ensures support from all providers.

194 ATV TERRAIN VEHICLE SAFETY EDUCATION IN DILLON, MONTANA

A. Bateman University of Washington School of Medicine, Seattle, WA.

Purpose of Study: Nationally, all terrain vehicle (ATV) use has risen dramatically in recent years. Subsequent injuries related to ATV accidents have risen 95% since 1998, with deaths related to ATV accidents increasing 5%. Dillon, Montana is no exception to this rule. It is a rural community where most people either own ATVs or have access to one. Research suggests that safety education is a huge component in preventing ATV-associated injury. Residents in Dillon do not have access to a safe riding course, so an ATV Safety Fair for youth riders was designed and executed to teach safe ATV riding rules and techniques.

Methods Used: The safety fair was developed using guidelines from the National Association of ATV Safety. The curriculum included the most important aspects of ATV safety as found in a review of recent literature, including proper safety gear, riding technique, navigation of terrain, and size of best fit. All youth ages 8-18 in the community were invited to attend the fair. Important community members also contributed to the planning and implementation of the fair, including local ATV competitors, ATV shop owners, and medical staff. The fair was advertised on the local radio station, newspaper, and with fliers displayed throughout the community.

Summary of Results: Twenty-three youth from the community attended the ATV fair. They took a hands-on approach to learning ATV safety by trying on safety gear, learning to stop and start an actual ATV, practicing different riding techniques on an ATV, and by undergoing an interactive obstacle course to practice critical thinking and decision making skills. Two children in particular who were not previously allowed to ride their family’s ATVs were able to do so after successfully completing the safety course. The curriculum of the fair was left in the hands of 4H members who plan to continue the course in the future.

Conclusions: Safety education in the form of community ATV safety fairs is an effective way to reduce the likelihood of ATV-associated injuries and deaths. Making courses interactive and involving prominent members of the community make them more appealing to the youth who are most at risk when riding ATVs.

195 SPEAKING UP ABOUT HEARING PROTECTION IN AN AGRICULTURAL COMMUNITY

E. Verzemnieks University of Washington School of Medicine, Seattle, WA.

Purpose of Study: Sidney, Montana, is an isolated community of approximately 5,000 residents, representing a rich agricultural center in Eastern Montana. Those working in agriculture have a greatly increased risk of noise-induced hearing loss (NIHL) compared to other industries. Long hours, proximity to heavy machinery, and low compliance wearing hearing protection contribute to this unfortunate problem.

Methods Used: A two-part educational program was implemented to help combat this preventable condition in a dispersed and essential rural workforce. This plan was based on a literature review and community research regarding the risks of noise exposure and compliance with the use of hearing protection devices. It was determined to educate farmers via print media and educate first-hand individuals who frequently served the agricultural community. This approach took into great consideration the inherent difficulties of reaching a labor force scattered over a vast expanse of land.

Summary of Results: Stage one incorporated providing educational materials to workers and managers at local businesses, including hardware, tractor and farming supply stores. Prepared materials were distributed addressing NIHL and the increased risks to the farming community.

Conclusions: A two-pronged approach was carried out to help reduce the occurrence of NIHL within an agricultural community. One effort focused on increasing awareness directly through print media. It is hoped that by reaching a large reading audience, the maximum number of farmers will become aware of the risks and dangers of their work environment and the efforts they can take to reduce NIHL. Also, these individuals can now receive additional information at their frequent areas of business. In reality, this is a much more likely prospect than a visit to the doctor. It is hoped that employees at these locations will become a proactive front line in combating NIHL in Sidney.

196 GLOBAL HEALTH EXPERIENCE IN UGANDA: A UNIQUE PLATFORM FOR ENTERING DENTAL SCHOOL

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Purpose of Study: The Brighter Uganda Program provides opportunities for undergraduates to become involved in global health. Dental care is an
ongoing health issue of concern in both developed and developing countries. Children with poor oral health and associated periodontal disease face other health issues as they mature including: diabetes, heart disease, stroke and premature labour. Brighter Smiles has proven successful in reducing caries in aboriginal children in British Columbia, Canada. Purpose: To describe the value of participation in a global oral health initiative in Uganda providing a unique platform for entry to dental school.

Methods Used: The Uganda 2008 Project consisted of a multidisciplinary team of undergraduates, medical students, dental students, doctors, researchers and a dentist. My key role was as the videographer to provide high video footage for production of educational and promotional videos. Three video themes were: 1) The School of Dentistry, Makerere University and international partnerships 2) Community education and assistance to an orphaned youth group in Kampala. 3) Global health education modules for a new global health curriculum for medical students under development at our Canadian university. I also assisted with oral health project delivery in the rural Ugandan communities enrolled in the program.

Summary of Results: 25 hours of quality video material were filmed for educational use and video production. Video interviews were conducted for Canadian team (T = 11) and for Ugandan team (T = 7) and teachers (T = 6) in the rural communities during project delivery. Children in 4 rural Ugandan communities received fluoride varnish to prevent caries and oral examinations with DMSF scoring. Collaboration with other university students from Canada and Uganda promoted cooperative international team building.

Conclusions: Participation in a global oral health initiative focusing on preventative dentistry provided a unique experience for a pre-dental student. Opportunities to learn about data collection, dental scoring and applying dental fluoride to Ugandan children were valuable. Educational videos produced will be incorporated into teaching material. Collaboration with the Canadian team and overseas with Ugandan team proved fulfilling, and demonstrate steps towards global citizenship.

197 PREVENTING AGRICULTURE-ASSOCIATED CHRONIC OBSTRUCTIVE PULMONARY DISEASE THROUGH EDUCATION IN BAKER, MONTANA

A.J. Torvie University of Washington School of Medicine, Seattle, WA.

Purpose of Study: Agriculture is a primary industry in the rural community of Baker, Montana. High rates of Chronic Obstructive Pulmonary Disease (COPD) in the local population reflect the prevalence of occupational risks and smoking in this area. A multi-tiered education program was created to identify and reduce exposure to risk factors associated with the development of COPD; the program also proposed patient-centered methods of improving lung function once symptoms arise.

Methods Used: Community leaders were consulted to determine points of interest in this topic as well as an effective strategy to target a widespread farming population. A literature review was then completed to elucidate the link between farming and COPD, determine methods to prevent contact with harmful particulate matter, and explore steps that patients can take to improve breathing and quality of life once lung damage has occurred. Informative seminars were held for the public and the Chamber of Commerce and Agriculture, and materials outlining tips for disease prevention and lung function improvement were distributed. Discussions were also held with care providers to review a checklist for comprehensive COPD patient education.

Summary of Results: 42 care providers, COPD patients, agricultural workers and other community members attended two educational sessions exploring the causes of COPD, ways to reduce occupational risk in agriculture, tips to quit or reduce smoking, methods to improve lung function in symptomatic patients, and further resources for prevention and treatment of this disease. Questions were actively discussed and brochures, exposure reduction checklists and patient education outlines were retained by the local clinic for future use.

Conclusions: Multiple Baker residents with elevated particulate exposure did not identify themselves as being at increased risk for developing COPD. Continued education and prevention tools are necessary to both ensure awareness and decrease individual contact with harmful dust, molds, smoke and other particulates. Members of this community are receptive to learning about COPD and modifying their habits, as possible, to reduce its prevalence. COPD patients are particularly interested in efforts to improve their breathing and, consequently, their quality of life.
element, albeit 88.5 kb upstream, regulates the expression of NOGO-A during development.

Conclusions: This enhancer may provide insights into the roles of NOGO-A during development and the inhibition of CNS regeneration. Further studies are in progress to determine the specific transcription factors and binding sites that regulate this NOGO-A-associated enhancer.

200 PRENATAL GROWTH OF INFANTS EXPOSED TO PREGNATAL METHAMPHETAMINE: RESULTS FROM THE INFANT DEVELOPMENT, ENVIRONMENT AND LIFESTYLE (IDEAL) STUDY


Purpose of Study: Previous studies suggest prenatal methamphetamine (MA) exposure inhibits fetal growth. This study examines the fetal growth effects of prenatal methamphetamine exposure in the multicenter, longitudinal Infant Development, Environment and Lifestyle (IDEAL) study.

Methods Used: IDEAL screened 34,833 subjects at 4 clinical centers; 3708 were eligible and consented of which 204 were MA exposed (EXP) and 3,504 unexposed (unEXP). EXP were identified by self-report and/or GC/MS confirmation of amphetamine and metabolites in infant meconium. Women in the unEXP group denied amphetamine use and had a negative meconium screen. Both groups included prenatal alcohol, tobacco and marijuana use, but excluded use of opiates, LSD, PCP or cocaine only. Neonatal parameters included birth weight and gestational age in weeks. Small for Gestational Age (SGA) was calculated using Alexander’s algorithm. One way ANOVA and linear regression analysis were conducted on birth weight by exposure. The relationship of MA exposure and the incidence of SGA was analyzed using multivariate logistic regression analyses.

Summary of Results: Mothers in the EXP group used more tobacco (80 vs. 20%; P < 0.001), alcohol (39 vs. 21%; P < 0.001) and marijuana (34 vs. 4%; P < 0.001) during pregnancy. In addition, the EXP group sought prenatal care later (first visit: 15 ± 8 vs. 9 ± 5 wk; P < 0.001) and gained less weight during pregnancy (31 ± 16 vs. 34 ± 16 lb; P = 0.02) than the unEXP group. Birthweight (mean ± SD) was lower in the EXP than the unEXP group (3179 ± 609 vs. 3369 ± 557 g; P < 0.001). In addition, the incidence of SGA was higher in the EXP group (17 vs. 9%; P < 0.001). After adjustment for covariates, the EXP group had an increased likelihood of being born SGA (OR = 1.80, CI 1.13-2.99).

Conclusions: These findings suggest prenatal MA use is associated with fetal growth restriction after adjusting for covariates. Longitudinal follow-up will determine if these infants are at increased risk for future growth abnormalities or other medical problems associated with being born SGA.

201 CONCENTRATION OF S100B IN CSF IN INFANTS WITH POST-HEMORRHAGIC VENTRICULAR DILATATION

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Purpose of Study: Premature infants are at risk for developing intraventricular hemorrhage (IVH). Post hemorrhagic ventricular dilatation (PHVD) is a major complication of IVH and contributes to long-term developmental delays. Ventricular dimensions are measured by cranial ultrasound, specifically the distance from the falx to lateral wall of the ventricle (the ventricular index (VI)) (Levene, 1981) and the width of the anterior horn (AHW) of the lateral ventricle (Davies, 2000). VI exceeding the 97% is considered PHVD. Severe PHVD is present when the VI exceeds 97% + 4 mm and the AHW is >6 mm. Progressive PHVD is treated with placement of an Omaya reservoir to facilitate removal of CSF. S100B, a marker for neuronal injury, is elevated in the CSF after brain injury. We hypothesize that S100B concentration is directly related to severity of IVH and ventricular measurements.

Methods Used: Infants with post-hemorrhagic hydrocephalus were admitted to Primary Children’s Medical Center for placement of Omaya reservoir between 10/06 and 5/08. Ventricular measurements were made using cranial ultrasound. At the time of the reservoir placement, the concentration of S100B in the CSF was measured by immunoassay (Diasorin). Data were analyzed with the Mann-Whitney test.

Summary of Results: Eleven infants were enrolled in the study. The average gestational age was 28.3 ± 1 weeks (range 26.7 to 30.27) with birth weight 1155 ± 326 gm and OFC 26.3 ± 1.8 cm. Three infants had grade 3 IVH and 8 infants had grade 4 IVH noted by cranial ultrasound in the first week of life. Average postnatal age at time of reservoir placement was 32.5 ± 2.1 days (range 20-52). All infants had severe PHVD. There was no effect of grade of IVH or ventricular measurements on CSF concentration of S100B. The average concentration of S100B in the CSF was 3.6 ± 4.2 ug/L. Six infants (55%) who required ventricular-peritoneal shunt placement had significantly elevated concentration of S100B (5.17 ± 5.3 ug/L) compared to infants who did not require shunt placement (1.71 ± 1.07 ug/L) (P < 0.01).

Conclusions: S100B was not related to grade IVH or ventricular size but was significantly elevated in those infants who required shunt placement. We speculate that infants who require shunt placement have greater CNS damage. Future studies will investigate the impact of PHVD on other biomarkers of CNS damage.

202 ROLE OF CHROMATIN IN COPPER HOMEOSTASIS IN YEAST

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Purpose of Study: Copper is an essential cofactor but becomes toxic at high levels. Therefore, cells must balance copper uptake and export/sequestration. In copper homeostasis, metallothioneins bind and deliver excess copper to transporters that export it from the cell. In the yeast S. cerevisiae, the CUP1 gene is activated robustly within minutes of exposure to excess copper, leading to rapid sequestration of the excess copper by the CUP1 protein. Within 20-30 minutes, transcription of the CUP1 gene is rapidly shut down. However, strains of yeast with mutations in certain chromatin-related components (deletions of the transcriptional activator SPJ10 and the chromatin remodeler SWI1; and point mutations in histone H2A) fail to downregulate CUP1 after the initial response. Here we examine CUP1 expression levels in these strains in extended time courses to determine their response to prolonged exposure to copper.

Methods Used: Time courses (0-240 minutes) were conducted by exposing wild type and mutant strains to 0.25-5 mM CuSO4, harvesting cells, and isolating total RNA. Real-time RT-PCR analysis was performed to detect CUP1 mRNA.

Summary of Results: In wild type cells, CUP1 mRNA levels peak at 10 minutes after induction, then decrease rapidly within 40 minutes, then increase slightly and reach a new stable expression level that depends on the amount of copper the cells are challenged with. In a swi1Δ mutant and spt10Δ-hisΔS122A mutant, the expression peaks around 20 minutes, and subsequent increases around 50 minutes and stabilizes at a lower level than wild type. Expression in a spt10Δ-hisΔS24 strain peaks similarly to the other two mutants, but stabilizes at a higher level than wild type, consistent with the previously observed shutdown defect.

Conclusions: The H2A mutants behave differently than wild type both in their short- and long-term response to copper exposure, suggesting that these residues play an important role in CUP1 regulation. Interestingly, RT-PCR reveals a subtly different pattern of regulation than previously seen by northern blotting, raising the possibility that degrading and/or 5’ end degradation may also play a role in the regulation of CUP1 mRNA. Future studies will be directed towards identifying the specific roles the H2A residues play, such as mediating interactions with other chromatin-associated proteins.

203 FETAL ALCOHOL SYNDROME PHENOCOPIES SPONDYLOCARPOTARSAL SYNOSTOSIS SYNDROME

J. Wall1, R. Rupps1, D. Krako2, N. Pavanachandran2, J. Gardiner3, C. Busko1, 1University of British Columbia, Vancouver, BC, Canada and 2 University of British Columbia, Vancouver, BC, Canada.

Case Report: We present a 6 year 7 month old female who has skeletal anomalies characteristic of spondylocarpotarsal synostosis syndrome (SSS) and was exposed to alcohol prenatally. SSS, an inherited condition, is characterized by progressive fusion of vertebrae, carpal and tarsal bones and is caused by mutations in the filamin B gene. The proposita was <3rd
204 MICRODELETION OF CHROMOSOME 15q26.2 IN A MALE: CASE REPORT

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Purpose of Study: A two year old male child was referred to dysmorphology clinic for developmental delay. He was born via Cesarean section weighing 7 lb 0 oz and measuring 21 inches. He had global developmental delay and was estimated to have low-average to borderline intelligence. His personality was described as easy-going and happy. Physical examination was significant for bilateral single palmer creases, three café au lait spots and sloping shoulders.

Methods Used: Karyotype analysis was normal 46, XY at the 500 band level. His fragile X DNA analysis was normal. A comparative genomic hybridization study revealed a deletion of chromosome 15q26.2 between 169 Kb and 1.7 Mb in size. Parental studies were normal.

Summary of Results: He was tested shortly before age three years and was behind one year in speech and six months in gross motor skills. He also has developed apraxia. His height and weight and head circumference at age three years and eight months were all between the 25th and 50th centiles.

Conclusions: Chromosome 15q26-qter deletions are uncommon, and occur as part of unbalanced translocations, de novo terminal deletions or due to ring chromosome formation. The phenotype of 15q26 deletion consists of growth retardation, developmental delay, and minor malformations. The more severe end of the spectrum includes congenital diaphragmatic hernia and dysplastic kidneys. The milder end of the spectrum includes minor facial dysmorphism with growth and developmental retardation. Café au lait macules, asymmetry and 5th finger clinodactyly in some patients have lead some authors to consider that 15q26 deletions are one cause of Russell-Silver syndrome (RSS). However, microcephaly and developmental impairment are two noticeable differences between RSS and 15q26 deletion. Interstitial 15q26 deletions that leave the telomere intact are decidedly rare. It is tempting to notice differences between RSS and 15q26 deletion. Interstitial 15q26 deletions are one cause of Russell-Silver syndrome (RSS). However, microcephaly and developmental impairment are two noticeable differences between RSS and 15q26 deletion. Interstitial 15q26 deletions that leave the telomere intact are decidedly rare. It is tempting to notice differences between RSS and 15q26 deletion. Interstitial 15q26 deletions that leave the telomere intact are decidedly rare. It is tempting to notice differences between RSS and 15q26 deletion. Interstitial 15q26 deletions that leave the telomere intact are decidedly rare. It is tempting to notice differences between RSS and 15q26 deletion. Interstitial 15q26 deletions that leave the telomere intact are decidedly rare. It is tempting to notice differences between RSS and 15q26 deletion. Interstitial 15q26 deletions that leave the telomere intact are decidedly rare. It is tempting to notice differences between RSS and 15q26 deletion. Interstitial 15q26 deletions that leave the telomere intact are decidedly rare. It is tempting to notice differences between RSS and 15q26 deletion. Interstitial 15q26 deletions that leave the telomere intact are decidedly rare. It is tempting to notice differences between RSS and

205 ASSESSMENT OF AUTONOMIC DAMAGE IN DIABETICS USING AN ISOMETRIC HANDGRIP TEST

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Purpose of Study: Isometric handgrip exercise was evaluated for its usefulness as an assessment of autonomic damage associated with type II diabetes.

Methods Used: Fifteen young adult control subjects (30.6 ± 8.6 years), 15 senior control subjects (65.8 ± 8.8 years), and 15 type II diabetics (63. ± 14.4 years), whose average body fat percentages were 40.1 ± 12.9, 36.1 ± 9.3, and 39.6 ± 15.5%, respectively, participated. Cutaneous blood flow and perspiration responses of the forearm, chest, and forehead were measured using a laser Doppler flowmeter (Biopac® module LDF100C using AcqKnowledge 3.9.1 software, Biopac Inc., Goleta, CA) and a “Q sweat” system® (WR Instrument, Stillwater, MN). Measurements were recorded at rest, during, and after isometric contractions at several tensions (10%, 25%, and 40% of maximum contraction).

Summary of Results: Cutaneous blood flow and perspiration response rates were greatest in the younger controls (P < 0.05), significantly less in the older controls (P < 0.05), and significantly even less in subjects with diabetes (P < 0.05).

Conclusions: Recent studies show that there is an impaired release of or bioavailability of nitric oxide from vascular endothelial cells associated with damage from diabetes. Since vasodilation and perspiration are mediated by nitric oxide release, it is not surprising that the present study demonstrated significantly impaired vasodilation and sweating in diabetic subjects. Ultimately, local changes in cutaneous blood flow and perspiration during isometric exercise may be a viable tool to determine the extent of autonomic damage associated with diabetes.

206 EFFECTS OF KL4-PEPTIDE SYNTHETIC SURFACTANT (LUCINACTANT) ADMINISTRATION ON CEREBRAL BLOOD FLOW IN PREMATURE LAMBS

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Purpose of Study: Exogenously administered pulmonary surfactants have significantly improved the survival of premature infants with respiratory distress syndrome. However, there is concern that endotracheal administration of large surfactant volumes may result in adverse disturbances of cerebral blood flow and oxygenation, exacerbating the risk of hypoxia or intraventricular hemorrhage. This study examined the effects of intra-tracheal administration of the KL4-peptide-containing synthetic surfactant (lucinactant [Surfaxin®]; Discovery Laboratories, Inc., Warrington, PA), on pulmonary compliance (Cpl) and cerebral and cardiovascular alterations in blood pressure (BP), heart rate (HR), cerebral blood flow (CBF) and brain tissue PO2. We hypothesized that surfactant administration would not adversely affect cerebral blood flow or oxygenation.

Methods Used: Five premature lambs (126 to 129 days gestation) were delivered by cesarean section, tracheostomized, and mechanically ventilated. The fetal head was instrumented with cerebral laser Doppler and tissue PO2 probes. Pulmonary compliance and tidal volumes were continuously monitored. Following baseline measurements, pulmonary surfactant was administered as an endotracheal bolus instillation and lambs were monitored for 3 h after surfactant administration.

Summary of Results: Following surfactant administration, significant improvements in arterial PCO2, pH, Cpl, and tidal volume (all P < 0.01) were observed. There were no significant changes in arterial BP, HR, or CBF when data were evaluated as either 1 min averages throughout the 3 h experiment, or as 1 sec averages during the 5 min following surfactant administration. Brain tissue PO2 averaged 29 ± 7 Torr during baseline and 44 ± 14 Torr during the 5 min after surfactant instillation (NS).

Conclusions: These results demonstrate the efficacy of exogenously administered surfactant, lucinactant, in improving pulmonary function in the premature ovine lung. Our data demonstrate that lucinactant administration is not associated with adverse cerebral hemodynamics and oxygenation.

207 POSSIBLE ROLE OF THE 2ND TO 4TH DIGIT RATIO AS A MARKER FOR THE DEVELOPMENT AND SEVERITY OF TYPE 2 DIABETES

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Purpose of Study: Research shows that type 2 diabetes has altered sex steroid levels in adulthood. Females have higher androgen levels, while males
have lower levels. It is unclear if diabetics also have had altered production of or exposure to sex hormones during development. This study examines whether diabetics show evidence of abnormal early hormone exposure and whether the level of early hormone exposure relates to the severity of the disease. As a proxy for early hormone exposure, we examined the 2nd to 4th digit ratio, which is thought to reflect the prenatal endocrine environment. The hypothesis is that diabetics have different 2D:4D ratios than control subjects and that the 2D:4D ratios differ in those with more severe diabetes.

**Methods Used:** The lengths of the 2nd and 4th digits on each hand were measured in triplicate with a digital caliper and averaged. The severity of the patient’s diabetes was assessed by the presence or absence of insulin use, changes in medication, hospitalization related to the disease, and secondary disorders. Data were analyzed by ANOVA or linear regression.

**Summary of Results:** ANOVA results showed a significant effect of ethnicity (F = 5.49; DF = 2, 176; P = 0.0049), i.e., white, Hispanic, black female diabetics have significantly different digit ratios, and a significant interaction between ethnicity and diabetes in females (F = 12.24; DF = 2, 176; P < 0.0001). The 2D:4D ratios were higher in white and Hispanic female diabetics vs. controls, while the ratios were lower in black female diabetics vs. controls. Analysis of the 2D:4D ratios and severity of diabetes indicated an increase in 2D:4D ratio in the left hand of females as severity of diabetes increased (P = 0.0046). When analyzed according to ethnicity, only Hispanic females demonstrated an increased digit ratio with increased severity of diabetes (P = 0.0135).

**Conclusions:** Diabetics and controls differ in 2D:4D ratios, which suggests that there may have been different levels of hormone exposure in the two groups at some time prior to the termination of bone growth. Early hormonal abnormalities may have programmed individuals to be more susceptible to diabetes. The fact that Hispanic female diabetics with severe disease also have higher digit ratios supports this conclusion.

### 208

**THE EFFECT OF NUCLEUS PULPOSUS REMOVAL ON CARTILAGE DEVELOPMENT IN MOUSE LUMBAR VERTEBRAL GROWTH PLATE**

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**Purpose of Study:** Back pain only falls behind the common cold as the most repeated reason for sick leave from work. Disk degeneration of the lumbar spine is considered to be an underlying factor of low back pain. However, little is known about the growth and differentiation of intervertebral disks and vertebrae. Disks resist compression in the vertebral column and allow flexibility between vertebrae. Disks have a central core of nucleus pulposus (NP) surrounded by a dense fibrocartilagenous ring called the annulus fibrosus (AF). It was once thought that the NP was just a semi-liquid shock absorber but now a main question is if the NP actually acts as a vertebral signaling center for growth and differentiation?

Our lab found that NP cells express brachyury and sonic hedgehog signaling leaving away from its sole shock absorber stigma. It is also known that disks do not differentiate normally in the absence of NP but become fibrotic, mimicking degeneration in older humans. In the past we have also seen that collagen in the growth plate (GP) is reduced with NP ablation, but why?

**Methods Used:** The NP were removed from disks of mice in the lumbar region shortly after birth and collected at time intervals thereafter. I took sections prepared in the lab from lumbar vertebral columns of mice of different ages, or mice from which one lumbar NP had been surgically ablated. I used a specific antibody against the collagen transcription factor Sox9 to identify the amount and localization of its expression in the NP adjacent to the ablated NP and compared this with untreated vertebrae.

**Summary of Results:** I did a preliminary age study showing that Sox9 expression peaks at 2 weeks of age in the normal mouse GP. I also saw reduced expression of Sox9 on NP ablated samples in the GP.

**Conclusions:** These studies may indicate that the NP is in fact a local controller of vertebral GP differentiation, which veers from the once-taught dogma. A better understanding of disk differentiation could create modern treatments for back pain. Since disk degeneration is a large medical issue due to aging and diseases, advancements would enhance the quality of life for many patients.

### 209

**COMPARISON OF APOLIPOPROTEIN E4 GENOTYPING BY SINGLE NUCLEOTIDE POLYMORPHISM GENOTYPING WITH RESTRICTION ENZYME DIGESTS IN ASSESSING ASSOCIATION WITH HIV-DEMENTIA**

N. Villanueva, A. Marshall, M. Agsalda, D. Troelstrup, B. Shiramizu

**Purpose of Study:** The Apolipoprotein E4 (ApoE4) allele has previously been documented in older HIV-1-infected individuals with dementia. Genotyping for the ApoE gene was performed using the gold standard of amplification of the allele followed by restriction enzyme digest mapping. While the gold standard assay is reliable, the method is a labor-intensive and is subject to misinterpretation of digested fragment sizes. Recently single nucleotide polymorphism (SNP) analyses have been used for ApoE genotyping but the reliability compared to the gold standard is variable. The objective of the current study was to compare the gold standard with SNP genotyping on a clinical cohort of subjects who were well characterized clinically.

**Methods Used:** Previously-characterized extracted DNA from peripheral blood mononuclear cells from HIV-1-infected subjects were used. For SNP genotyping by real-time PCR, two separate SNP assays were used for each specimen to determine the SNP present at codons 158 and 112. Each assay used four control samples: two homozygotes, one heterozygote, and one no template control. The resulting SNP present for each codon were used to determine the ApoE genotype. The SNP assay was performed blindly on all previously genotyped specimens.

**Summary of Results:** Eighty-one specimens were available from the previously-characterized specimens. There was a 100% concordance with genotyping that was performed using PCR and restriction digestion. Using the clinical characteristics previously reported on the cohort (J Neuroimmunol., 157:197, 2004), an independent risk of HAD relating to E4 was seen in older participants (>50 years) compared to the younger participants (<40 years).

**Conclusions:** The TaqMan SNP Genotyping Assay is a more efficient and less time-consuming method for genotype a large number of specimens for the ApoE gene compared to restriction digest of amplified products. Reliability of interpreting results using the real-time assay is greater due to the subjective nature of interpreting amplified band sizes from digested products on an agarose gel. The 100% concordance of the TaqMan SNP Genotyping Assay provides further evidence for using the assay in future studies. Support by NIH Grant #R01NS053345.

Adolescent Medicine and General Pediatrics

**Concurrent Session**

1:30 PM

Friday, January 30, 2009

### 210

**AGE ADJUSTMENT: A POOR STRATEGY FOR PREDICTING OUTCOME IN CHILDREN BORN PREMATURELY**

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**Purpose of Study:** Adjusted scores on developmental tests are commonly used for children who are born preterm to determine eligibility for early intervention (EI) in the first 24 months of life. Research is needed to determine whether adjusting versus chronologic scores best reflect a child’s abilities and need for EI services.

**Methods Used:** Seventy subjects were identified from a database of premature infants at Lucile Packard Children’s Hospital, Palo Alto, California. All subjects were born before 37 weeks gestation, had at least one California Children’s Services high risk criterion, and resided in San Mateo County. The Bayley Scales of Infant Development-2nd edition (BSID-II) was administered between 18 and 24 months of age. The BSID-II has two major scales: the Mental and the Psychomotor Development Indices (MDI and PDI). The Wechsler Preschool and Primary Scale of Intelligence-3rd edition (WPPSI-III) was administered between 31 and 38 months of age. Scores based on adjusted and chronologic ages were calculated for the BSID-II. The sensitivity and specificity of adjusted and chronologic BSID-II scores for predicting delay (scores <85) on the WPPSI-III were measured. Receiver operating characteristic

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(ROC) curves were generated to assess predictive ability and to estimate appropriate cutoff scores, using adjusted and chronicologic BSID-II scores. Summary of Results: While predictive of school WPBS-III delay, the chronicologic toddler MDI scores showed a sensitivity and specificity of 1.00 and 0.27, respectively. In contrast, the adjusted toddler MDI scores showed a sensitivity and specificity of 0.71 and 0.97, respectively. Chronicologic MDI scores of 77 were highly sensitive indicators (95% sensitive) of later delay with an area under the ROC curve (AUC) of 0.795. However, adjusted MDI scores up to 96.5 were needed to maintain the same sensitivity.

Conclusions: The use of chronicologic scores provides greater sensitivity when identifying preterm children who will likely be delayed at preschool age and therefore benefit from EI. High sensitivity ensures that all children at risk for delay will be identified. If using adjusted scores, a score of 96.5 should be used as the threshold for predicting delay to preserve sensitivity.

211 NORMATIVE POPULATION DATA FOR ANOGENITAL DISTANCE IN NEWBORN INFANTS
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Purpose of Study: In toxicological animal studies, anogenital distance (AGD) is a sexually dimorphic trait that is a well established reproductive toxicity endpoint. AGD develops under the influence of dihydrotestosterone and other androgens during fetal development, yielding a longer AGD in males when compared to females. A shortened AGD is associated with a variety of genital abnormalities in animal studies, including hypospadias and cryptorchidism. While human studies have examined the reliability and preliminary clinical significance of the measurement, little data exists on the determinants and normal variance of the measurement in a large heterogeneous population.

Methods Used: We conducted a standardized training to learn AGD measurement methodologies for humans and implemented a standardized anthropometric protocol to measure infants in the University of Washington newborn nursery in 2008. Reliability, both inter-rater and intra-rater, was evaluated prior to the start of the study. We measured 173 (86 male, 87 female) newborn infants for AGD. In addition to AGD, standard anthropometric data was collected (weight, length, and occipital head circumference) along with race and relevant gestational complications. In this study, we examined AGD for sexual dimorphism, normal population variance, and predictors of the measurement in infants using linear regression modeling.

Summary of Results: Intra-rater reliability for AGD measurement in infants was 0.75 for females and 0.92 for males. For all infants measured in the study, the mean male AGD was 51.98 mm (SD ± 3.53) and mean female AGD was 37.19 mm (SD ± 3.73) with little overlap in the male and female distributions. Multivariate analyses including all covariates, weight and length were significant predictors of AGD. Race and occipital head circumference were not associated with AGD in these models.

Conclusions: We found that AGD is an easily learned and performed measurement in newborn infants. We demonstrated that AGD is a sexually dimorphic measurement that is most strongly predicted by infant weight. The application of this measurement to clinically relevant outcomes related to in utero androgenization remains to be explored in further depth.

212 INTERNUCLEAR OPHTHALMOPLEGIA AS A PRESENTATION OF MULTIPLE SCLEROSIS IN A PRE-PUBESCENT FEMALE
K.D. Dixon, K.A. Molas-Torreblanca
University of Nevada, Las Vegas, Las Vegas, NV.

Purpose of Study: To report an unusual presentation of possible multiple sclerosis (MS) in a 6-year-old female consisting of multiple neurologic complaints. A thorough evaluation including lumbar puncture, MRI of the brain, and various serologic tests were obtained together with pediatric neurology, infectious disease, and ophthalmology consultations. This case report describes her evaluation, diagnosis, and eventual management along with a high index of suspicion for MS. The pertinent literature regarding the prevalence, diagnostic tools and management of MS in children will be reviewed.

Methods Used: We described the investigation and subsequent management of our patient with internuclear ophthalmoplegia and optic neuritis. Initial diagnosis was made on clinical suspicion and laboratory data was sent to support and confirm our diagnosis after a careful approach to exclude other common etiologies of acute non-progressive demyelinating diseases.

Summary of Results: The patient presented with sudden onset of left eye lateral deviation and pain, double vision, ataxia, along with expressive aphasia. She denied fever, vomiting or diarrhea and no recent travel. Review of systems was unremarkable and her past medical history was noncontributory. Her physical exam was significant for internuclear ophthalmoplegia. Preliminary ophthalmological tests were obtained to rule out infectious and autoimmune causes which were unremarkable. Visual Evoked Potential was consistent with optic neuritis. Initial T2-weighted MRI of the brain with contrast showed bright signals in the deep white matter of the right parietal lobe consistent with demyelinating lesions. The patient was placed on high dose corticosteroids. A lumbar puncture was obtained on admission and a MS panel was sent for Cerebrospinal Fluid (CSF) analysis demonstrating oligoclonal bands which confirmed our clinical suspicion. Repeat MRI of the brain obtained prior to discharge still showed lesions in right parietal lobe and new bright lesions in the left cerebral white matter.

Conclusions: Multiple Sclerosis, although rare in the pediatric population, should not be disregarded as a diagnosis based on age alone. Although this patient was outside of the age range for which one would consider a diagnosis of MS, her clinical and laboratory findings suggest otherwise.

213 HAIR GROOMING SYNCOPE IN A LARGE COHORT OF CHILDREN AND ADOLESCENTS
W.N. Evans, R.J. Acherman, K.T. Kip, H. Restrepo
Children’s Heart Center, Nevada, University of Nevada, School of Medicine, Las Vegas, NV.

Purpose of Study: Reflex syncope is common in children and adolescents. Hair grooming (HG) can trigger syncope (S). However, HG literature describes few patients. To assess patient profiles with HGs referred to our pediatric cardiology program for syncope

Methods Used: We identified 1,525 patients with syncope out of 65,510 consults between 5/99 and 8/08.

Summary of Results: Of the 1,525 syncope patients, 111 had HSG. 87 (78%) were girls and 24 (22%) were boys. Average age was 11.4 (4.8-17.5 years) with no sex differences. Hair cutting was significantly higher in boys: 17 of 24 (71%) boys vs 6 of 87 (7%) girls, P < 0.001. 67 (60%) had a prodrome and 49 (44%) had previous non-HGS events. Out of 111, 63 listed position before syncope: 48 (76%) standing, 8 (13%) kneeling, 7 (11%) sitting. Of 111, 69 noted a syncope duration: 59 (86%) ≤60 secs. Only 4 of the 111 described jerking motions. 109 had ECGs: 106 (97%) normal, 1 PVCs, 1 PACs, 1 junctional rhythm. 100 had echocardiograms (Echo): 95 (95%) normal, 5 minor abnormalities.

Conclusions: Hair cutting accounted for about 7% of our patients with reflex syncope. Despite reports of girls cutting hair more than 20% were boys. Hair cutting related HGS was more common in boys. Seizure-type activity was rare. Most were standing before syncope, most had prodrome, almost half had previous non-HGS episodes, durations were usually ≤60 secs, and ECGs and Echoes were frequently normal.

214 FEASIBILITY OF A WALKING SCHOOL BUS PROGRAM TO PREVENT OBESITY IN HISPANIC ELEMENTARY SCHOOL CHILDREN
C. Conklin, N. Burks, C. Roldan, A. Kong
UNM SOM, Albuquerque, NM.

Purpose of Study: Hispanic children have the highest prevalence of being overweight or obese in the US at 42.8%. Walking to school is an affordable mode of transportation that may help reduce this high prevalence. The purpose of this study was to assess the feasibility of a 10 week trial of the Walking School Bus (WSB) Program among a population of Hispanic elementary school students as a strategy to prevent obesity.

Methods Used: Kindergartners through 5th grade students who lived within a one mile radius of the participating school were recruited. Children walked on designated routes to and from school supervised by parent volunteers. Four health themes were emphasized: (1) get up and play, (2) turn off your television, (3) eat five servings of fruit and vegetables per day, and (4) reduce soda and juice intake. Pre/post questions taken from CDC 2005 Youth Risk Behavior Survey, 24-hour diet recalls, and height and weight measurements were performed to assess health outcomes.
Summary of Results: Among the 28 children who initially enrolled, three dropped out. Remaining 25 were Hispanic with 56% reporting that Spanish served as their preferred language at home, ages 5-11 years, and 64% were female. Seventy-six percent of participants walked an average of three or more times per week. BMI percentile remained fairly stable from 50.8% pre-WSB to 49.3% post-WSB (P = 0.1). According to pre/post surveys, participants increased physical activity from a mean of 4.3 to 5.3 days/week (P = 0.08) and increased their consumption of fruit from 0.83 to 1.59 servings/day (P = 0.01). Vegetable intake more than doubled according to 24-hour diet recalls (P < 0.001). There were no significant changes in television viewing time and soda/juice intake.

Conclusions: The WSB program was feasible with no excessive weight gain in the group of children and self-reported obesity reduction behavior changes. The WSB with health themes may be an important childhood obesity prevention strategy from a public health promotion perspective.

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A CURRICULUM IN CHILDHOOD AND ADOLESCENT OBESITY FOR PEDIATRIC HOUSE STAFF: A PILOT PROJECT
U. Shaikh, D. Syne University of California Davis School of Medicine, Sacramento, CA.

Purpose of Study: Approximately 35% of children and adolescents in the United States are overweight or obese. Pediatric healthcare providers have multiple opportunities to contribute to the prevention and management of pediatric obesity. Our preliminary data indicate that healthcare providers are inadequately trained in the prevention and management of pediatric obesity. Our purpose was to design and pilot test an educational program on the prevention and management of childhood and adolescent obesity in our pediatric residency training program.

Methods Used: In 2008, the authors designed and piloted a curriculum in childhood and adolescent obesity for pediatric housestaff at the University of California Davis Medical Center. The curriculum is organized into three one-hour interactive seminars presented over three months that cover all six Accreditation Council of Graduate Medical Education competencies as they relate to pediatric obesity. The seminars were based on the 2007 American Medical Association expert committee recommendations for the prevention and management of pediatric obesity. The first seminar introduced key recommendations and the evidence behind them. The second seminar included case-based problem solving. The third session introduced motivational interviewing and brief focused counseling techniques, using role-playing and case scenarios.

Summary of Results: Thirty two residents (89% of pediatric house staff) completed both the pre- and post-curriculum questionnaires. Evaluation of the program was very positive with average ratings of more than 4 on a 5-point Likert scale. Pre-post knowledge scores increased significantly. There was a statistically significant increase in the perception of house staff of the effectiveness of pediatricians in preventing and treating obesity, as well as their self-efficacy in preventing and treating obesity.

Conclusions: The pilot curriculum successfully improved knowledge, and modified attitudes and beliefs related to pediatric obesity, and showed strong participant satisfaction and educational value. Our next steps include more rigorously evaluating the effectiveness of this curriculum in changing house staff knowledge, attitudes and skills related to pediatric obesity.

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DOUBLE PORTION: AN ATYPICAL PRESENTATION OF AN MDA IN AN ADOLESCENT FEMALE
O. Ekeh, C. Barangan
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Purpose of Study: To describe the unusual presentation of a 12 year old Mexican female affected by a Muellarian Duct Anomaly (MDA) characterized by uterus didelphys, obstructive hemi-vagina and ipsilateral renal agenesis. This patient presented with a 7 month history of worsening abdominal pain. She also had urinary symptoms, vomiting, constipation and decreased oral intake. Menarche occurred 7 months and LMP 2 weeks prior to presentation.

Methods Used: Pelvic examination under anesthesia showed two vaginas in the upper 2/3; right vagina was obstructed; normal cervix visualized on the left. Pelvic CT showed hydrometrocolpos; left hydrenephrosis; duplex left collecting system; absent right kidney. Pelvic ultrasound showed uterus didelphys and congenital occlusion of one hemivagina and absent ipsilateral kidney. Pelvic MRI showed 2 uterine horns, right markedly distended; duplicated vagina with distension of right; absent right kidney. Lysis of adhesions; aspiration of right hydrometrocolpos of 600 ml of blood; posterior colporrhapy was done during laparoscopy.

Conclusions: Early and accurate diagnosis of MDAs is important. This patient presented with progressive lower abdominal pain, urinary symptoms; constipation from compressive hematocelpos. Patients with MDAs usually present with primary amenorrhea, unlike our patient. This led to an initial work up for acute appendicitis. Radiologic examinations were invaluable in making the diagnosis in this patient. Aspiration of fluid by laparoscopy was a key factor in pain management. High clinical suspicion of an MDA despite a lack of typical symptoms is important in making a correct diagnosis. Renal anomalies should also be evaluated when an MDA is diagnosed.

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RISK FACTORS FOR THE FEMALE ATHLETE TRIAD IN ELITE SWIMMERS
K.A. Bell1, R. Peebles2, M. Jacobs3, L. Bachrach4 Stanford University, Mountain View, CA; 1Stanford University, Stanford, CA and 4Stanford University, Stanford, CA.

Purpose of Study: Elite swimmers have not been thoroughly investigated for the Female Athlete Triad despite showing high rates of menstrual irregularities and that swimming is not a weight-bearing sport. We hypothesized that elite female swimmers would have a higher prevalence of the disordered eating and menstrual irregularity risk factors for the Female Athlete Triad than non-athletes.

Methods Used: Elite, NCAA Division I female swimmers (n = 43) and female non-athlete controls (n = 45), ages 18-26, from three universities in the US, were recruited using a social networking website; controls were also recruited via swimmer referrals. Study participation involved completion of online and in-person surveys and height, weight, and body fat measurements. Our primary outcome variables were 1) disordered eating pathology based upon Eating Disorder Examination Questionnaire (EDE-Q) Global scores, and 2) self-reported amenorrhea in past year (defined as 0 to 6 periods).

Summary of Results: Swimmers were significantly younger [20.0 ± 1.2 vs. 20.8 ± 1.3], taller [175.9 ± 5.7 vs. 164.1 ± 6.0 cm], and heavier [70.0 ± 6.0 vs. 66.6 ± 8.0 kg] than controls (P < 0.001), though BMIs were not significantly different between groups [22.6 ± 1.6 vs. 22.5 ± 3.0]. 97.7% (n = 42) of the swimmer group competed at the national level and trained more than 19 hours a week. Swimmers reported considerable weight pressures: 18.6% reported team weigh-ins (n = 8), 32.6% reported team body fat checks (n = 14), and 39.5% (n = 17) had been told by a coach to lose weight. Our primary outcomes revealed that while EDE-Q global scores were not significantly different between groups, significantly more swimmers than controls reported amenorrhea in the past year [20.9% (n = 9) vs. 6.7% (n = 3); P < 0.05].

Conclusions: These findings indicate a trend towards greater weight pressures in elite swimmers than previously assumed, with confirmation of menstrual irregularities in this population. Future studies should investigate bone mineral density in swimmers, especially since swimming is a non-weight-bearing sport. These data implicate a need for increased education, prevention, and treatment of the Female Athlete Triad in elite swimmers.

Cardiovascular II
Concurrent Session
1:30 PM
Friday, January 30, 2009

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ADDED STRESS TO TREADMILL EXERCISE TESTING: THE LONG AND SHORT OF IT
L.W. Raymond1, T.A. Barringer1, T.H. Blackwell2 1Univ of North Carolina, Chapel Hill, Charlotte, NC and 2University of North Carolina at Chapel Hill, Chapel Hill, NC.

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Purpose of Study: We examined testing methodology to add thermal stress to the exertion created by Bruce Protocol treadmill electrocardiography in the medical evaluation of workers exposed to hazardous materials (Hazmat) who typically sustain body temperature increases of 1.8-2.2 degrees F in Hazmat exercises.

Methods Used: We studied potential and actual Hazmat workers who wore gym clothes with (Hot Walk, HW; goal 45 minutes) and without (Standard Bruce, SB) thermally restrictive “Sauna Suits” (SS). Later subjects were tested while wearing the above, plus cotton sweat suits and a diver’s foam neoprene hood. Core temperature was measured sublingually, by tympanic membrane thermometer, and ingested thermistor. Subjective heat stress was estimated by the Young Index (neutral = 4, very hot = 8).

Summary of Results: Use of SS during HW led to increases in core temperature equal to those of Hazmat exercises. Similar increases were induced by Bruce Protocol exertion when subjects wore a sweat suit and diver’s hood in addition to SS (Hot Bruce, HB). HB is much shorter and hence more practical when testing multiple examinees.

Conclusions: Both HW and HB testing induced the desired increase in core temperature, not achieved by SB testing. The Young Index was 6.3±0.9 for SB, 6.9±0.9 for HW and 7.2±0.7 for HB (P < 0.001). HW simulates actual Hazmat responses, but is more time-consuming than HB testing.

<table>
<thead>
<tr>
<th>Number of Subjects</th>
<th>Age</th>
<th>BMI</th>
<th>Type of Testing</th>
<th>Treadmill Duration</th>
<th>Core Temp Increase</th>
<th>Rate of Increase</th>
<th>Maximum Heart Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>84</td>
<td>28.3</td>
<td>17.9</td>
<td>Standard Bruce</td>
<td>12.2 ± 2.9</td>
<td>1.1 ± 0.9</td>
<td>0.96 ± 0.4</td>
<td>181 ± 13</td>
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<tr>
<td>33</td>
<td>26.6</td>
<td>18.8</td>
<td>Hot Walk</td>
<td>17.1 ± 4.2</td>
<td>2.2 ± 0.4</td>
<td>0.49 ± 1.0</td>
<td>167 ± 11</td>
</tr>
<tr>
<td>30</td>
<td>25.7</td>
<td>3.5</td>
<td>Hot Bruce</td>
<td>14.0 ± 4.3</td>
<td>2.4 ± 1.2</td>
<td>1.08 ± 0.6</td>
<td>176 ± 11</td>
</tr>
</tbody>
</table>

219 ABNORMAL OXYGEN-PULSE KINETICS MEASURED BY CARDIOPULMONARY EXERCISE STRESS TESTING CORRELATE WITH ECHOCARDIOGRAPHIC EVIDENCE FOR LEFT VENTRICULAR DIASTOLIC DYSFUNCTION

T. Pinkert, N. Shikuma, G. Nielsen, K. Cappagli, L. Becker, J. Eaton, D. Ast, J. Groom, S. Gingrich, J. Dawson, J. Lucas North Hawaii Community Hospital, Kamuela, HI.

Purpose of Study: We sought to evaluate the relationship between echocardiographic evidence for left ventricular diastolic dysfunction and the oxygen-pulse kinetics exhibited during Cardiopulmonary Exercise Testing (CPET). The oxygen-pulse is expressed by the quotient: VO2/heart rate. CPET is a modality used to detect exercise limitation due to coronary and/or pulmonary disease.

Methods Used: 34 patients serially referred for echocardiography and CPET were enrolled. The trans-mitral Doppler signal obtained during echocardiography was used to identify the presence or absence of left ventricular diastolic dysfunction. CPET was performed on an ECG-monitored cycle ergometer to physical tolerance. The oxygen-pulse curve generated by CPET was subjectively assessed at peak exercise as follows: 1) No loss of linearity (N-LOL), 2) loss of linearity (LOLI). All enrolled patients had normal left ventricular systolic function. Among those patients who had myocardial perfusion studies, all studies were normal and had been performed within 3 months of echocardiography and CPET. The oxygen-pulse kinetics and echo-derived diastolic function data were compared using ANOVA and chi square.

Summary of Results: Among the 34 patients studied, 17 had normal diastolic function by echo (NDF), and 17 had echocardiographic evidence for abnormal left ventricular diastolic function (ADF). 13/17 (76%) of NDF patients had NLOL, whereas 14/17 (82%) of those with ADF had LOLI (P < 0.05). The mean VO2 max values for the NLOL vs. LOLI groups were 2285.75 cc/min and 1614.83 cc/min, respectively (P = 0.008). The mean VO2 max value for those with NDF measured 2136.41 cc/min, while the mean VO2 max value for those with ADF measured 1671.06 cc/min (P < 0.05).

Conclusions: Oxygen-pulse kinetics observed during CPET is a useful tool to screen for the presence of left ventricular diastolic dysfunction. LOLI may relate to hemodynamic compression of the myocardial microvasculature reflective of an elevated left ventricular end-diastolic pressure, resulting in a decrease in effort-related stroke volume and thus, the VO2.

220 OBESITY AND CARDIAC ALLOGRAFT VASCULOPATHY AFTER HEART TRANSPLANTATION

S. Carr, M. Hamilton, J. Kobashigawa David Geffen School of Medicine at UCLA, Los Angeles, CA.

Purpose of Study: There is conflicting evidence on the role of obesity in the development of cardiac allograft vasculopathy (CAV) post heart transplant. Some studies indicate that obesity with body mass index (BMI) >30 kg/m2 is associated with an increased incidence of cardiac allograft vasculopathy (CAV) but other studies have not confirmed this observation. The purpose of this single center observational study was to examine the impact of obesity on the development of CAV.

Methods Used: Between 1994 and 2008, 75 patients who underwent heart transplant were obese, defined as a pre-transplant BMI >30 kg/m2. These patients were compared with 714 nonobese patients with BMI <30 kg/m2. Outcomes for a higher obesity group, defined as BMI >33 kg/m2 (N = 19), were also assessed. Outcomes included 5-year survival, freedom from 5-year CAV (angiographic stenosis ≥50%), freedom from 5-year non-fatal major adverse cardiac events (NF-MACE; myocardial infarction, heart failure, percutaneous intervention, stroke, peripheral vascular disease), and freedom from 1-year any-treated rejection.

Summary of Results: The incidence of diabetes was comparable between the obese and nonobese patients (31.3% vs. 21.5%, P = NS). 5-year survival and freedom from NF-MACE were similar between obese and nonobese patients (74.7% vs. 77.9%, P = 0.48 and 89.3% vs. 93.0%, P = 0.19, respectively). Freedom from first-year any-treated rejection was also similar between the two groups (90.7% vs. 90.2%, P = 0.93). However, freedom from 5-year CAV was significantly higher in the obese group compared to the nonobese group (90.7% vs. 77.3%, P = 0.015). The higher obesity group yielded similar results: patients with BMI >33 kg/m2 had greater freedom from CAV compared to controls (100% vs. 78.1%, P = 0.037).

Conclusions: Obese patients with BMI >30 kg/m2 have less CAV five years after heart transplantation with comparable survival to nonobese patients. Freedom from CAV is also an apparent benefit of highly obese patients (BMI ≥33 kg/m2). The mechanism of the basis of this observation requires further investigation.

221 THE PREDICTIVE VALUE OF CARDIOPULMONARY STRESS TESTING AFTER HEART TRANSPLANTATION

K. Lo, M. Hamilton, J. Kobashigawa David Geffen School of Medicine at UCLA, Los Angeles, CA.

Purpose of Study: While heart transplantation affords recipients with improved survival and quality of life, these patients often have poor exercise tolerance due to denervation. This study examines the role of reduced peak oxygen consumption (VO2max) as a marker for poor outcome after heart transplant.

Methods Used: Between November 1996-June 2007, we evaluated 38 transplant recipients without rejection or cardiac allograft vasculopathy (CAV) who underwent cardiopulmonary stress testing (CPX). Patients were a mean 3.7 years after transplant (range 0.9-13.3 years) at the time of CPX and were assessed for: 5-year actuarial survival, CAV (+/− 30% stenosis by angiogram), non-fatal major adverse cardiac events (NF-MACE; myocardial infarction, heart failure, percutaneous intervention, pacer, stroke, peripheral vascular disease). All were on standard immunosuppression. Patients were divided into two groups, VO2max<14 ml/kg/min (n = 24) and VO2max>=14 ml/kg/min (n = 14). The baseline demographics were similar except for fewer females in the lower VO2max group (7% vs 42%, P = 0.007). Patients with lower VO2max had lower 5-year actuarial survival (70.8% vs. 92.9%, P = 0.048, Figure). 6/7 deaths in the lower VO2max group were from cardiovascular causes. There was no difference in 5-year actuarial CAV and NF-MACE.

Conclusions: A VO2max <14 ml/kg/min predicts greater 5-year mortality after the sentinel study. Lower peak VO2max may be a marker for early or
small vessel CAV not detected by angiography, and indicates the need for heightened awareness in the management of such patients.

**222**

RIGHT VENTRICULAR DYSFUNCTION IN HEART TRANSPLANT RECIPIENTS

N. Moradzadeh, M. Hamilton, J. Kobashigawa
David Geffen School of Medicine at UCLA, Los Angeles, CA.

**Purpose of Study:** Right ventricular dysfunction (RVD) immediately post heart transplantation may be due to many causes. These include pulmonary hypertension, primary graft dysfunction, insufficient preservation, and inadequate cooling. Most patients with RVD do recover function after heart transplantation, but it is not clear as to whether their long-term survival is compromised.

**Methods Used:** Between 1994 and 2008, we identified 115 patients out of 823 patients (14%) with RVD in the absence of left ventricular dysfunction. RVD was suspected by abnormal hemodynamics usually with high right atrial pressures (RAP>12 mmHg, mean RAP = 14.6) in the presence of normal pulmonary artery systolic pressures (PAS<30 mmHg, mean PAS = 22.8) and lower cardiac index (CI<2, mean CI = 1.5). RVD was then confirmed by echocardiography. All RVD was identified within the first week after transplant. The remaining 708 patients without RVD served as controls.

**Summary of Results:** 5-year survival was significantly lower in the RVD group than the control group (70.3% vs. 78.7%, P = 0.026). There was no difference in 5-year freedom from cardiac allograft vasculopathy or 1-year freedom from rejection between the two groups (see table). The causes of RVD were pulmonary hypertension (65%) and primary graft failure (35%). The major causes of death were rejection (n = 12), infection (n = 10), and CAV (n = 3) for the RVD group.

**Conclusions:** Early RVD appears to have long ranging detrimental effects on 5-year survival. Further investigation into therapies to ameliorate this poor effect on outcome is warranted.

**223**

A NON-INVASIVE MEANS TO DETECT RISK FOR REJECTION AND INFECTION IN HEART TRANSPLANT PATIENTS IN A LARGE COHORT OF PATIENTS

K. Kiyosaki, M. Hamilton, J Kobashigawa
David Geffen School of Medicine at UCLA, Los Angeles, CA.

**Purpose of Study:** ImmuKnow (Cylex, Columbia, MD) is a non-invasive immune monitoring (IM) assay that measures in vitro ATP activity of stimulated CD4 lymphocytes. A low score suggests over-immunosuppression while a high score suggests under-immunosuppression. However, in a recent small study, scores did not correlate with infection or rejection. We now review the largest IM experience in heart transplantation.

**Methods Used:** We identified 337 heart transplant patients with 864 IM assays between December 2000-July 2008. IM assays were performed 2 weeks-10 years post transplant (61% within year 1). Samples from patients with infection or rejection in the previous month were excluded. The link between IM scores of patients with and without infection (defined as requiring antimicrobial therapy; n = 38) or treated rejection (n = 8) within 1 month post IM test were examined.

**Summary of Results:** The mean IM score was significantly lower in patients who developed infection within 1 month than in patients with no ensuing infection (186.5 ± 125.8 vs 280.2 ± 126.1, P < 0.001; Figure). The mean IM score was non-significantly higher in patients who developed rejection within 1 month (326.9 ± 175.1 vs. 280.2 ± 126.1, P = 0.30), 3 of 7 rejection episodes had hemodynamic compromise, where the mean IM score was higher (491.0 ± 121.1 vs. 280.2 ± 126.1).

**Conclusions:** The non-invasive IM test appears to predict infection but the association with future rejection is inconclusive due to small number of rejection episodes, and further study with a large sample size is required. This study offers promise for the utility of IM testing in individualization of immunosuppression to balance the risks of infection and rejection in heart transplant recipients.
group (25.0% vs. 9.5%, P = 0.015). All patients with positive retrospective DSXMs were treated with triple drug immunosuppression and 6/16 received thymoglobulin, IVIG, and/or plasmapheresis immediately post-transplant. Conclusions: Retrodictive flow cytometry DSXMs does not portend poor prognosis if treated aggressively. [table]

### 225

**CARDIAC ALLOGRAFT SIZING IN HEART TRANSPLANT CANDIDATES WITH PULMONARY HYPERTENSION**

A. Ankrom, M. Hamilton, J. Kobashigawa David Geffen School of Medicine at UCLA, Los Angeles, CA.

**Purpose of Study:** Oversized donor hearts are favored for candidates with mild to moderate pulmonary hypertension (PHTN). This stringent selection may exacerbate the donor organ shortage by bypassing otherwise suitable smaller donor allografts. We hypothesize that both undersized and oversized donor hearts fare equally well in the setting of perioperative pulmonary hypertension.

**Methods Used:** 107 Patients from 2003 to 2008 were retrospectively reviewed and divided into two groups: those receiving organs from undersized donors (Donor/Recipient Weight 0.90, n = 37) and those receiving organs from oversized donors (Donor/Recipient Weight > 1.2, n = 70). PHTN was defined as systolic pulmonary arterial pressures (SPAP) > 40 mmHg. Hemodynamic data as well as 1-month and 1-year mortality were examined.

**Summary of Results:** Perioperative PHTN was seen in 49% of undersized and 57% of oversized donors (p = NS). 1-month and 1-year survival for undersized donors was 94.7% and 89.5% and for oversized donors was 100% and 90%, respectively (p = NS). Left ventricular and right ventricular ejection fractions were normal in all patients at 6 months after transplant. There was no difference between groups in SPAP at any time point from one week to 6 months post-transplant. Both groups showed reductions in SPAP over 6 months after transplant (P < 0.001; Figure).

**Conclusions:** Hearts from undersized and oversized donors fared equally well with respect to both short and long term survival as well as hemodynamic recovery and normalization of pulmonary arterial pressures over time. The selection bias favoring oversized donor hearts for patients with pulmonary hypertension may therefore be unwarranted and unjustifiably decrease the overall donor pool.

### 227

**FIRST YEAR HEART RATE AND OUTCOME AFTER HEART TRANSPLANTATION**

B. Arbib, M. Hamilton, J. Kobashigawa David Geffen School of Medicine at UCLA, Los Angeles, CA.

**Purpose of Study:** Due to denervation of the transplanted heart, the baseline heart rate (HR) after transplant is usually 90-110 beats per minute (bpm). However, some recipients have HR >90 bpm off amiodarone or beta-blockers, and the significance is unclear. This study examines the impact of HR on long-term outcome after heart transplant.

**Methods Used:** Between 1994-2008, we evaluated 528 heart transplant recipients and measured mean HR at 1, 2, 3, 4, 5, 6, 8, 10, and 12 months post transplant. No patients received amiodarone or beta blockers. Patients were divided into three groups by mean first year HR: HR >90 (range 74-90), HR 90-110, HR <= 110 (range 110-117). Endpoints including 5-year survival, freedom from cardiac allograft vasculopathy (CAV, >30% angiographic stenosis), and freedom from non-fatal major adverse cardiac events (NF-MACE, myocardial infarction, heart failure, percutaneous intervention, pacemaker, stroke, new peripheral vascular disease) were assessed.

**Summary of Results:** 5-year survival and freedom from CAV were not significantly different between groups (Table). However, 5-year freedom from NF-MACE was significantly lower in patients with HR >110 compared with patients with HR 90-110 (75% vs. 93%, P = 0.004). 3/4 patients with HR >110 had NF-MACE of heart failure or percutaneous intervention. 2/14 patients with HR >90 required permanent pacemakers.

**Conclusions:** After heart transplant, patients with slower mean HR (<90 bpm) have comparable outcome to patients with common (between 90-110 bpm) and high HR (HR >110 bpm). Faster mean HR (HR >110 bpm) is associated with the development of NF-MACE. While this is a small study that requires confirmation in a larger population, the results suggest that higher HR may be a marker for graft dysfunction and poor outcome in heart transplant recipients.
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THE VALUE OF SOCIAL WORKER AND PSYCHIATRIC PRE-HEART TRANSPLANT EVALUATION

S. Wong, M. Hamilton, J. Kobashigawa David Geffen School of Medicine at UCLA, Los Angeles, CA.

Purpose of Study: Social work and psychiatric evaluations are an essential part of the pretransplant evaluation. Candidates are defined as high-risk (HR) if they have potential for non-compliance with medications and follow-up. The post-transplant team is notified of such candidates in an attempt to ensure adequate postoperative support. However, it is not clear if a high risk (HR) pretransplant evaluation portends poor outcomes posttransplant.

Methods Used: We evaluated 567 heart transplant candidates between January 1994 and May 2008. 46 were deemed HR by psychiatry and social services. The reasons for pre-transplant HR designations were: alcohol and drug abuse history (n = 12, 26.1%), non-compliance with medications (n = 9, 19.6%), lack of social support (n = 4, 8.7%), and history of significant mood disorder (n = 21, 45.7%).

Summary of Results: Patients were followed for an average of 4.3 years after transplant and were compared to a control group who were deemed not HR during the same era. Demographics (age, gender, CMV mismatch, ischemic time, reason for transplant) between groups were similar. Compared to controls, the HR group had a trend toward lower 5-year survival (67.4% vs. 79.1%, P = 0.09), and lower first year freedom from rejection (82.6% vs. 91.2%, P = 0.06). The HR group had significantly lower 5-year freedom from cardiac allograft vasculopathy (defined as > = 30% stenosis by angiogram; 69.6% vs. 79.7%, P = 0.048) and lower 5-year freedom from non-fatal major adverse cardiac events (defined as myocardial infarction, heart failure, percutaneous intervention, pacemaker, stroke, peripheral vascular disease; 84.8% vs. 94.0%, P = 0.010).

Conclusions: Patients deemed HR by social worker/psychiatry pretransplant evaluations are at risk for worse outcomes after heart transplant, despite heightened awareness and increased surveillance by the post-transplant team. This study suggests that further discussion on whether to transplant these patients and also how to better provide posttransplant support is needed.

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THE VALUE OF SURVEILLANCE CARDIAC CATHETERIZATION FOLLOWING TOTAL CAVOPULMONARY CONNECTION PROCEDURES

K.T. Kip, W.N. Evans, A. Rothman, A. Galindo, C.M. Zeidenweber, J.C. Collazos, H. Restrepo Children's Heart Center Nevada, University of Nevada, School of Medicine, Las Vegas, NV.

Purpose of Study: Patients undergoing total cavopulmonary connection (TCPC) procedures have complex intra and extra-cardiac anatomy and physiology. Routine follow up including noninvasive testing may not detect all anatomical and physiological findings that may affect patients’ long-term prognosis.

Our aim was to evaluate the anatomical and physiological findings and concomitant interventional procedures during surveillance cardiac catheterizations in 18 asymptomatic patients who underwent TCPC.

Methods Used: We performed retrospective chart review of 18 patients who underwent surveillance cardiac catheterization between March 2003 and April 2008. We excluded patients undergoing cardiac catheterization for elective fenestration closure.

Summary of Results: Of 18 patients (PTS), 13 (72%) had an interventional procedure during the surveillance cardiac catheterization. Ten patients had coil occlusion of either an aortopulmonary (A-P) or venous (V-V) collateral; 2 patients underwent stent placement, one in the left pulmonary artery (LPA) and the other in the innominate vein (IV); 1 patient underwent balloon dilatation for aortic re-coarctation (Ao CoA). Oxygen saturation increased (92% to 95%, P = 0.02) in patients with venous collateral coil occlusion. In the 3 patients with stent placement or balloon dilation, the diameter of the stenotic vessel increased (approximately 70%), and the pressure gradient decreased. There were no complications. Table summarizes number of cases, diagnoses, and procedures.

Conclusions: Surveillance catheterization in patients with a TCPC may uncover anatomical and physiological findings amenable to intervention, which may in turn affect long-term prognosis.

Gastroenterology and Hepatology

Concurrent Session

1:30 PM

Friday, January 30, 2009

230

THE REGULATION OFHEME TRANSPORT IN THE LIVER AND DUODENUM

E. Broussard¹, Z. Yang², J.L. Akkowitiz³ ¹University of Washington, Seattle, WA and ²University of Washington, Seattle, WA.

Purpose of Study: FLVCR (feline leukemia virus, subgroup C, receptor) is a cytosolic heme exporter that protects erythroid precursor cells when heme synthesis initiates and exceeds globin translation. Although the traditional view is that heme iron is uniformly degraded to elemental iron prior to export from cells or storage, there is evidence that heme is exported intact from hepatocyte to bile and exported intact from enterocyte to the circulation. These experimental observations, plus our finding of iron overload in the livers of Flvcr deleted mice, but not in the livers of mice with Flvcr deleted only in bone marrow-derived cells (Keel et al, Science 319: 825-828, 2008), prompted the study of FLVCR function and localization in the duodenum and liver.

Methods Used: Zinc mesoporphyrin (heme analog) uptake and washout, Generation and characterization of GFP-linked FLVCR, Confocal fluorescence microscopy, 55Fe-heme transport studies, RNA isolation and quantitative RT-PCR, Immunohistochemistry, Western blot analysis

Summary of Results: FLVCR protein expression was highest in human liver and duodenum, lower in the colon, and near absent in stomach and pancreas. Gastrointestinal (Caco-2) and liver (HepG2) cell lines containing FLVCR export heme. FLVCR preferentially localizes to the apical or luminal surface of polarized Caco-2 cells when heme is in excess and to the basal surface of Caco-2 cells when iron is deficient to facilitate the directional transport of heme. FLVCR localizes similarly in HepG2 cells.

Conclusions: These observations suggest that FLVCR modulates systemic iron overload by decreasing heme uptake through the duodenum, including in hemochromatosis, where hepcidin is inappropriately low, and by allowing for the exit of heme from liver through bile. In the setting of iron deficiency, FLVCR may facilitate iron uptake. Thus, the trafficking of heme, and not only inorganic iron, may be important for maintaining systemic iron homeostasis.

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MECHANICAL VENTILATION OF PRETERM LAMBS FOR 3-4 WEEKS IS ASSOCIATED WITH NECROTIZING ENTEROCOLITIS


Purpose of Study: Necrotizing enterocolitis (NEC) is associated with bronchopulmonary dysplasia. The pathogenesis of NEC is not known, in part because large-animal models are lacking. Surgical pathology indicates mucosal disruption associated with inflammation, ischemia, and enterocyte apoptosis. We recently showed similar results at 3d of mechanical ventilation (MV) compared to high-frequency nasal ventilation (HFNV) of preterm lambs (Worthen, J Invest Med 2008). Whether preterm lambs develop NEC following 3-4 weeks of MV is not known. We hypothesized that MV for 3-4 wks will lead to flat histological architecture and loss of enterocytes in the distal ileum of preterm lambs.

Methods Used: Preterm (PT) lambs (~132d gestation; term ~150d), treated with antenatal steroids and postnatal surfactant, were managed by MV
or HFNV for 3-4 wks. Controls were term (T) lambs that breathed spontaneously for 1d or 3-4 wks. Physiological levels of arterial blood gases were maintained. Lambs were fed fresh ewe's milk. Distal ileal tissue was analyzed by morphometry and immunoblot.

**Summary of Results:** The PT MV group was the least tolerant of enteral feedings and gained the least weight. End-stage NEC was evident in 2 of the group. The group also had the shortest villi, shallowest crypts, and least amount of PCNA protein (*P < 0.05; table). The group also has less cleaved caspase 3 protein (μg < 0.05) compared to the PT HFNV group.

**Conclusions:** Villi of preterm lambs for 3-4 wks leads to histopathological evidence of NEC. Those changes were not evident with HFNV. We speculate that differences in sedation may have affected outcomes. Our model provides a unique opportunity to examine the pathogenesis of NEC. (HL62875, HL56401, HD41075, CHRC)

### 232 REMOVABLE FULLY COVERED BILIARY METAL STENTS IN BENIGN BILIARY DISEASE

D.M. Varela, S. Reicher, B. Pham, D. Chung, V. Eyssselein Harbor-UCLA Medical Center, Torrance, CA.

**Purpose of Study:** Traditionally, benign biliary diseases such as bile leaks and biliary strictures are managed with plastic stents. However, plastic stents require frequent replacements secondary to occlusion risk. Recently a fully covered metal stent was developed and is increasingly used in benign biliary disease. The aim of our study was to evaluate the efficacy and complications of removable fully covered biliary metal stents in benign biliary disease.

**Methods Used:** Fully covered biliary metal stents (Viabil, ConMed) were placed in 8 patients (sizes 10 mm diameter, length 6 cm-10 cm). Diagnoses pre-procedure were bile leaks (n = 3) and biliary strictures (n = 5). Prior to placement, patients with bile leaks failed standard therapy (biliary sphincterotomy and plastic stents) and were poor surgical candidates or denied surgery. Biliary strictures were anastomotic (n = 1) and benign/stone disease (n = 4). Strictures were located in the distal bile duct; leaks were from cystic duct stump. Removal of the stents was done by a snare device or grasping forceps. Clinical success was resolution of bile leak or stricture with normalization of laboratory values.

**Summary of Results:** Five patients had stents removed so far with resolution of bile leak (n = 2) and stricture (n = 3). Three patients are awaiting stent removal. There were no procedure-related complications.

**Conclusions:** Fully covered biliary metal stents offer a new approach to the management of benign biliary diseases such as bile leaks and strictures. They are easy to use with no significant complication rate and patency duration of 3-4 months.

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>INDICATION FOR STENT</th>
<th>STENT DURATION</th>
<th>FOLLOW UP TIME SINCE STENT REMOVAL</th>
<th>SYMPTOMS POST PROCEDURE</th>
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<td>1</td>
<td>Anatomic biliary stricture</td>
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<td>10 months</td>
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<td>2</td>
<td>Persistent bile leak</td>
<td>14 weeks</td>
<td>7 months</td>
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<tr>
<td>3</td>
<td>Persistent bile leak</td>
<td>13 weeks</td>
<td>5 months</td>
<td>No complaints, no jaundice</td>
</tr>
<tr>
<td>4</td>
<td>Biliary stricture</td>
<td>13 weeks</td>
<td>2 months</td>
<td>No complaints, no jaundice</td>
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<tr>
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<td>Biliary stricture/ elevated LFTs</td>
<td>12 weeks</td>
<td>1 week</td>
<td>No stricture seen, LFTs normalized</td>
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<tr>
<td>6</td>
<td>Biliary stricture</td>
<td>16 weeks</td>
<td>Stent in place</td>
<td></td>
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<tr>
<td>7</td>
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<td>18 weeks</td>
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<tr>
<td>8</td>
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<td>16 weeks</td>
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</table>

### 233 RISK FOR RECURRENT HEPATITIS B IN LIVER TRANSPLANT RECIPIENTS

K.T. Nguyen, M. Yeganeh, S. Saab David Geffen School of Medicine at UCLA, Los Angeles, CA.

**Purpose of Study:** Hepatitis B virus (HBV) and hepatocellular carcinoma (HCC) recurrence after orthotopic liver transplantation (OLT) is associated with increased graft failure and reduced patient survival. We investigated clinical and pathological factors associated with HBV recurrence and evaluated the long-term outcome of these patients.

**Methods Used:** 175 patients underwent OLT for HBV-related liver disease from 1997-2008 and were included in this retrospective study. Demographic, virologic, biochemical and tumor factors were evaluated using univariate and multivariate analyses to assess risk factors for HBV and HBV-related HCC recurrence as well as post-OLT survival.

**Summary of Results:** 12 patients (6.9%) developed HBV recurrence after transplantation. Mean HBV recurrence time was 28.7 ± 26.4 months. 10 of the 12 patients (83.3%) with HBV recurrence had a history of HCC prior to transplantation and 5 of these patients (50%) developed recurrence of HCC. Pre-OLT HCC and recurrent HCC were significantly associated with recurrent HBV infection after transplantation (P = 0.001 and 0.005 respectively). Age greater than 60 years at transplantation (P = 0.01), lack of pre-transplant antiviral therapy (P = 0.03), and pre- and post-OLT systemic chemotherapy (P = 0.02 and 0.005 respectively) were found to be independent predictors of recurrent HBV infection. Of 88 patients diagnosed with HBV and HCC, 13 patients (14.8%) developed HCC recurrence after transplantation. Mean HCC recurrence time was 15.8 ± 6.2 months. HBsAg positivity (P = 0.005), greater than 3 total tumors on explant (P = 0.02), total tumor burden of greater than 5 cm on preoperative imaging and on pathologic examination (P = 0.006 and 0.004 respectively), tumors exceeding UCSF criteria on explant (P = 0.005), and the presence of lymphovascular invasion (P < 0.001) were independently associated with HCC recurrence. Patients transplanted with tumors beyond UCSF criteria based on pathologic examination, had decreased survival among HCC patients (P = 0.03).

**Conclusions:** Several factors are associated with HBV recurrence after transplantation. The presence of pre-OLT HCC as well HCC recurrence post-OLT is clearly associated with HBV recurrence. Orthotopic liver transplantation of patients with tumor burden outside known staging criteria is a predictor of poor patient survival.

### 234 ANORRECTAL ULCERATIONS: A RARE PRESENTATION OF MILIARY TUBERCULOSIS

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**Case Report:** Miliary tuberculosis refers to a disseminated form of tuberculosis.Review of the literature suggests that anorectal involvement of miliary TB. A 64 year old male with no medical history presented with two weeks of anal pain.Exam revealed a large ulcer at the right aspect of the anus. This case illustrates an unusual presentation of miliary TB. The disease is uniformly fatal if untreated, so prompt diagnosis and treatment requires practitioner vigilance. Gastrointestinal TB occurs in <1% of all TB cases. PPD and CXR are unreliable, and thus diagnosis of colonic TB requires either detection of AFB or evidence of caseating granulomas. Although gastrointestinal tuberculosis is rare, our patient had anorectal disease, which occurs in only 1% of digestive tract TB. Standard four drug approach should be used for treatment of anorectal disease. In conclusion, colonic tuberculosis is a rare disease with anorectal involvement being much more unusual. A high index of suspicion must be maintained as symptoms and signs are often nebulous.
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YIELD OF ENDOSCOPIC ULTRASOUND-GUIDED FINE-NEEDLE ASPIRATION IN PATIENTS PRESENTING WITH PANCREATIC ABNORMALITIES

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Purpose of Study: Endoscopic Ultrasound-Guided Fine-Needle Aspiration (EUS-FNA) is a new method to acquire tissue for cytology. The objective of our study was to determine the sensitivity/specificity of EUS-FNA for detection of pancreatic malignancies.

Methods Used: Retrospective chart review on all patients undergoing EUS/FNA from 06/06-06/08 was done. Fifty charts were reviewed by the time of abstract submission. All the procedures were performed by the same GI specialists. Mean number of samples obtained per procedure was 2 (range 0-4). Seventy-five percent of aspirations done using a 22-gauge needle. Sixty-nine percent were done transduodenally (31% transgastric).

Summary of Results: The mean age at presentation was 63 (n = 50, 28-87) of which 30 (60%) were male. Presenting symptoms prompting investigations were abdominal pain (52%), jaundice (28%) and weight loss (26%). Diagnostic procedures prior to EUS included CT (88%), abdominal ultrasound (44%) and ERCP (42%). EUS identified a mass in 35 (70%) of patients. Of these, 25 (71%) were 1-3 cm, and 6 (17%) greater than 3.1 cm. Forty-three percent of these were in the head of the pancreas, 17% uncinate, 14% body, 11% tail and neck. Thirteen (27%) were determined malignant on cytological evaluation, 3(6%) as suspicious, 11(22%) atypical, 15(31%) benign. Of the 49 biopsies, 7(14%) samples were insufficient for diagnosis. Of the 13 malignancies, 5 were adenocarcinomas and 3 neuroendocrine tumors. Thirty final diagnoses were available for data analysis. Of these, 5 had insufficient sample during biopsy for cytological interpretation; nevertheless, they were all diagnosed as non-malignant conditions. All suspicious/malignant reports were confirmed to be malignant (n = 12); 9 of the 13 cases that were assessed to be benign/atypical were subsequently confirmed to be benign. Based on these results, the sensitivity and specificity of EUS-FNA were calculated to be 75% and 100% respectively.

Conclusions: EUS-FNA is an accurate method for tissue diagnosis of patient with pancreatic lesions. Patients with suspicious/indeterminate EUS-FNA cytology are usually malignant.

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ATYPICAL CELLS ON EUS-GUIDED PANCREATIC FNA: LONG-TERM OUTCOME

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Purpose of Study: Obtaining tissue diagnosis of the pancreatic mass can be challenging. Endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) has emerged in recent years as a leading diagnostic modality. FNA results are usually reported by the pathology as benign, malignant or atypical cells. The aim of our study was to evaluate incidence of atypical cell diagnosis in EUS-guided FNA of pancreatic masses and long-term outcome of patients with this diagnosis.

Methods Used: We retrospectively reviewed all EUS-guided FNAs of pancreatic masses from 2001-2008 done at the tertiary level medical center. All FNAs were performed by one endoscopist with extensive experience in EUS (VE). The final diagnosis was made by clinical follow up, and from pathology specimens obtained endoscopically, surgically or post-mortem.

Summary of Results: 74 patients with FNA of the pancreas masses were reviewed. 80% had pancreatic head mass; 9% had mass in the body and 9% in the tail; one patient had diffusely swollen pancreas. 29 patients (39%) had an atypical cell diagnosis; 20 patients (27%) were benign and 25 patients (34%) had malignant results. Of the 29 atypical diagnoses, 17 were diagnosed on long term follow up as malignant (59%), 7 cases as benign (24%), and 5 were unknown (17%).

Conclusions: Atypical cell diagnosis on EUS-guided FNA of pancreatic masses is common. Majority of atypical FNAs had malignancy as a final diagnosis. Pathological diagnosis of atypical cell on pancreatic FNA requires further investigation and close follow up. Diagnostic yield can be improved with additional immunohistochemical staining. Studies evaluating utility of immunohistochemical staining for various tumor markers in pancreatic FNAs are ongoing at our institution.

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EFFECTIVENESS OF FERIDEX MRI CONTRAST AGENT FOR MRI OF THE LIVER AND DIAGNOSING LIVER LESIONS

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Purpose of Study: Feridex is a nanoparticle molecular imaging contrast agent that is used for liver MRI studies to improve the conspicuity of lesions. Specifically, it is used to identify hepatocellular carcinoma (HCC) and metastases to the liver, as well as focal nodular hyperplasia (FNH), a benign lesion that has variable amounts of reticuloendothelial system (RES). The objective of this study is to determine the effectiveness of Feridex, as a contrast agent for MRI of the liver, in diagnosing FNH and differentiating benign from malignant liver lesions.

Methods Used: The design is a retrospective analysis of Feridex MRI imaging reports of 60 patients who underwent a Feridex MRI of the liver between 6/28/2002 and 10/1/2007, and who either had a tissue diagnosis or serial follow-up for at least one year and an imaging diagnosis of FNH. Radiology and pathology records were searched and reviewed for patients with FNH and a comparison group of patients who had liver lesions other than FNH.

Summary of Results: There were 41 patients with FNH (24 proven by biopsy, 17 diagnosed with one-year follow-up) and 19 patients without FNH (1 hepatocellular adenoma, 4 hemangioma, 6 HCC, 6 metastases to liver, 2 cholangiocarcinoma). Fisher’s exact test discriminating FNH from all other lesions, and benign from malignant histologies, yielded P-values of < 0.001 for both per patient and per lesion analyses.

Conclusions: This study proposes that Feridex-enhanced MRI of the liver aids in diagnosing FNH and differentiating benign from malignant lesions, but its statistical rigor is limited by its retrospective nature. This analysis suggests that Feridex-enhanced MRI is sensitive and specific for FNH, but a prospective randomized controlled trial, or a more comprehensive retrospective analysis of all Feridex-enhanced MRI, is necessary to better quantify its efficacy.
Purpose of Study: Breast milk contains TGFβ which is vital for gut and immune development in infants. Little is known about TGFβ levels and bioactivity in infant formula and its capability to deliver bioactive TGFβ to the gastrointestinal tract. This is also difficult to predict since adequate in-vitro models mimicking infant stomach digestion are lacking. IFR has implemented a novel dynamic gastric digestion model to more accurately simulate gastric digestion and study survival of bioactive compounds.

Methods Used: The model was fed an acid solution comprised of HCl, NaCl, CaCl2, and NaH2PO4 to simulate the residual gastric condition after emptying. Then reconstituted commercially available infant formula (Enfamil® Lipil®) or human milk was introduced and gastric-enzymatic secretions, NaCl, CaCl2, NaH2PO4, phosphatidyl choline, pepticin and gastric lipase added to mimic real-time digestion (T = 37°C). Furthermore, the pH was titrated over time to a final pH = 2. Samples were collected over a 72 min. period exceeding the estimated stomach passage time for liquid nutrition. TGFβ levels were measured using an R&D Systems ELISA kit. TGFβ bioactivity was determined in a Mv1Lu (mink lung cell line) growth inhibition assay. Specificity of the TGFβ activity was supported using TGFβ antibodies. All samples were tested in dose response using triplicate determinations. Inhibition of cell growth was determined using the Picogreen reagent (InvitroGen) as a measure of DNA content.

Summary of Results: Reconstituted infant formula and human milk TGFβ concentrations were measured and compared to levels during digestion. Substantial levels of TGFβ were detected until 36 min of digestion followed by a gradual decline over time. In addition, TGFβ bioactivity measurements followed a similar pattern revealing almost complete retention within 36 minutes of digestion.

Conclusions: Substantial recovery of TGFβ immuno-reactivity and bioactivity was measured during infant formula and human breast milk digestion in the stomach. Our study suggests that infant formula can provide bioactive TGFβ to the infant’s gastrointestinal tract similar to breast milk.

239 HUMAN MILK AND SOME INFANT FORMULA EXHIBIT TRANSFORMING GROWTH-FACTOR BETA RELATED ACTIVITY IN THE HT-2 CELLS

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Purpose of Study: Transforming growth factor beta (TGF-β) provided through human milk (HM) is thought to play a key role in maintaining appropriate immune function in infants. In the present study we assessed and compared the overall and TGF-β2 specific activity in HM and infant formula using an IL-2 dependent assay of HT-2 murine cells.

Methods Used: This bioassay has been used to study the regulation of T-cell growth by TGF-β inhibiting the S-phase progression of murine HT-2 cells stimulated with interleukin-4. It is an inhibition cell growth over a dose-response of TGF-β, which is usually a two-fold sequential dilution. Mature HM samples containing different concentrations of TGF-β were collected over the course of the first three months of lactation from mothers in the US and Mexico, while infant formula samples (Enfamil® Lipil®/A+) containing 4900 ± 1400 pg/ml TGF-β were obtained from US, China, Mexico, Thailand, and the Philippines from the manufacturer.

Summary of Results: TGF-β in HM was predominantly in the latent form, as evidenced by substantial increase in activity following acidification. Although the majority of TGF-β in infant formula was in the active form, acid activation still yielded increased bioactivity. HM inhibited cell growth in a dose-dependent manner within TGF-β ranging from 600 to 14000 pg/ml. HM at a concentration of TGF-β equivalent to that found of Enfamil (4900 ± 1400 pg/ml) exhibited a 2-fold higher total bioactivity, which may be explained in part by additional functional factors in HM that also inhibit cell proliferation in this model system, differences in physicochemical properties of the two milk sources, or potential matrix effects. The TGF-β related activity in infant formulas did not vary by location; similarly, TGF-β related activity in HM was not different between US and Mexican mothers. TGF-β2 specific neutralizing antibody decreased the activity 2-3 folds for infant formula and 2-7 folds for HM in this assay, suggesting that some, but not all, of the observed activity in either HM or infant formula is due to TGF-β2.

Conclusions: These results demonstrate that both infant formula and HM exerted similar TGF-β related activities in HT-2 cells.

240 PREDICTORS OF STIGMA & DISCLOSURE AMONG PATIENTS INITIATING ANTIRETROVIRAL THERAPY IN RURAL RWANDA

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Purpose of Study: This study examined predictors of HIV-related stigma, disclosure, and family member HIV-testing among patients initiating antiretroviral therapy (ART) in rural Rwanda.

Methods Used: Clinical, demographic, and perceived stigma data were collected at ART initiation for 501 patients receiving one of two ART delivery models (community-based or clinic-based). Multivariate logistic regression was used to identify predictors of enacted stigma, internal stigma, disclosure, and HIV testing of family members.

Summary of Results: Patients receiving ART in the area where HIV care was clinic-based, rather than community-based, reported significantly less enacted stigma (OR = 0.05, 95%CI [0.03-0.09]) and internal stigma (OR = 0.4, 95%CI [0.2-0.6]). Men were also significantly less likely to report enacted stigma. Illiterate individuals and those with higher incomes were less likely to report internal stigma.

Conclusions: A community-based model of ART delivery may foster higher levels of disclosure, which may in turn, lead to increased levels of perceived stigma; however the relationship between region/type of care and perceived stigma persisted even after controlling for disclosure. Regional variability in perceived stigma or other unmeasured characteristics may explain these differences.

241 BARRIERS TO EFFECTIVE IMPLEMENTATION OF IMMUNIZATION INFORMATION SYSTEMS IN A PRIVATE PROVIDER SETTING

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Purpose of Study: In 2006, Nevada ranked lowest in the nation on childhood immunization rates at 71.5% for the 4:3:1:3 and 59.5% for the 4:3:1:3:3:1 vaccine coverage rates. To increase immunization rates, the state established a web-based immunization information system (IIS) and passed a law mandating all state providers of VFC to report data to the state by July 1, 2009. The aim of this pilot study was to determine the barriers to the effective implementation of the IIS in a private provider setting.

Methods Used: A computer was dedicated to IIS in a general pediatric facility located in the suburbs of Las Vegas, Nevada. The practice has 7 full time pediatricians, 9 medical assistants, and served 27,000 patients in 2006. Staffs were trained on the use of IIS. The study period from January - September 2008 was divided into 3 quarters. Educational and technical support was provided by the research team, once in the first quarter, once in
the second quarter, and nine times in the third quarter. During these visits, the practice was provided with feedback on their entries. Data was collected on entry times, feedback and if the feedback was received by the staff. Staffs were surveyed on their experiences in implementing the IIS.

Summary of Results: During the study period, the practice provided care to 20,000 children between the ages of 0 - 9 years and a total of 246 (1.2%) new records were created in the IIS. Participating physicians were aware of benefits of IIS. New records were mostly created in the months when the research team provided feedbacks: 93% versus 7% in other months. The highest number of entries was noted in the months when the physician investigator provided feedback to the physicians. More entries were made to existing records as staffs tended to update existing records rather than create new ones. Time was the greatest obstacle reported. Conclusions: Although pediatricians in private practice are aware of the benefits of IIS, it appears to be underutilized in its effective implementation. IIS with initial entries from birth records and mandatory reporting may potentially improve private providers effective implementation of an IIS.

242 EFFECTIVENESS OF IMMUNIZATION REMINDER/RECALL PROGRAM IN A HIGHLY TRANSIENT COMMUNITY

I. Jack1, E.E. Ezanholue1, L. Shah1, K. Larsen1, Crocc2, Neyland1 1University of Nevada School of Medicine, Las Vegas, NV; and 2School of Public Health, University of Nevada, Las Vegas, NV. Purpose of Study: Client reminder/recall has been a proven effective intervention to increase immunization rates. In 2006, Nevada ranked the lowest in childhood immunization rates at 59.5% for the 4:3:1:3:3:1 vaccines. This can be attributed to the higher transient community. Methods Used: A reminder/recall program was established in a medical school outpatient clinic in Las Vegas, Nevada. Intervention: From December 2007 through June 2008, a chart review was performed and postcard reminders were sent to patients seen at the clinic 1 month before they turned 12 and 18 months. A postcard recall (first recall) was sent 1 month following the scheduled 12 and 18 months well child visit to patients who missed the appointment. A phone recall (second recall) was made 2 months after the scheduled 12 and 18 month well child visit to patients who missed their initial appointment and did not respond to the postcard recall. During the phone recall, patients were asked if they received the postcard reminder/recall and if they received immunization at another location. Summary of Results: 607 postcard reminders were sent to patients who turned 12 and 18 months during the study period. Ninety-one percent (551/607) received the reminders and 16.2% (89/551) responded by receiving immunization. 474 received 1st postcard recall and 11.8% (56/474) responded. 305 received phone recalls and 9.8% (30/305) responded. 46 (7.6%) patients who received the reminder responded by getting immunized at another healthcare facility. Overall, 40% (221/551) of patients who received an initial reminder received immunization. There was a statistically significant trend in the cumulative percentage of patients responding to the postcard: χ²(4) = 6.02, p = 0.050. Conclusions: An immunization reminder/recall program appears effective even in a transient community. A single reminder appears to be a more efficient method compared to recalls (either by postcard or by phone) in improving immunization rates in our highly transient populations.

243 ALCOHOL CONSUMPTION MAY BE RESPONSIBLE FOR RESIDUAL EXCESSIVE DAYTIME SLEEPINESS IN TREATED SLEEP APNEA PATIENTS

R. Shrivastava, S. Grewal, R. Khan, S. Kapre San Joaquin General Hospital, French Camp, CA. Purpose of Study: This study aims to address the management of residual daytime sleepiness despite Continuous Positive Airway Pressure (CPAP) therapy, due to effects of alcohol on the sleep apnea. Patients with nightly ethanol use at home have suboptimal polysomnography test done in sleep laboratory. This understimates their sleep apnea and results in inaccurate CPAP pressure titration. Abstinence from alcohol may be effective therapy for these patients. Methods Used: In this study patients who returned with a complaint of residual daytime sleepiness (n = 103) were screened for alcohol use (n = 37). They were evaluated for the CPAP compliance. Using the standard methods of assessing compliance, two groups of compliant (n = 23) and non-compliant (n = 14) subjects were created. All subjects were initially diagnosed with sleep apnea in the sleep laboratory where alcohol use was not permitted. A questionnaire addressing their alcohol use and sleep quality was introduced to both groups. Other causes of residual sleepiness were ruled out. Two subjects (n = 2) from compliant group were removed due to confounding effect of shift work. The daytime sleepiness was measured by a validated scale, Epworth sleepiness scale in both groups. All subjects were counseled regarding the effects of alcohol on sleep and possible worsening of sleep apnea. CPAP pressure as determined in the sleep laboratory without alcohol use may be suboptimal. They were advised to abstain from alcohol. Both groups were re-evaluated with Epworth sleepiness scale at 6 and 12 weeks with significant improvement in sleepiness scores in CPAP compliant group subjects who abstained from alcohol. One patient from non-compliant group was lost to follow up. Summary of Results: Thirty five percent subjects used alcohol nightly or many nights of the week. This reflected the characteristics of patient population of the sleep center. 34% subjects were compliant with CPAP therapy. 51% subjects (n = 12) of the compliant group (12/21) had a mean improvement in Epworth sleepiness scale from 19 to 8, whereas only 30% (n = 4) subjects improved from Epworth scale mean value of 21 to 15 in the non-compliant group (4/13) at 12 weeks. Conclusions: Alcohol is an important variable in the management of sleep apnea. Further studies are needed, in addition to abstinence to address this problem.

244 PROSTATE CANCER INFORMATION

R. Yousefi Fraser Valley BC Cancer Agency, Surrey, BC, Canada. Purpose of Study: In this study, we aim to evaluate the quality, adequacy and sufficiency of the information that prostate cancer patients are receiving from urologists and radiation oncologist within the Fraser Valley community. We hypothesize that 1) Patients are exposed to a variety of information sources that may not be adequate enough to answer all their questions and help them decide on what treatment choice works best for them. 2) Patients might not be receiving sufficient information regarding the potential side effects of their treatments, i.e. sexual side effects after radiation therapy. 3) There is variation on the information that different prostate cancer patients are getting from their urologists and radiation oncologists. Methods Used: A survey was designed and distributed to the offices of urologists and radiation oncologists in the Fraser Valley Community (B.C., Canada). The information gathered was analyzed and the adequacy and similarity of the information between different practices was evaluated. Summary of Results: 26 surveys were distributed. 13 urologists and 6 radiation oncologists have completed the survey, a response rate of 73%. 100% of respondents believe that distributing resources to their prostate cancer patients is important because it helps patients with their psychological issues. 89% of respondents felt distributing resources minimizes the time they need to spend with their patients in follow up. 74% of respondents felt that resources assist patients in decision making process and help them to standardize the information given to prostate cancer patients. 89% (give written information to their patients and pamphlets and booklets are the two most popular types of written information. Only 26% refer to internet resources and 37% refer to local prostate resource centers. While 53% of physicians state their written information covers side effects and risks and benefits of treatments, the sample written materials that the doctors included with the survey did not adequately cover these topics. Conclusions: In conclusion this survey reviews practices of urologists and radiation oncologists in a community cancer center. Results show that information is being distributed in the form of office discussions, pamphlets and booklets; but may not reflect the needs of patients.
Purpose of Study: Physicians face competing ethical values of truth telling and beneficence when deception may be employed in the patient care. The purposes of the current study were to assess resident physicians’ attitudes toward lying, types of lies that may be used, and what reasons were given for lying in healthcare.

Methods Used: Resident physicians from twenty-two specialties at Loma Linda University Medical Center responded to posed forum questions in required online courses taught from 2002 through 2007. After obtaining IRB review and determination of exempt status (OSR# 58013), lesson responses related to lying were collected, blinded, and manually coded by two individuals using NVivo software. Both qualitative and quantitative analyses of the responses were performed with links to various attributes such as gender, department, and location of medical school. A 95% binomial proportion confidence interval was used to analyze the attribute data.

Summary of Results: The majority of residents (90.3%) would reveal the truth about medical errors. Similarly, many residents (55.7%) would disclose the truth regarding unanticipated events, especially if the error was serious enough to result in a lawsuit. Finally, residents primarily lie for altruistic reasons and benefitting the patient and protecting themselves, three-quarters of the willingness to lie, only a small group (4.2%) was self-serving.

Conclusions: While the majority of residents studied will disclose a medical error, only half will be truthful with the insurance company, and only one-third will consistently disclose near misses. But to make a distinction between benefiting the patient and protecting themselves, three-quarters of the residents will disclose an unanticipated event, even if such disclosure might result in a lawsuit. Finally, residents primarily lie for altruistic reasons and less for egoistic or self-serving purposes that may or may not result in harm to patients, insurance companies, and/or physicians themselves.

246 ORAL HEALTH TRENDS AMONG PRIMARY SCHOOL CHILDREN IN RURAL UGANDA

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Purpose of Study: Poor oral health has been indicated in predisposing individuals to chronic health conditions such as cardiovascular disease. In Uganda, access to dental care is limited in rural communities as dental professionals are concentrated in urban areas. The Brighter Smiles Uganda Project began assessing oral health and providing annual fluoride treatment and oral health education to primary school students in rural Ugandan communities in 2006. It was hypothesized that with preventative fluoride care, the ratio of total carious teeth to total number of teeth would decrease in each community.

Methods Used: Total numbers of carious teeth were assessed in July 2008 in both non-fluoride and fluoride treated children in Kawolo and Kalisizo by Makerere University Dental Interns in collaboration with UBC project team members. Information regarding dental visits and overall utilization was obtained by questionnaire.

Summary of Results: In Kawolo, it was found that there was a significant decrease in the ratio of total carious teeth to total number of teeth in the fluoride treated group. Kalisizo, although not statistically significant, followed a similar trend (Table 1). The percentages of students reporting having seen a dentist and their reasons for dental visits were compared between communities. The primary reason for dental visits in each community was dental extractions/fillings in contrast to dental check-ups/cleanings (Table 2).

Conclusions: The main reason for dental visits was extractions/fillings, which shows that dental care is under-utilized for preventative measures such as check-ups and cleanings in these communities. After three years, there was a general trend in both communities showing a decrease in the ratio of carious teeth to total number of teeth with annual fluoride treatment.

Table 1

<table>
<thead>
<tr>
<th>Ratio of Carious Teeth to Total Teeth</th>
<th>Non Fluoride</th>
<th>Fluoride</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Kawolo</td>
<td>0.122</td>
<td>0.05</td>
</tr>
<tr>
<td>Kalisizo</td>
<td>0.105</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*indicates statistical significance

247 MEDICAL SCREENING EXAM STUDY: AN OPPORTUNITY TO MEASURE HEALTH OUTCOMES AND PATIENT SATISFACTION

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Purpose of Study: Emergency Departments (EDs) have become the largest providers of non-emergency care to persons who are insured or uninsured. In response, several hospitals have implemented medical screening exams (MSE) to detect and refer patients seeking ED care for non-emergent problems. We studied health outcomes and satisfaction among non-emergent patients who were screened out of the ED.

Methods Used: A telephone survey was completed by a convenience sample of patients who were screened out of an urban, academic ED during a 4-month period. Eligible participants included non-urgent patients with normal vital signs who presented to the ED with one of five pre-selected chief complaints (toothache, rash or skin problem, back pain, cough, cold or bronchitis, or extremity problem). Participants were called 4 to 6 days after being discharged from the ED. Questions addressed the symptom improvement or resolution, satisfaction with the screening process, ability of screened out patients to contact a primary care provider or clinic, and ED recidivism.

Summary of Results: Of 320 known eligible patients, 162 (51%) were asked to participate in the study, and 57 consented (18%). Of those who consented, 46 (14%) of the total eligible population completed the questionnaire. Respondents’ age ranged from 20-64 years old, 59% were men, and 63% were uninsured. The study showed that 43% (95%CI 29-58%) reported improvement of their symptoms, 39% (95%CI 25-53%) were unchanged, and 17% (95%CI 6-28%) had worsened. Regarding their ED visit, 50% (95%CI, 36-64) were satisfied, 24% (95%CI 12-36%) were neutral, and 26% (95%CI 13-39) were unsatisfied. In addition, 41% (95%CI 27-56%) accessed a community health provider, and 6% (95%CI 0-14%) returned to an ED within 6 days for a different complaint.

Conclusions: Although the data suggests half the participants who where screened out of the ED had symptom resolution and were able to access community health care, the study’s low enrollment rate severely limited our ability to generalize to the larger population of individuals who are screened out of EDs. This demonstrates the difficulty in studying a patient population who is reluctant to consent to follow-up. The safety and efficacy of MSE programs have yet to be assessed successfully. Other methods of accessing this population and incentives for participation should be considered.

248 MONTANA PRIMARY CARE PHYSICIAN WORKFORCE STUDY

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Purpose of Study: To identify primary care physician shortages in Montana, in which counties these shortages exist, and what primary care specialties are most needed.

Methods Used: 922 allopathic and osteopathic primary care physicians were identified using the 2006-07 Montana Medical Association Physician Directory. Primary care was defined as family medicine, general internal medicine, general pediatrics, and obstetrics-gynecology. From June through December 2007, all the physicians or their office managers were surveyed by phone to determine actual patient care hours worked per week; this was converted to full-time equivalent hours. Thirty-four or more hours per week of direct patient care was defined as one full-time equivalent (FTE). The number of FTEs for each primary care specialty in each county was summed, giving the county’s actual number of FTEs. This calculated total county FTE number was then compared to the county’s expected FTE number as defined by its population (compared to the national average physician to population ratios). The calculations were applied on a statewide level as well.
Summary of Results: There was an oversupply in family medicine of +106.93 full-time equivalent hours statewide and in 32 of Montana’s 56 counties. There was a significant undersupply of FTEs in obstetrics-gynecology (~38.15 FTEs statewide and in 50 of 56 counties), internal medicine (~62.59 FTEs statewide and in 52 of 56 counties), and pediatrics (~72.17 FTEs statewide and in 54 of 56 counties). The physician response rate was 88.9%.

Conclusions: The study concluded that there is a relative oversupply of family medicine FTEs and a relative undersupply of the other primary care specialties in Montana, as compared to the national averages. It is postulated that the oversupply of family medicine FTEs may be due to the wide scope of family practice; this may partially compensate for the undersupply of other primary care specialties. While the cause of the relative over- and undersupply of primary care specialties in Montana remains unclear, it is evident that Montana has a great many rural counties that are in dire need of every, and any, kind of primary care specialty.

249 SEEKING BEHAVIORS, HEALTH SERVICES UTILIZATION, AND RECEIPT OF COUNSELING BY CLINICIANS AMONG LATINO PATIENTS IN PUBLIC SECTOR CLINICS
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Purpose of Study: Although several studies have shown positive associations between patients’ health seeking behaviors and health outcomes, less is known about these relationships in disadvantaged patients. This study examined the association between patients’ interest in seeking health information, using health services, and receiving clinician counseling among a sample of low-income Latino patients. The hypothesis is that patients with high services utilization and who seek health information proactively are more likely than those who are not to receive health promotion counseling by clinicians.

Methods Used: An analysis of an interval patient assessment conducted at four adult health clinics within the Venice Family Clinic (VFC) system in Los Angeles County was carried out to test the hypothesis. Analysis was focused on data collected from 301 survey respondents who identified themselves as Latinos. Study variables included patients’ socio-demographics, health seeking and utilization patterns, and reports of receiving clinician counseling on health habits, such as nutrition and physical activity.

Summary of Results: Analysis revealed that out of a list of 14 topics, only 5 topics on health-related information were sought by survey respondents, with “managing chronic disease” (58%) and “maintaining healthy weight” (60%) being the most frequent. Also, from a list of 13 available services in the clinics, an average of 1.4 services per person were used, with “reproductive care” (19%) and “prenatal care” (12%) being the most frequent. Patients who acquired greater amounts of health-related information were more likely to use a higher number of services rendered in the clinic (r = 0.31, P < .001). Additionally, a higher number of services used in the clinic was associated with a greater frequency of communication between patient and clinician (r = 0.28, P < .001). Better communication with clinicians was also positively correlated with receiving more health promotion counseling (r = 0.41, P < .001).

Conclusions: Strategies to encourage and motivate Latino patients to become more proactive in utilizing health-related services may facilitate patient-centered care and receipts of higher health promotion counseling.

250 DEVELOPMENT OF A METHOD FOR ASSESSING STRENGTH IN THE EXTENSOR DIGITORUM BREVIS MUSCLE
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Purpose of Study: A dynamometer was developed and tested to determine its usefulness in measuring strength of the extensor digitorum brevis muscle (EDB).

Methods Used: An ankle-foot orthosis was developed to isolate and measure the strength of the EDB. This dynamometer placed the foot in 15° of inversion, which has been shown to isolate EDB from EDL in preliminary studies. It also involved a small band placed on the second and third toes. The band was connected to a stainless steel bar, which bent slightly in response to flexion of the EDB and contained four strain gauges that were wired as a Wheatstone bridge. Ten healthy male and female subjects (ages 20-40), without neurological/orthopedic deficits, participated in 9 trials. First, electromyography (EMG) established maximum strengths for each of EDB’s agonist muscles—extensor digitorum longus (EDL) and tibialis anterior (TA). Then, during maximal EDB contraction, EMG activity was recorded for each muscle: EDB, EDL, and TA.

Summary of Results: Average EDL and TA activity during maximal contraction of EDB was less than 30%. The day-to-day coefficient of variation for each subject was less than 10% of each muscle’s maximum strength.

Conclusions: Because of its superficial location, the EDB may be used to evaluate a variety of neuromuscular disorders. Although its electrical activity has been extensively studied, isolated EDB strength has been difficult to assess. In this pilot study, total activity of the accessory muscles EDL and TA was <30% of their respective maximum strengths (<10% variation) during maximum EDB contraction. Thus, the dynamometer provided a reliable means of evaluating EDB strength with minimal involvement of the agonist muscle groups.

251 CORRECTING MISCODED MORTALITY DATA: HEART FAILURE AS A CASE STUDY
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Purpose of Study: Garbage codes in mortality data are those codes which do not signify an underlying cause of death, including ill-defined, intermediate, immediate, and unlikely or ambiguous causes of death. Garbage codes lead to inaccurate assessment of the relative importance of causes of death. The goal of this work is to redistribute garbage codes to correct underlying causes of death to provide better information to policymakers. Because of its multiple etiologies, heart failure (HF) is the largest garbage code and is used as a case study for our redistribution model.

Methods Used: Data was abstracted from the WHO mortality database, which totals 100,552,416 deaths across 601 country years. 3.5% of all deaths were coded to HF. 39 underlying causes to be redistributed to (targets) were defined via literature review. The HF universe was defined as deaths due to HF and each of the 39 targets. Country years were stratified as developed and developing using the World Development Indicators, 2008. A linear regression was applied to estimate the relationship between the proportion of garbage within the HF universe to the proportion assigned to each target. Summary of Results: The model mimics redistribution, with the y-axis representing an all target, no garbage universe. Ischemic Heart Disease (IHD) accounted for the highest rate of mis-coded heart failure deaths yielding beta = -0.847 (P < 0.001). 15 out of 39 targets had negative beta values signifying that as HF garbage is redistributed to its targets, the proportion of target within the HF universe increases.

Conclusions: The results support our hypothesis that this method can predict ideal, no garbage situations to improve cause of death data. The predicted post-redistribution target proportions align with high income vs. developing country epidemiological profiles. This method can be applied to other causes of death to maximize the use of available data and provide better evidence on the major causes of death by country to inform policy decisions.

Immunology and Rheumatology I
Concurrent Session
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Friday, January 30, 2009

252 HUMAN TRANSITIONAL B CELLS IN ADULT AND FETAL SPLEEN

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\textbf{Purpose of Study:} Mouse studies show that immature B cells derived from bone marrow (BM) travel to the spleen where they become mature follicular and marginal zone B cells. Multiple models of mouse splenic B cell development have been proposed. Two, and in some cases three, developmentally sequential populations of transitional B cells (T1, T2 and T3) in mouse spleen have been postulated. Studies of transitional B cells in human spleen have not been reported, although data from peripheral blood suggests that surface markers used to define transitional B cell subsets in the mouse can be used to identify their human counterparts. The aim of this study is to identify human transitional B cell populations in human adult and fetal spleen based on patterns of surface marker expression that have been used to define transitional B cell subsets in the mouse spleen.

\textbf{Methods Used:} Human adult and fetal spleen samples were stained for four-color flow cytometry to assess co-expression of CD24, IgD, IgM, CD21, and CD23.

\textbf{Summary of Results:} Surface phenotypes observed in adult human spleen were consistent with those for murine T1, T2 and mature B cell populations reported by Carsetti’s group, although CD21+ cells were rare in our samples. A population with a phenotype that corresponds to the murine CD21\textsuperscript{INT} T2 B cells described by Rawlings’ group was present in adult human spleen. These CD21\textsuperscript{INT} T2 B cells were larger than cells with a follicular mature B cell phenotype, suggesting that this population is more likely to contain cycling cells as reported in the mouse. In 18-week fetal spleen, IgM+ B cells were detected. In contrast to the adult spleen, splenic fetal B cells at week 18 displayed a prominent CD24\textsuperscript{–}CD21\textsuperscript{–} (T1) population as well as CD21\textsuperscript{INT} T2 B cells with few cells expressing the follicular mature phenotype or high levels of CD21. Consistent with murine studies, a comparison of size indicated that human fetal CD21\textsuperscript{INT} T2 B cells, but not T1 cells, are likely to be cycling.

\textbf{Conclusions:} Our data suggest that markers of murine transitional B cells can be used to distinguish subsets of human splenic B cells. The emergence of B cells that exhibit a T1 phenotype early in the fetal period suggest that these cells are likely to be the developmental counterparts of T1 B cells identified in mice.

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\textbf{RAS EXPRESSION IN LUPUS LYMPHOCYTES}

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\textbf{Purpose of Study:} Ras proteins are small guanine triphosphatases that play a complex role in cell activation, proliferation and inflammatory responses. Ras has three isoforms, H-Ras, K-Ras and N-Ras, which are structurally similar, however have subtle yet important differences in tissue expression, intracellular localization and signal transduction. Several studies suggest that Ras overexpression, as well as other abnormalities in activation and signaling, may play a role in the pathogenesis of systemic lupus erythematosus. The purpose of this study was to quantify Ras and its isoforms (H-ras, K-ras, N-ras) in active and inactive lupus patients, as compared to healthy controls.

\textbf{Methods Used:} Seven consecutive patients with active and inactive lupus were recruited from our rheumatology clinic, as well as five healthy controls. Peripheral blood leukocytes were separated from whole blood and used in immunocytochemical studies to measure the levels of Ras using anti-ras antibodies and those specific for H-Ras, K-Ras and N-Ras. Immunocytochemical quantification was conducted using a laser scanning cytometer. Western blot analysis was used as an additional measure of Ras levels in the experimental and control subjects. Lymphocyte activity in the SLE subjects was assessed clinically and by SLE disease activity index (SLEDAI) scores. Student t-test was used to assess statistical significance.

\textbf{Summary of Results:} From the samples analyzed, there were significantly higher levels of pan-Ras in patients with lupus as compared to healthy controls. Looking at the individual Ras isoforms in inactive lupus patients (SLEDAI 0-3) and controls, there was no predominance of one isoform over another. However, in active lupus patients (SLEDAI 4-16) there was a clear predominance of H-Ras and N-Ras versus K-Ras, with H-Ras being the most abundant form.

\textbf{Conclusions:} In this study, there seems to be an overexpression of Ras in lupus patients, with a predominance of H-ras and N-ras in active lupus patients. A number of functional differences between Ras isoforms have been reported. Recent research has shown that different Ras isoforms can signal from both the plasma membrane and Golgi apparatus thereby leading to an increased probability of one isoform versus another might offer an explanation for the differences in Ras signaling observed in lupus versus normal T cells. We are planning to further investigate the Ras pathway abnormalities in lupus.
on prednisone (1 mg/kg). On hospital day three she developed dyspnea and respiratory distress subsequently requiring mechanical ventilation.

Additional laboratory studies revealed positive acetylcholine receptor antibodies. Plasmapheresis was started, symptoms dramatically improved and patient was extubated. Prednisone was gradually tapered down. CT of chest did not show a thymoma. At discharge cosinophilia resolved and CK level normalized.

Polymyositis is rarely found in association with MG. If it occurs, MG usually precedes polymyositis, however polymyositis may occasionally be the first manifestation or both may present concomitantly as in our case. Thus the treatment will include both corticosteroids and plasmapheresis.

256 DETECTING HYDROXYCHLOROQUINE-RELATED RETINOPATHY: SENSITIVITY AND SPECIFICITY OF CLINICAL ELECTROPHYSIOLOGICAL AND PSYCHOPHYSICAL TESTS

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Purpose of Study: Hydroxychloroquine (HCQ or Plaquenil) is an oral medication used to treat many chronic autoimmune diseases including systemic lupus erythematosus and rheumatoid arthritis. In rare cases, HCQ induces retinopathy that if detected early, may be reversible. Despite the many testing methods screening for this, there has yet to be a consensus as to which test has the highest degree of sensitivity. The purpose of this study was to answer this question.

Methods Used: Tests commonly used for HCQ patients include the multifocal electroretinogram (mERG), electro-oculogram (EOG), color vision testing, visual field testing, and full-field electroretinography (ERG), along with a comprehensive ophthalmic examination. In this retrospective study, medical records of consented participants were obtained from which test results were abstracted and correlated with clinical impressions.

Summary of Results: Test data from 41 participants were examined. Their clinical examinations noted evidence of retinal changes in six patients. The etiology was attributable to HCQ toxicity in two of them. Both patients had abnormal mERGs and visual field testing defects. As a group, patients taking HCQ had a slight trend towards reduced mERG amplitudes and delayed timing in central and paracentral regions even with normal ophthalmic examinations. EOG and ERG were not diagnostic.

Conclusions: In our group of patients with HCQ-induced retinopathy, mERG and visual field testing demonstrated localized abnormalities consistent with toxicity. Color testing, EOG and ERGs were generally within normal limits and not informative. The trend in the direction of local sensitivity reductions observed in HCQ patients as a group merits further prospective study to determine if there is a correlation between these reductions and cumulative dose exposure. Also it would compare the current testing methods and a non-invasive procedure such as autofluorescence. Based on this preliminary data, mERG combined with visual field testing and a comprehensive ophthalmic exam are most suitable in managing HCQ patients.

257 MULTICENTRIC RETICULOHISTIOCYTOSIS PRESENTING WITH CLINICAL FEATURES OF DERMATOMYOSITIS AND RHEUMATOID ARTHRITIS

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Case Report: Multicentric reticulohistiocytosis (MRH) is a rare multisystemic disease characterized by prominent cutaneous and articular findings. It causes a papulonodular skin eruption due to histiocytic infiltration of the skin. The cutaneous findings with a prodrome of erythematous, predominantly photodistributed maculopapular eruption can be clinically consistent with dermatomyositis (DM). Joint manifestations of bilateral symmetric polyarthritis can lead to a misdiagnosis of rheumatoid arthritis (RA). We present a case of MRH presenting with clinical features simulating DM and RA.

A 67-year-old Cuban lady presented with a 6 month history of skin lesions and painful joints. Joint pains involved the interphalangeal and MCP joints of the hands, wrists, shoulders, and knees. Pain was associated with morning stiffness and swelling. Skin rash was initially erythematous and involved face, neck, upper trunk and hands. Physical examination revealed confluent, erythematous maculopapular rash on face, neck and joints of the hands. V-shaped pattern erythema on the chest was remarkable. Peri-orbital edema with swelling was significant. Symmetric polyarthritis of joints of the upper extremities and knees was detected. Labs revealed elevated ESR & CRP. Muscle enzyme levels were normal. Rheumatoid Factor was negative. X-rays showed no erosions. Biopsy of skin lesion revealed a dermal infiltrate mainly composed of histiocytic multinucleated giant cells containing cosinophilic cytoplasm with a ground-glass appearance. The cells were positive for CD68. The pathologic findings were consistent with MRH. Prednisone with methotrexate was introduced with significant improvement of symptoms.

A 67 yr old female patient with diffuse, bilateral, symmetric polyarthritis similar to RA and a skin rash simulating DM but the ultimate diagnosis was MRH.

It is important to consider the possibility of MRH when evaluating a patient with a diagnosis of dermatomyositis and/or rheumatoid arthritis. Differentiating between these entities is of importance because of therapeutic and prognostic significance. The treatment options and future complications vary greatly between these diseases.

258 RHEUMATOID ARTHRITIS (RA)-RELATED AUTOANTIBODIES ARE ASSOCIATED WITH PULMONARY AIRWAY ABNORMALITIES IN INDIVIDUALS WITHOUT RA

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Purpose of Study: In RA autoantibodies are often elevated prior to the onset of joint symptoms. However, the site where autoantibodies are generated during pre-clinical RA is unknown. The association of smoking with RA and the known high prevalence of lung disease early in articular RA has led to the hypothesis that the lung may be a site of early RA-related immune dysregulation. The purpose of this study was to determine if lung abnormalities are detectable in subjects with RA-related antibody positivity and no clinically-apparent joint disease.

Methods Used: Seven healthy subjects (cases) with highly specific RA-related antibody positivity (anti-CCP and/or 2 or more RF isotypes [IgG, IgA, IgM]) were selected from a cohort of first-degree relatives (FDRs) of probands with RA created to investigate the pre-clinical phase of RA development. Seven antibody negative FDRs (controls) were selected matched to the FDR cases on age, sex, race, and smoking-status. All FDRs underwent questionnaire analysis for joint and lung disease, joint and pulmonary physical examination, pulmonary function testing (PFTs), and lung imaging with high-resolution computed tomography (HRCT). All HRCts were interpreted by a radiologist blinded to the antibody status of the subjects.

Summary of Results: The mean age of antibody positive FDRs was 57 (range 36-78), and 5/7 (71%) were female. All FDRs had no joint disease by history and examination at time of lung evaluation. All FDRs were non-smokers and had normal lung examinations and PFTs. However, 6/7 (86%) autoantibody positive FDRs had abnormal HRCT with evidence of airway disease consistent with air trapping/bronchiolitis, versus 0/7 of antibody negative FDR controls (P = 0.03; non-parametric paired analysis).

Conclusions: In FDRs with RA-related antibody positivity but no clinical evidence of articular RA there is evidence of lung airways disease - even in the absence of smoking. As airways are a site of interactions between environmental exposures and the immune system, the lung abnormalities reported here suggest that the lung is either a site of pre-symptomatic RA-related immune dysfunction or that the lung is a site of early RA-related target-organ injury.

259 A CASE OF KIKUCHI-FUJIMOTO DISEASE

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Case Report: Kikuchi’s disease, also called Kikuchi–Fujimoto disease or Kikuchi’s histiocytic necrotizing lymphadenitis, is a rare, benign condition of unknown cause, usually characterized by cervical lymphadenopathy (LAD) and fever. We present a case of kikuchi’s disease in a young female.

The patient was 20-year-old Southeast Asian lady presented with recurrent fevers (highest 102°F), rashes, severe fatigue, sore throat and malaise. She denied any sick contact. No arthralgia, myalgia or oral ulcers. On physical exam patient had cervical LAD up to 4 cm, involving posterior cervical nodes on the left side of the neck. No skin rash was identified and no joint inflammation noticed.

Laboratory finding on presentation were as follows: white blood cell counts: 3.5 bil/L (mild leucopenia), hemoglobin 11.0 g/L, erythrocyte sedimentation rate (ESR) 45 mm/hr, Anti-nuclear antibody (ANA) negative, rheumatoid factor negative. Patient had tuberculin skin test positive at age 16 years and was treated with isoniazid and pyridoxine for 9 months.

Serology for ebstein bar virus, cytomegalovirus, HIV, human herpes virus 6 and 8, toxoplasmosis, yersinia enterocolitica, and cat scratch disease was negative. Computed tomography (CT) of chest, abdomen and pelvis were normal without any evidence of LAD in other parts of the body. Surgical excision of cervical lymph node was done and biopsy showed interfollicular areas containing immunoblasts, histiocytes, plasmacytoid T-cells and lymphocytes. Cell necrosis and pyknosis, karyorrhectic debris, and deposits of fibrinous material were seen. Flow cytometry did not show evidence of lymphoproliferative disorder or lymphoma. Cultures for viral, fungal, tuberculosis (acid fast bacilli) and bacterial etiology were negative.

The biopsy was consistent with kikuchi-Fujimoto disease. Thus a 20-year-old with fever and cervical LAD along with finding of mild leucopenia and anemia, elevated ESR, diagnosed with kikuchi disease based on lymph node biopsy.

Kikuchi’s disease can be associated with B-cell lymphoma and Still’s disease. Biopsy should be performed, despite the self-limited nature of this syndrome. Other causes of fevers and LAD must be ruled out as in our patient. Some patients with Kikuchi’s disease subsequently develop lupus, thus ANA test should be performed in patients with suspected Kikuchi’s syndrome.

260 PERFORMANCE OF THE CONNECTIVE TISSUE DISEASES SCREENING QUESTIONNAIRE (CSQ) AND AUTOANTIBODY TESTING FOR IDENTIFYING PATIENTS WITH UNDIAGNOSED RHEUMATOID ARTHRITIS (RA) IN AN URBAN COMMUNITY HEALTH FAIR

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Purpose of Study: The purpose of this study was to determine the sensitivity and specificity of the CSQ with and without antibody testing for identifying subjects with findings suspicious for RA in an urban community health fair arthritis screen.

Methods Used: Health fair participants were offered free, single-visit RA screening with CSQ, rheumatoid factor (RF) and anti-CCP testing, and joint examination by a rheumatologist of PIPs, MCPs, wrists, elbows, and MTP squeeze testing. Subjects were excluded if they had a prior RA diagnosis. Patients were categorized from their CSQ responses as possible RA (3 RA symptoms) or probable RA (7 RA symptoms) - not including erosions or RF testing. Without knowledge of CSQ or antibody results, at the end of the screening visit the examining rheumatologist classified subjects as suspicious for RA or other inflammatory arthritis based on abnormal joint exam.

Summary of Results: 600 health fair participants were screened: mean age 58; 74% female; 88% White, 2% Black, 6% Hispanic, and 1% Asian. Reason for screening: 31% joint symptoms, 25% relative with RA, 21% general check-up, 9% RF positive, 4% CCP positive. 24% reported 3 or more ACR RA criteria on CSQ, 6.2% had a joint exam suggesting possible RA. 11% subjects were CCP positive but had a negative CSQ and no tender or swollen joints. CSQ positivity was 46% sensitive and 74% specific for the rheumatologists’ designation of possible RA. CSQ and the addition of RF and anti-CCP testing changed the sensitivity to 64.3% and specificity to 72.9%.

Conclusions: The combination of CSQ and RA related autoantibody testing has fair sensitivity and specificity for detecting possible RA in a community arthritis screen. These results suggest that CSQ and antibody testing can be used in population screening to identify patients with possible RA that may benefit from further evaluation.

Infectious Diseases

Concurrent Session

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Friday, January 30, 2009

261 VIRAL ENVELOPE STRUCTURE DETERMINATION OF NEUTRALIZING ANTIBODY ESCAPE IN MOTHER TO CHILD TRANSMISSION OF HIV-1

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Purpose of Study: Mother-to-child transmission of HIV-1 has been shown to occur in utero, during delivery, and through breastfeeding. It is unique among the different modes of communication in that the infant is exposed to antibody before viral infection. While the presence of antibodies antagonizes viral transmission, certain variants can nonetheless escape neutralization. The precursor envelope glycoprotein gp160 and its mature derivatives gp120 and gp41 are integral determinants of such escape. Structurally, the HIV envelope protein is flexible and can thus tolerate mutation without compromising target cell binding and entry. We hypothesize that discrete amino acid changes between viral envelope variants are responsible in part for differences in neutralization resistance of vertically transmitted variants.

Methods Used: In our studies, we compare the full length gp160 coding sequence in three mother-infant pairs where highly resistant infant variants are selected from among a population of maternal viruses that include variants both sensitive and resistant to neutralizing antibodies.

Summary of Results: Early neutralization assays indicate that recapitulation of a unique maternal viral envelope sequence in the infant backbone in the V5 region of gp120 renders the viral construct sensitive to neutralization comparable with levels seen in the native maternal variants.

Conclusions: Further testing of the construct against maternal plasma will provide more insight into the role of the V5 region in antibody neutralization.

262 COMPARISON OF HIV VARIANTS IN BREAST MILK AND BLOOD: SENSITIVITY TO VIRAL ENTRY INHIBITORS

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Purpose of Study: Chronically HIV-infected individuals harbor a diverse population of virus. However, transmission to another host selects for only a few variants, which predominately utilize the CCR5 co-receptor for cell entry. Although this transmission “bottleneck” was recognized over a decade ago, the biologic basis for this phenomenon has yet to be elucidated. Our lab has shown that variants in breast milk are genetically distinct from variants circulating in blood, yet what these genetic differences mean functionally remains unknown. Breast milk abounds with substances that limit access to CCR5, thus we hypothesized that HIV variants emerge from this milieu with enhanced abilities to interact with CCR5.

Methods Used: Pseudovirions were generated using clonally amplified env from the plasma and cell-free breast milk of 10 HIV-infected women from the Zambia Exclusive Breastfeeding Study. As an indirect measure of viral transmission, certain variants can nonetheless escape neutralization. The biologic basis for this phenomenon has yet to be elucidated. Our lab has shown that variants in breast milk are genetically distinct from variants circulating in blood, yet what these genetic differences mean functionally remains unknown. Breast milk abounds with substances that limit access to CCR5.

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trend towards greater sensitivity of breast milk clones to both drugs compared to plasma clones. However, when using a Generalized Estimating Equations model to account for each IC50 value and the correlation between samples in the same woman, the differences were not significant.

Conclusions: Despite the lack of statistical significance, these preliminary findings suggest that HIV variants perhaps evolve in the breast milk milieu towards a phenotype that renders them more sensitive to entry inhibitors. However, further investigation is needed with an expanded sample size of patients and clones to confirm these findings.

263 TREATMENT OF HELMINTH CO-INFECTION IN HIV-1 INFECTED INDIVIDUALS IN RESOURCE-LIMITED SETTINGS

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Purpose of Study: The HIV-1 pandemic has disproportionately affected individuals in resource-constrained settings where other infectious diseases, such as helminth infections, are also highly prevalent. There are biologically plausible reasons for these effects and findings from multiple studies suggest that helminth co-infection may adversely affect HIV-1 progression. Since publishing a systematic review of this topic, additional randomized controlled trial (RCT) data have become available. Thus, we sought to re-evaluate the available evidence to determine the impact of helminth eradication on HIV-1 progression as determined by changes in CD4 count, viral load, or clinical disease progression.

Methods Used: Using a search strategy developed with the Cochrane Hiv/AIDS Group, we searched for published and unpublished randomized and quasi-randomized controlled trials in The Cochrane Library, MEDLINE, EMBASE, CENTRAL, and AIDSEARCH. We also searched databases listing conference abstracts, scanned reference lists of articles, and contacted authors of included studies. Upon study identification, data were extracted from the studies and authors were contacted for further information where necessary.

Summary of Results: We identified 7,019 abstracts, of which three RCT’s met inclusion criteria. All three trials showed beneficial effects of helminth eradication on markers of HIV-1 disease progression. When data from these trials were pooled, the analysis demonstrated significant beneficial effects of deworming on both HIV-1 RNA levels (standard mean difference = -0.22 [95% CI -0.44 to -0.01]; P = 0.04) and CD4 counts (standard mean difference = -0.23 [95% CI -0.44 to -0.02]; P = 0.03).

Conclusions: Meta-analysis of all available RCT data suggests that deworming co-infected individuals may delay HIV-1 disease progression. These studies evaluated different helminth species and different interventions and further trials are necessary to evaluate species-specific effects and to document long-term clinical outcomes following deworming.

264 RED BLOOD CELL VIRAL TRAP

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Purpose of Study: Viruses must attach to cell surface receptors to enter and infect host cells, an essential stage in the early viral life cycle. Human Immunodeficiency Virus type 1 (HIV-1) is restricted primarily to CD4+ T cells and certain monocyteic cells because they express the receptor and coreceptors required for viral adhesion, CD4 and CCR5/CXCR4. CD4 and CCR5 can be expressed ectopically on host cells that lack the ability to support viral replication. This may redirect the virus to the non-permissive cells, potentially lowering viremia and lessening negative manifestations of infection. Red blood cells are abundant, found throughout the body, enucleated and lack transcriptional machinery. Co-expressing CD4 and CCR5 on red blood cells may allow these cells to act as a sink, trapping the virus inside a dead-end host cell, preventing viral replication and minimizing viral entry into CD4+ T cells.

Methods Used: A CD4-CCR5 fusion gene has been constructed and will be placed under the control of the erythroid-specific Rhd promoter in the FG11F lentiviral vector. The Rhd promoter controls the expression of the antigenic determent Rh factor D protein, which is expressed specifically and robustly on red blood cell membranes. The FG11F lentiviral vector can integrate into cell lines or in primary human hematopoietic stem cells. The CD4-CCR5 fusion gene was created through a two step PCR: the first step amplifies the two individual genes creating an overhanging complementary region; then the two PCR products are combined by fusion PCR via the newly created complementary sequences.

Summary of Results: The constructs have been made, and further studies are in progress. The FG11F lentiviral vector can be used to examine the activity of this fusion receptor in vitro on red blood cells derived from human hematopoietic progenitors, or in vivo in humanized mouse xenograft models of HIV-1 infection.

Conclusions: The goal is to determine whether red blood cells expressing the CD4-CCR5 fusion receptor can limit HIV pathogenesis. The advantages of expressing CD4 and CCR5 as a single, bi-functional receptor are the simplicity of having a single transcript yielding a 1:1 ratio of the two receptors, and the potential enhanced viral trapping due to the proximity of the receptors because of their common linkage. These studies will examine the efficacy of a red blood cell viral trapping approach to inhibit HIV-1 replication.

265 SEXUALLY TRANSMITTED INFECTIONS AND BACTERIAL VAGINOSIS AMONG HIV-1 INFECTED PREGNANT WOMEN IN NAIROBI: IS SYNDROMIC MANAGEMENT EFFECTIVE?

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Purpose of Study: HIV-infected women with sexually transmitted infections (STI) or bacterial vaginosis (BV) during pregnancy are at increased risk for vertical HIV transmission, premature delivery, low birthweight babies, and neonatal infection. In resource-limited settings, diagnostic laboratory testing for STI and BV is not routinely available and most pregnant women are managed using syndromic algorithms developed for non-pregnant, non-HIV-infected women.

Methods Used: HIV-1-infected pregnant women were interviewed and cervicovaginal swabs were collected for chlamydia, gonorrhea, trichomonas, and bacterial vaginosis. Blood was collected for RPR, CD4 count, and HIV-1 viral load. Independent t-tests and Chi-square tests were performed to define risk factors for STI and BV. Sensitivity, specificity, positive and negative predictive values were calculated using laboratory results as the gold standard.

Summary of Results: Among 441 pregnant, HIV-1-infected women, 223 (51%) were found to have abnormal discharge on exam. Prevalence of BV was 37%, trichomonas 16%, chlamydia 4%, syphilis 3%, and gonorrhoea 2%. Twenty-two percent of women had one or more STI. Compared to women without BV, women with BV had higher CD4 counts (493 vs 454 cells/µL; P = 0.01) and higher frequency of abnormal vaginal discharge on exam (5% vs 47%, P = 0.05). Women with one or more STI also had significantly higher CD4 counts than women without STI (P = 0.03). Compared to women without STI, significantly more women with one or more STI were <21 years old, had not attended secondary school, and had a history of a previous STI. Employing a syndromic diagnostic algorithm using abnormal discharge on exam and the presence of one of these 3 risk factors resulted in a positive predictive value (PPV) of 30% and a sensitivity of 45%. The sensitivity of using abnormal discharge on exam to predict BV was 57% with a PPV of 42%.

Conclusions: One of 5 women in this cohort had an STI on routine screening, and 1 of 3 had BV. Syndromic management performed poorly for diagnosis of STI and BV among pregnant HIV-1-infected women in this cohort. Rapid, inexpensive, and accessible diagnostic tests would facilitate diagnosis and treatment of these women who are at risk of complications during pregnancy.

266 OUTER MEMBRANE VESICLES IN SALMONELLA TYPHIMURIUM

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Purpose of Study: All Gram negative bacteria release outer-membrane derived vesicles (OMVs). These OMVs have been shown to be an important toxin delivery system and mediate the effects of endotoxin and enterotoxin, among others. Preliminary data has shown that macrophages can induce...
OMV release and may, in fact, represent a means by which macrophages sample bacterial antigens. Finally, intravascular pathogens like Salmonella may use OMV release to change their outer membrane identity as they transition from an extracellular to intracellular existence. The purpose of this study was to devise methods to study Salmonella typhimurium OMVs, characterize macrophage induced OMV release, and elucidate the regulation of OMV release.

Methods Used: Molecular cloning techniques were used to generate S. typhimurium mutants. Western blotting was used to assay OMV production. Cultured murine macrophage lines were used to test the effect of macrophages on OMV production.

Summary of Results: A new method of OMV purification was devised utilizing smaller culture volumes and provided for more efficient assay of OMV production. It was demonstrated that culture media from the RAW macrophage cell line induced increased OMV release by S. typhimurium. Finally, a targeted knockout of the Crp (cAMP regulatory protein) gene in S. typhimurium was shown to abrogate OMV release.

Conclusions: Outer membrane vesicles are an important component of the Gram negative host-pathogen interaction. However, relatively little is known about the process of their production and release. This study has shown that macrophages release a soluble factor into culture media that increases OMV production by S. typhimurium. In addition, knockout of the Crp gene in S. typhimurium greatly diminished both basal OMV and macrophage induced OMV release. This finding provides evidence that OMV release is a regulated process affected by cAMP signaling.

267 CHITOSAN NANOPARTICLES FOR ANTIMICROBIAL TREATMENT AGAINST CUTANEOUS PATHOGENS

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Purpose of Study: Skin infections are a major concern due to the increasing prevalence of antibiotic resistance in two of the most common bacteria: Staphylococcus aureus and Propionibacterium acnes. Methicillin-resistant S. aureus (MRSA) is responsible for an estimated 18,000 deaths each year while 60-70% of P. acnes are resistant to common antibiotics. One potential new antimicrobial is chitosan, a derivative of the crustacean shell chitin. It is a polycationic polymer with broad spectrum antibiotic activity and low toxicity towards mammalian cells. The positively charged chitosan molecule is thought to interact with the negatively charged bacterial cell membrane and cause cell lysis. This mechanism of killing makes it difficult for bacterial resistance to develop. Studies on nasal and oral drug delivery have also found chitosan to enhance paracellular transport of drugs across the epithelium by opening tight junctions. Alginate, a polymer extracted from brown algae, can be used with chitosan to form nanoparticles (NP) with antimicrobial activity that can also enhance delivery of other therapeutics.

Methods Used: Alginate was first gelated to form the core of the NP using CaCl2 to cross-link its guluronic acid units. Chitosan was then dissolved in distilled water and ready for use. The bacterial activity of the NPs and controls were assessed using colony forming unit (CFU) assays. The two bacteria used for testing were P. acnes and S. aureus. Effectiveness of killing was judged relative to no treatment.

Summary of Results: Chitosan’s bacterial activity was found to be pH dependent, with optimal killing at pH 6. In addition, S. aureus appears much less susceptible to chitosan’s antimicrobial activity than P. acnes. Alginate was shown to be non-bacterial at all the pH’s tested.

Conclusions: Future formulations of chitosan-alginate NP’s need to take into account the pH of the environment and the pathogen targeted. Further antimicrobial activity of chitosan and NP will need to determined using in vivo skin infection model.

268 DOES DISSEMINATED METHICILLIN RESISTANT STAPHYLOCOCCAL AUREUS(MRSA) CAUSE VENOUS THROMBOSIS: A CASE SERIES AND LITERATURE REVIEW

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Purpose of Study: ITP is found in younger individuals and no definitive specific etiology. A few reports from Europe suggest that antimicrobial therapy of H.pylori may correct ITP.

Methods Used: Two elderly males presented with bruising and thrombocytopenia. Both were found to have elevated IgA and IgG antibodies to H. pylori by serologic testing. Platelet bound antibodies were absent in both patients.

Summary of Results: Both patients responded to omeprazole, clarithromycin and metronidazole administered over 10 days. Both individuals had nadir platelet counts of 52,000 and 60,000/mm3 respectively. Platelet counts began to rise in 4-12 weeks following initiation of therapy and normalized 10 months after therapy. Indeed one patient was found to have lung cancer one year later and tolerated chemotherapy without thrombocytopenia.

Conclusions: ITP is found in younger individuals and no definitive precipitating events have been described. Both of our patients had serologic evidence for H.pylori infection and responded to specific antimicrobial therapy directed to this organism with resolution of thrombocytopenia within 10 months. Cross reactive antibodies were suspected but not serologically confirmed.

270 CONSTRUCTION OF A RECOMBINANT YELLOW FEVER 17D CLONING VECTOR

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Purpose of Study: Yellow Fever virus vaccine (YF 17D) has been shown to generate highly proliferative and functional memory T-cells against YF virus. Its insertion into a stable plasmid has made it a valuable player in the development of recombinant vaccines. Previous studies have shown that insertion of foreign genetic elements can result in the expression of protein while not comprising the competence of the YF17D. The goal of our research was to design a recombinant YF17D virus for use as a vaccine vector to deliver HIV-1 antigen. Our strategy was to insert a cloning site between the Env and NS1 genes in a bacterial plasmid containing the YF17D genome.

Methods Used: The YF17D plasmid, pACNR, was grown in E.coli DH5a cells and purified. Since YF is translated as a single polypeptide, appropriate cleavage sites needed to be engineered upstream and downstream of the cloning site. We used fusion PCR to join three DNA fragments, generating the cloning site. The first 9 amino acids of the NS1 sequence were duplicated, codon optimized, and inserted at the 5' end of the cloning site to facilitate appropriate processing of the inserted genetic element and enhance its stability. Downstream of the cloning site, a Dengue-4 stem anchor sequence was used in lieu of YF stem anchor sequence to enhance stability and preserve appropriate processing. This construct was then inserted into pACNR using restriction enzyme digestion and ligation.

Summary of Results: To date, we have generated the fusion PCR products and have inserted the cloning cassette into the YF17D plasmid. It has not yet been shown if this construct is stable in bacterial culture.

Conclusions: The Yellow Fever Vaccine is an excellent HIV vaccine prospect given its proven immunogenicity and safety. Other studies using YF17D to deliver antigen have garnered positive results. Here, we characterized a strategy for the development of a recombinant YF17D cloning vector. Successful construction of this vector will permit foreign genes to be introduced into the Yellow Fever genome following standard cloning techniques. The potential for this system to test large numbers of genes is promising. Ultimately, recombinant YF vaccine vectors will be tested in animal models to determine their potential for use in human subjects.

Morphogenesis and Malformations

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A POPULATION-BASED STUDY OF HYPOPLASTIC LEFT HEART REVEALS NOVEL CHROMOSOME ABNORMALITIES

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Purpose of Study: Hypoplastic left heart (HLH) is a form of congenital heart disease of unclear etiology. Although this disorder causes substantial morbidity, HLH has been difficult to study since cases at individual hospitals are relatively infrequent. We sought to identify factors that lead to HLH by systematically analyzing a large population for cases of HLH and identifying potentially associated genetic changes.

Methods Used: We ascertained all cases of infants with HLH born between 1987-2003 in the California Birth Defects Monitoring Program. Cases of HLH confirmed by autopsies, echocardiography, and surgical reports were included. We assessed for the presence of chromosomal abnormalities and of non-cardiac malformations and associated these with specific heart malformations.

Summary of Results: From a population of over 4 million live births, we ascertained over 700 cases of HLH. The incidence in males was greater than in females. We found several novel chromosome abnormalities in addition to aneuploidies and deletions on distal 11 q. HLH cases were categorized to discern classic HLH from those with unbalanced atrioventricular canal defect, heterotaxy, or transposition. These data were combined with non-cardiac malformations to determine unique associations.

Conclusions: Hypoplastic left heart represents a phenotypically heterogeneous disorder with syndromic and non-syndromic forms. Detailed chromosome analyses are recommended, as lesions can be associated with specific chromosomal abnormalities. Identification of specific genes that predispose an individual to HLH will help to predict disease, categorize malformation subtypes, and decipher relevant molecular pathways in disease.

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NOT ALL CARDIAC RIGHT VENTRICULAR OUT-POUCHES ARE CREATED EQUAL

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Purpose of Study: We report 4 morphologically diverse congenital right ventricular outpouches (RVO) and their different therapeutic approaches. Right ventricular diverticula and aneurysms are rare. Whether invasive or noninvasive imaging can distinguish the two, rather pathological examination is needed. Nonetheless, Echocardiography (Echo), computed tomography (CT) scanning, and angiography can image cardiac cameral outpouches.

Methods Used: Case Report

Summary of Results: Case 1. A 30-week fetus’s prenatal Echo demonstrated a thin-walled 5-mm apical RVO associated with a peri-cardial effusion. Postnatal Echo confirmed the findings. A newborn noncardiopulmonary-bypass mattress suture eliminated the RVO.

Case 2. A 6-month-old with a dysplastic pulmonary valve underwent cardiac catheterization and angiography that demonstrated a RVO of the RV outflow tract. CT scanning confirmed the RVO and its associated thin-walled morphology. At cardiac surgery, the origin of the RVO was patched with Dacron and pulmonary valvotomy was undertaken.

Case 3. A 24-week fetus’s prenatal Echo demonstrated a 3-cm RVO of the RV anterior wall associated with a pericardial effusion. Both postnatal Echo and CT-scanning confirmed the RVO along with areas of wall thinning. The RVO was repaired with a double pericardial patch technique.

Case 4. A newborn with a fetal diagnosis of Ebstein’s anomaly underwent postnatal Echo that demonstrated Ebsteins, aortic arch hypoplasia and a large thick-walled RVO off the RV lateral wall directed superiorly. CT-scan confirmed the findings. The patient underwent aortic arch repair but the thick-walled RVO was not resected. The RVO is being followed via Echo.

Conclusions: Congenital RVOs arise from cardiac cameral defects. Presentation may occur during fetal, neonatal, or later age. Management usually requires surgery, especially for thin-walled RVO. A thick-walled contractile RVO can be followed conservatively with noninvasive imaging.

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THYMIDYLATE SYNTHASE VARIANTS AMONG INFANTS BORN WITH CONOTRUNCAL CARDIAC DEFECTS

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Purpose of Study: We previously reported that maternal use of prenatal vitamins containing folic acid lowers risk for the most common congenital heart defects. The biological mechanism that underlies this protective effect remains unknown, however. In a large association study employing 118 SNPs involved in folate transport and metabolism, we recently found three polymorphisms of thymidylate synthase that were associated with increased risk for spina bifida: TYMS (rs2847149) OR = 2.2; TYMS (rs1001761) OR = 2.4; and TYMS (rs502396) OR = 2.1. A thymidylate synthase haplotype was also associated with spina bifida risk [Shaw et al, unpublished]. Based on this observation, we genotyped a large population of infants with conotruncal defects and controls for seven TYMS variants.

Methods Used: This is a population-based case-control study. We ascertained all fetuses/infants born with tetrology of Fallot or d-TGA between 1998-2004 to mothers residing in three CA counties. Cases were confirmed by autopsies, echocardiography, catheter, and surgical reports were included. Controls were unaffected infants born from the same base population. Geno- typing was performed using gel-based methods and MALDI-TOF mass spec.

Summary of Results: We are genotyping 391 conotruncal defect case infants and 863 controls for two functional TYMS promoters and 5 other SNPs. Genotypic distributions of controls met Hardy-Weinberg expectations.
Conclusions: Initial results do not show increased risk for conotruncal defects from genotype alone for the 28-hp promoter insdel variant. Data for individual variants and TYMS haplotype analyses are being performed, as well as potential interactions of these TYMS variants with dietary and supplemental folate.

274 ULTRASOUND IMAGING OF THE FETAL CISTERNA MAGNA: DIFFERENTIATION OF MEGA CISTERNA MAGNA FROM DANDY-WALKER VARIANT BY RATE OF GROWTH OF THE FETAL CISTERNA MAGNA IN THE SECOND AND THIRD TRIMESTERS

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Purpose of Study: Mega cisterna magna (MCM) and Dandy-Walker variant (DWV) represent a spectrum of cystic posterior fossa malformations within the Dandy-Walker complex. Due to their shared embryology and frequently overlapping appearance on prenatal ultrasound, differentiation is particularly challenging. However, discrimination between these posterior fossa lesions is critical for improved prognostication and prenatal counseling. The purpose of this study was to describe a growth of the fetal cisterna magna from the second through third trimester by transabdominal sonography of fetuses with MCM and DWV to identify distinguishing characteristics that may assist in diagnosis.

Methods Used: Sequential second and third trimester transabdominal sonograms of fetuses with MCM and DWV were retrospectively evaluated. In the standard planar approach, posterior (AP) diameters of the fetal cisterna magnas were measured and charted against gestational age. The neurodevelopmental outcome of each fetus was retrospectively reviewed.

Summary of Results: From 2000 to 2008, adequate second and third trimester transabdominal sonography of 11 fetuses with DWV and 17 with MCM was identified in our ultrasound database. The cisterna magna growth ranged from 0.16-0.74 mm/week for DWV’s (mean, 0.38 ± 0.17 mm/week) and 0.08-0.98 mm/week (mean, 0.53 ± 0.22 mm/week) for MCM’s. The area under the ROC curve for differentiating MCM from DWV was 0.735 with a 95% confidence interval of 53.5-88.2. A critical value of 0.48 mm/week for the growth slope corresponds to a sensitivity of 52.9% and a specificity of 90.9% for prediction of MCM (P = 0.0128) for selecting MCM vs. DWV. On evaluation of postnatal neurodevelopmental outcome, all 17 (100%) fetuses with MCM were found to be developing normally, whereas 2 (18%) of the fetuses with DWV were developmentally normal.

Conclusions: On average, fetuses diagnosed with MCM appeared to have a moderately increased rate of cisterna magna growth relative to that of fetuses diagnosed with DWV. This characteristic may support the differentiation of MCM and DWV on prenatal ultrasound.

275 INTRAVENTRICULAR HEMORRHAGE IN KYPHOSCOLIOTIC EHLERS-DANLOS SYNDROME

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Purpose of Study: To describe two siblings with Ehlers-Danlos Syndrome (EDS) kyphoscoliotic form with intraventricular hemorrhage (IVH) and seizures in the newborn period.

Methods Used: Patient 1 is a female, born via spontaneous vaginal delivery at 36 weeks after premature rupture of membranes who was noted to have hypotonia at birth. She developed tonic clonic seizures in the first 24 hours of life and cranial imaging identified bilateral intraparenchymal hemorrhage. A brain MRI showed subacute hemorrhages suggestive of in-utero bleeding. Patient 2 is a female, born via cesarean delivery at 37 weeks gestation and the mother labored at home for 4-6 hours prior to presenting for C-section. The patient developed seizures at 24 hours of age and was found to have IVH and intraparenchymal hemorrhage. A brain MRI showed subacute hemorrhages suggestive of in-utero bleeding.

Summary of Results: Kyphoscoliotic form of EDS is a rare, autosomal recessive connective tissue disorder characterized by scoliosis early in life, hypotonia, easy bruising, friable, hyperextensible skin, and scleral fragility. Individuals are at risk for rupture of medium sized arteries. One case series reported vasculature rupture in 3 out of 10 patients including one patient with IVH, who did not have a traumatic delivery. Since many cases of kyphoscoliotic EDS are not diagnosed until well past the newborn period, under-reporting of neonatal IVH is likely. The suggestion of bleeding prior to labor in our second patient suggests that mechanisms other than contractions during labor may be responsible.

Conclusions: Rupture of medium sized arteries is a known complication of EDS kyphoscoliotic form but IVH is rarely reported. These two cases confirm the risk of neonatal IVH in these patients.

276 MORPHOLOGICAL FEATURES IN NETHERTON SYNDROME

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Purpose of Study: Netherton syndrome is a rare autosomal recessive disorder characterized by congenital ichthyosiform skin and hair shaft anomalies along with atopic diathesis and failure to thrive. While this condition is thought to involve primarily the skin and hair, we report the clinical findings in five patients, focusing particularly on associated dysmorphic features and development disabilities.

Methods Used: We retrospectively reviewed the clinical information of patients seen in Medical Genetics consultation, with the findings of exfoliative skin and sparse hair, over the past five years.

Summary of Results: Our retrospective chart review identified five patients (two of whom were sisters) with clinical diagnosis of Netherton syndrome. Two of the five patients were described with obvious dysmorphic features: full lips, long prominent ears, sparse eyebrows, brittle hair, and small hands. One patient had facial fullness with mild asymmetry. All five patients experienced global developmental delay, with abnormal cognition in two patients that were older than 10 years of age.

Conclusions: Our results suggest that individuals with Netherton syndrome manifest global developmental disabilities, dysmorphic features, and short stature. Comprehensive literature review revealed mainly the characteristic skin and hair findings. However, the literature rarely mentions information on growth, development or anomalies not involving the skin or hair. We propose that individuals with Netherton syndrome have short stature, developmental disabilities, and dysmorphic features characterized by fullness of the lips and cheeks, prominent ears and small hands. We believe that clinicians should be aware of these pleiotropic effects so that they may counsel families appropriately regarding the natural history and prognosis.

277 BILATERAL PROXIMAL INTERPHALANGEAL JOINT CONTRACTURES: EXPANDING THE SPECTRUM OF HAND ANOMALIES IN AARSKOG-SCOTT SYNDROME

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Purpose of Study: Aarsskog-Scott syndrome (AAS) (OMIM: 203600) is a X-linked recessive condition resulting from mutations in the FXD1 gene. It is clinically characterized by facial, genital and hand anomalies. Hand findings in AAS include mild interdigital webbing, brachydactyly and hyperextensible proximal interphalangeal (PIP) joints. Less commonly clinodactyly and camptodactyly involving the 5th digit have been observed. We diagnosed a 19 month old boy with AAS due to a FGD1 mutation. He had typical facial and genital anomalies, but his hand findings were unusual. In contrast to the usual hyperextensibility, he had bilateral contracture of the proximal interphalangeal (PIP) joints of digits 2-4. This presentation will discuss the spectrum of hand malformations in AAS, highlighting the unique findings in our case, and review current understanding of their developmental origins.

Methods Used: Retrospective examination of case records and literature review were performed.

Summary of Results: The patient was born at term by cesarean delivery performed for breech presentation. His birth height, weight and head circumference were appropriate for gestational age. Circumcision was performed.
postponed due to partial scrotal concealment of the phallus. At 19 months of age his height was below the third percentile for age. On examination he had hypertelorism and a shortened nose were also observed. The patient’s mother’s hands demonstrated flexion of the distal interphalangeal joints when the PIP joints were extended. Molecular studies identified a previously unreported insertion mutation c. 364delA in FGDF1 predicted to result in frameshift and premature protein truncation.

**Conclusions:** To date, 25 distinct FGDF1 mutations have been reported in 26 AAS families. Although published data on hand malformations in these families are incomplete, literature review suggests that bilateral contractures of multiple PIP joints is a novel finding. Our case extends the range of hand anomalies in individuals with AAS. Recognition of the full spectrum of digital anomalies in AAS should be helpful in case identification and in advancing our understanding of its genetic pathogenesis.

**278 MOTOR PROFICIENCY AND COORDINATION IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1**

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**Purpose of Study:** Neurofibromatosis type 1 (NF1) is a common autosomal dominant disorder. Our clinical experience suggests that NF1 children have poor motor coordination, and preliminary data show that 79% of parents (N = 28) reported that their NF1 children were “uncoordinated”. We therefore designed an investigation to quantify motor function in NF1 children.

**Methods Used:** NF1 children were recruited from the University of Utah NF1 Clinic and assessed at the Shriners Movement Analysis Lab. Children ≤ 13 yrs of age were excluded due to limitations of the instrument. All individuals were assessed using the Bruininks-Oseretsky Test (BOT-2) instrument, which quantifies motor coordination and proficiency in several categories, and compared to age and sex-matched validated control data. P-values generated using a paired t-test.

**Summary of Results:** Thirteen children with NF1 were enrolled (age: 5-14 yr, ave. 8 yr; 9M, 4F). Statistically significant decreases were observed in all subtest point scores except for manual dexterity (P = 0.36) [fine motor precision (P = 0.002); fine motor integration (P = 0.034); upper limb coordination (P < 0.001); bilateral coordination (P = 0.049); balance (P = 0.0001); run speed agility (P = 0.001); combined strength and agility (P = 0.004)]. Well below or below average scores were observed in 11/13 for total motor composite (z-score: -1.5); 7/13 for fine manual control (z-score: -0.8); 6/13 for manual coordination (z-score: -0.7); 11/13 for body coordination (z-score: -1.3); 8/13 for strength and agility (z-score: -1.4).

**Conclusions:** NF1 children display impaired motor proficiency and coordination. The effects of NF1 haploinsufficiency on motor coordination are not well understood, but could be a function of abnormal neuromotor learning, hypotonia, and/or weakness. Skeletal abnormalities including decreased bone mineral density are part of the NF1 phenotype, and we posit that abnormal motor proficiency is a contributing factor to osteopenia in NF1. Given that activity levels impact bone mass accrual, targeted physical therapies to improve motor proficiency and coordination may subsequently increase activity levels resulting in improvement of bone architecture and bone mineralization.

**279 OSTEOFIBROUS DYSPLASIA: AN IMPORTANT AND UNDERSTUDIED CAUSE OF NON-NF1 Tibial Dysplasia**

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**Purpose of Study:** Tibial dysplasia (TD) is an intrinsic disorder of the tibia involving anterolateral bowing, often progressing to fracture and pseudarthrosis (PA). TD usually presents in the first 2 years, and the majority of patients have it as part of neurofibromatosis type 1 (NF1). About 50% of patients also have fibular involvement. Three classification systems for TD-PA have been proposed in the literature. The differential diagnosis of TD comprises several constitutional disorders of the tibia/fibula, including fibrous dysplasia and osteofibrous dysplasia (OFD). The latter is a fibrous osseous disorder rarely mentioned in the pediatric or genetics literature. It can be confused with the TD of NF1, as it is almost always unilateral and presents clinically as anterolateral bowing of the lower leg in early childhood. We report on a boy with OFD and propose a classification of TDs.

**Methods Used:** Case report and review. The patient presented at 8 months with (L)-sided anterolateral bowing of the lower right leg. Skeletal radiograph showed midshaft expansion, lucent lesions with well defined margins and pseudoarthrosis of the distal tibia. On evaluation at Genetics clinic, we documented an unremarkable medical history except for the OFD; family history and physical examination displayed no evidence of NF1. On follow-up at 20 months, he still had no signs of NF1.

**Summary of Results:** Our evaluation of this boy and review of the literature led us to propose a classification of congenital/early onset dysplasias of the tibia/fibula: 1) TD with/without PA (often in NF1); 2) the cystic form of PA; 3) monostotic fibrous dysplasia; 4) OFD; 5) tibial bowing with preaxial polydactyly; 6) ad-amnionita.

**Conclusions:** OFD needs more study of etiology, pathogenesis, and natural history. Our review suggests that the cystic form of PA mentioned in past years may be the same entity as OFD.

**280 DUPLICATION OF THE MILLER DIEKER REGION 17p13.3: A NEW SYNDROME**

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**Purpose of Study:** Duplications and deletions of small regions of DNA are increasingly recognized on genomic microarray. The three patients reported here have a duplication of variable size in the region encompassing the Miller Dieker Syndrome at 17p13.3.

**Methods Used:** Two patients were studied using BAC arrays; the third had an oligonucleotide array.

**Summary of Results:** The duplication size was 2.1-2.9 Mb. All were confirmed with FISH. Two are de novo whereas the third child’s parents have not been tested. The three children, all of different ethnic backgrounds and ages (10 months; 3 yrs; 14 yrs) share the common features of developmental delay, mild hypotonia, speech and articulation problems Two had early recurrent infections and one required gastrostomy for hiatal hernia and reflux.

One child is tall, another quite short and the third, the teenager, is of normal stature but obese with sleep apnea. All three patients have mega-cisterna magna with cerebellar vermis hypoplasia of varying degree and one has a mild Dandy Walker malformation. Craniofacial gestalt is difficult to establish because of age and ethnicity although there is mild mid face underdevelopment, a possibly long face and pointed chin in all three.

**Conclusions:** Identification of additional patients will be needed to confirm a craniofacial phenotype in this rare duplication syndrome. We hypothesize that duplication of LIS1 and/or adjacent genes in the region produces a variable brain phenotype in the Dandy Walker/mega-cisterna magna spectrum.

**281 CAUDAL APPENDAGE IN A NEONATE WITH CLOVERLEAF SKULL: CASE REPORT AND REVIEW OF THE LITERATURE**

D. Sureka, L. Hudgins Stanford University, Stanford, CA.

**Purpose of Study:** Caudal appendage, often referred to as a “tail”, is a rare and unusual finding in humans. We describe a newborn with craniosynostosis, cloverleaf skull and sacrococcygeal eversion (SCE) resulting in a caudal appendage. We reviewed the literature, focusing on the association of this very rare finding and craniosynostosis.

**Methods Used:** The patient was evaluated shortly after birth. Targeted mutation analysis of fibroblast growth factor receptor 2 (FGFR2) gene was performed. We searched the PUBMED database for all reports of craniosynostosis and human tail, sacral tag, sacral eversion, caudal appendage, pseudotail or SCE.

**Summary of Results:** Upon literature review, 18 case reports met inclusion criteria. Eleven patients were diagnosed with Pfeiffer syndrome, three with
Crouzon syndrome, three with Beare-Stevenson syndrome, and one with Apert syndrome. Despite the differing diagnoses, they shared findings of craniosynostosis and sacrococceal abnormalities. The sacrococceal anomalies varied from SCE, caudal appendage with bony protrusion, caudal appendage without bony components, dermal sinus tract or any combination of the above. Thirteen patients had mutations in FGFR2, most commonly in exon 10. Targeted mutation analysis of FGFR2 in our patient, including exon 10 was negative.

Conclusions: Craniosynostosis is rarely associated with SCE/caudal appendage. The majority of reported cases are caused by mutations in FGFR2. We suspect that SCE is a continuum, with a caudal appendage presenting in its severe form. In human embryology, caudal proliferation after the fourth week of gestation results in elongation of the tail bud, which curls beyond the hindgut. By the eight week of gestation, the tail has completely regressed. Amphibian models have shown FGFR2 to play a significant role in tail proliferation. We postulate that abnormal expression of FGFR2 in the tail bud prevents normal proliferation and curvature, resulting in SCE and caudal appendages. Further research into the role of FGFR2 in tail bud formation is needed.

282 MICROCEPHALY-LYMPHEDEMA-CHORIORETINAL DYSPLASIA IN TWO CHILDREN: CASE REPORT OF OPHTHALMOLOGIC VARIABILITY

K. Dent¹, P. Magoulas¹, R. Hoffman², D. Dries³, D. Stevenson¹, D. Viskochil¹ ¹University of Utah, Salt Lake City, UT and ²Texas Children's Hospital, Houston, TX.

Case Report: Congenital microcephaly and retinal dysplasia occur together in several syndromes. The additional finding of lymphedema with distinctive facial gestalt defines a specific condition. Microcephaly-lymphedema-chorioretinal dysplasia syndrome is a rare disorder characterized by severe microcephaly, lymphedema, and characteristic facial features. Ophthalmologic features include retinal dysplasia that can be stable or slowly progressive, retinal folds, microphthalmos, and visual defect. We describe two unrelated children with the microcephaly lymphedema chorioretinal dysplasia syndrome.

Patient 1 was a 11 month old male with microcephaly, mild developmental delay, dorsal lymphedema of the hands and feet, and unusual facial features including bitemporal narrowing, laterally protruding ears, large mouth with wide-spaced teeth, and long, upslanting palpebral fissures, with flaring of the lateral eyebrows. Ophthalmologic examination demonstrated bilateral atrophic chorioretinal lesions located in the inferior retina. Family history was negative and the parents were unrelated. Patient 2 was a 12 month old female with microcephaly, mild developmental delay, dorsal lymphedema of the hands and feet, and unusual facial features including bitemporal narrowing, prominent metopic suture, small and recessed palpebral fissures, and large-appearing ears. Ophthalmologic examination and MRI demonstrated retinal folds, bilateral optic nerve hypoplasia and bilateral globe abnormalities with fibrous strands. Family history was notable for a full brother and sister having microcephaly and developmental delays. Both parents required special education and the mother also had microcephaly (±2SD). The parents were unrelated.

This report further demonstrates the variable expressivity in this condition regarding the facial and ocular phenotypes. While it is not possible to rule out autosomal recessive inheritance, the most likely pattern of inheritance is autosomal dominant with the affected individuals having the condition as a result of a de novo mutation in a unique gene that plays a role in brain, eye, and lymphatic vessel development.

283 VENTILATION MODE AFFECTS OVINE PULMONARY IGF-1 EPGENETIC CHARACTERISTICS

M. McCoy, D.B. Metcalfe, B. Metcalfe, B. Beck, X. Ke, R.A. McKnight, L. Dong, M.J. Dahl, D.M. Null, B. Yoder, R.H. Lane, K.H. Albertine ¹University of Utah, Salt Lake City, UT.

Purpose of Study: Mechanical ventilation (MV) of premature neonates and lambs induces chronic lung disease. The lungs of MV preterm lambs are characterized by (1) alveolar simplification and (2) decreased lung expression of IGF-1 mRNA variants. IGF-1 mRNA expression is regulated by epigenetic mechanisms, such as histone acetylation and methylation. Treatment of MV preterm lambs with histone deacetylase inhibitors improves outcome. We hypothesized that MV of preterm lambs would affect the histone code of lung IGF-1 when compared to a more moderate mode of ventilation (high-frequency nasal ventilation; HFNV).

Methods Used: Preterm (PT) lambs were managed by either MV or HFNV for 3d, from which lung DNA was collected, as well as from lambs born at term (T) (n = 4 each). Ovine sequences were cloned to design primers/probes for 5 regions of the ovine IGF-1 gene at which epigenetic regulation is important. To determine the modifications for each region, chromatin immunoprecipitation was performed, using antibodies for acetyl histone 3 lysine 14 (AcH3K14), trimethyl histone 3 lysine 4 (Me3H3K4), and Me3H3K36, as well real time PCR for the aforementioned primers/probes. These antibodies were selected because the specific modifications are vulnerable to perinatal events.

Summary of Results: For AcH3K14, prematurity significantly decreased acetylation for both promoter regions of IGF-1, regardless of ventilation mode. For Me3H3K4, prematurity increased trimethylation in promoter 2 and exon 6, regardless of ventilation mode. Trimethylation in promoter 1 was significantly greater in PT MV lambs compared to PT HFNV or T lambs. For Me3H3K36, trimethylation in exon 4 also was significantly greater compared to PT HFNV or T lambs. Trimethylation in exon 6 was greater compared to PT HFNV lambs.

Conclusions: We conclude that both prematurity and mode of ventilation affect the histone code along the length of the IGF-1 gene in ovine lung. These findings are novel because they are among the first to demonstrate gene-specific epigenetic responses to prolonged ventilation of preterm neonates. (HL62875, HL56401, HD41075, CHRC).

284 APOPTOSIS OF GLIA IN CORTICAL WHITE MATTER IS INCREASED BY MECHANICAL VENTILATION OF PRETERM LAMBS FOR 3 DAYS


Purpose of Study: Prolonged mechanical ventilation (MV) of the premature human neonate is associated with lung injury. Frequently, the brain is injured as well, by molecular mechanisms that remain unclear. Our recent studies of prolonged MV of preterm lambs show that epigenetic changes in chromatin structure occur in the cortical white matter. Specifically, MV is associated with more methylation and less acetylation of histones compared to high-frequency nasal ventilation (HFNV). The consequence of MV on histone modifications in the brain can be reduced by administering the histone deacetylase inhibitors, valproic acid (VPA) or trichostatin A (TSA), during MV. We hypothesized that MV increases caspase 3 mRNA expression and protein abundance in cortical white matter.

Methods Used: Preterm (PT) lambs, treated with antenatal steroids and postnatal surfactant, were managed by MV or HFNV (n = 4 each). At the 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. Immunofluorescence was used to localize caspase 3. Gestation controls were fetal start (FS; ~132d gestation) and fetal end (FE; ~136d gestation).

Summary of Results: Temporal lobe white matter from the MV group had significantly more caspase 3 mRNA expression and protein abundance (P < 0.05) than the HFNV group (table). Cleaved caspase 3 was immunolocalized to oligodendroglia.

Conclusions: We conclude that MV for 3d increases caspase 3 mRNA expression and protein abundance in cortical white matter in preterm lambs. HFNV for 3d did not increase caspase 3 expression or abundance. We speculate that increased expression of caspase 3 results from epigenetic
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Inhibition of histone deacetylation increased Ac H3K27, as expected.

Methods Used:
1-, 3-, and 5-wk-old HO-1-luc mice, with a transgene containing the full-length mouse HO-1 promoter driving expression of the reporter gene - properties that may limit its clinical use. The objective of this study was to determine the efficacy of an alternative Mp, chromium mesoporphyrin (CrMP) at a low dose significantly inhibits HO activity in the liver with the greatest inhibition occurring in 1-wk-old mice. In addition, CrMP does not appear to cross the blood/brain barrier, nor induce any changes in HO-1 protein or gene transcription levels. Thus, we conclude that CrMP may be an attractive alternate compound to SnMP for use in the treatment of neonatal jaundice.

Conclusions:

Methods Used:
Preterm lambs treated with antenatal steroids and postnatal surfactant, were managed by MV, HFNV, MV+VPA, or MV+TSA (n = 4 each). At the end of 3d, cortical white matter in the temporal lobe was isolated and analyzed by immunoblot for acetylated (Ac) H3K27, and significantly more Tri-me H3K36, and HDAC1. Gestation controls were fetal start (FS) and fetal end (FE).

Summary of Results:
Temporal lobe white matter from the MV group had significantly less normalized abundance of Ac H3K27, and significantly more Tri-me H3K36 and HDAC1 (* P < 0.05) than the HFNV group (table). Inhibition of histone deacetylation increased Ac H3K27, as expected.

Conclusions:
We conclude that ventilation mode broadly affects histone modifications in cortical white matter of preterm lambs. We speculate that cerebral ischemia and pro-inflammatory cytokines/chemokines from the injured lung alter the white matter chromatin structure, which results in the expression of a specific subset of genes that injure white matter (H3, 2005, HD41075, CHRC)

Summary of Results:
Liver HO activity was significantly inhibited in mice at 1- and 3-wks of age, with inhibition decreasing with age. Spleen and brain HO activities were not significantly inhibited in mice of any age. In addition, no statistically significant effects on HO-1 transcription or HO-1 protein levels were found in any tissue or at any age.

Conclusions:
CrMP at a low dose significantly inhibits HO activity in the liver with the greatest inhibition occurring in 1-wk-old mice. In addition, CrMP does not appear to cross the blood/brain barrier, nor induce any changes in HO-1 protein or gene transcription levels. Thus, we conclude that CrMP may be an attractive alternative compound to SnMP for use in the treatment of neonatal jaundice.

% Inhibition of HO Activity (mean±SD) * P<0.05, n=3 for all ages

<table>
<thead>
<tr>
<th>AGE (Wks)</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIVER</td>
<td>66±7*</td>
<td>50±18*</td>
<td>33±27</td>
</tr>
<tr>
<td>SPLEEN</td>
<td>9±18</td>
<td>3±11</td>
<td>2±10</td>
</tr>
<tr>
<td>BRAIN</td>
<td>6±10</td>
<td>5±12</td>
<td>4±14</td>
</tr>
</tbody>
</table>

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DOSE-DEPENDENT EFFECTS OF ZINC BIS GLYCOL PORPHYRIN ON THE EXPRESSION OF HEME OXYGENASE IN NEWBORN MICE

CM. Campbell1,2, T. Morisawa1, R.J. Wong2, D.K. Stevenson2, Stanford University School of Medicine, Stanford, CA and 2Jefferson Medical College, Philadelphia, PA.

Purpose of Study:
Many neonates develop jaundice as a result of excess bilirubin levels, a condition known as neonatal hyperbilirubinemia. Because heme oxygenase (HO) is the rate-limiting enzyme in the degradation of heme to bilirubin, the use of metalloporphyrins (Mps), competitive HO inhibitors, are being studied for reducing neonatal bilirubin levels. Some of these compounds, e.g. tin mesoporphyrin, are photo-reactive and inducers of HO gene expression - properties that may limit their clinical use. In this study, we determined the efficacy of an alternative Mp, zinc bis glycol porphyrin (ZnBG) towards inhibiting HO activity and its effects on HO expression in newborn mice.

Methods Used:
7d-old transgenic mice, with a transgene containing the full-length mouse HO-1 promoter driving expression of the reporter gene luciferase (HO-1-luc), were given vehicle (controls) or ZnBG (30, 15, 7.5, and 3.75 μmol/kg) via oral gavage. After 3h, mice were sacrificed and the liver, brain and spleen were harvested and sonicated in phosphate buffer. HO activity was quantified using gas chromatography and expressed % inhibition from control values. HO expression was assessed by measurements of HO-1 protein and in vivo HO-1 transcriptional activity using Western Blots and in vivo bioluminescence imaging, respectively.

Summary of Results:
3h after administration, ZnBG significantly inhibited HO activity in the liver at all doses, ranging from 48% to 67%. No significant inhibition of HO activity was observed in the spleen and brain. In addition, no significant changes in HO-1 protein or HO-1 transcription were found in any tissue or at any dose.

Conclusions:
ZnBG is orally absorbed by neonatal mice and is effective at inhibiting HO activity quickly and at relatively low doses. We conclude that because ZnBG does not affect HO-1 protein or HO-1 transcription, it is an attractive compound for use in the treatment of neonatal hyperbilirubinemia.

Further study is required to determine the long-term effects of ZnBG.

% Inhibition of HO Activity (mean±SEM) * P<0.05, n=3 for all doses

<table>
<thead>
<tr>
<th>DOSE (μmol/kg)</th>
<th>7.5</th>
<th>15</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIVER</td>
<td>68±1</td>
<td>61±1</td>
<td>62±1*</td>
</tr>
<tr>
<td>SPLEEN</td>
<td>2±12</td>
<td>3±12</td>
<td>1±14</td>
</tr>
<tr>
<td>BRAIN</td>
<td>5±16</td>
<td>2±10</td>
<td>1±16</td>
</tr>
<tr>
<td>M/P süs</td>
<td>5±16</td>
<td>2±10</td>
<td>1±16</td>
</tr>
</tbody>
</table>

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REAL-TIME, NONINVASIVE MEASUREMENTS OF PLASMA BILIRUBIN LEVELS USING VISIBLE LIGHT SPECTROSCOPY

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**Purpose of Study:** Neonatal hyperbilirubinemia is a common problem encountered by the practicing pediatrician. If left untreated, it can lead to the development of acute bilirubin encephalopathy or kernicterus. Usual monitoring of circulating bilirubin levels requires frequent blood draws. Noninvasive techniques as substitutes for invasive bilirubin measurements are desirable. In this study, we evaluated the use of visible light spectroscopy (VLS) to measure noninvasively circulating plasma bilirubin levels in real-time.

**Methods Used:** A VLS oximeter (T-Stat® 303, Spectros Corp), FDA-approved for use to detect hypoxemia and ischemia, which uses shallow-penetrating visible light to measure the microvascular hemoglobin oxygen saturation, was modified to measure circulating bilirubin levels. Gunn rat (Harlan Laboratories) pups (n = 27, aged 1-7d), which are genetically jaundiced were used. T-Stat measurements (n = 3) were taken at the midsection of each pup. Pups were then immediately sacrificed and blood collected for plasma separation. Plasma bilirubin (PB) levels were quantitated (Harlan Laboratories) pups (n = 27, aged 1-7d), which are genetically jaundiced were used. T-Stat measurements (n = 3) were taken at the midsection of each pup. Pups were then immediately sacrificed and blood collected for plasma separation. Plasma bilirubin (PB) levels were quantitated using a Model UA-1, Arrows Co) and correlated to T-Stat values by linear regression using the method of least squares. Mean bias ± imprecision was calculated by the method of Bland and Altman.

**Summary of Results:** Linear regression showed a strong correlation between T-Stat and PB levels, y = 1.024 × -0.07, r² = 0.92. Mean bias ± imprecision of T-Stat was -0.049 ± 1.32 mg/dL (95% CI = 2.63 to 2.54).

**Conclusions:** We conclude that visible light spectroscopy can be used as a method to measure real-time plasma bilirubin levels noninvasively in rat pups, and should be further studied for its application to human newborns.

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**DIABETES MELLITUS ALTERS THE HEPATIC HISTONE CODE ALONG THE RAT IGF-1 GENE**

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**Purpose of Study:** Maternal diabetes increases the risk of postnatal morbidities in humans and rats. These morbidities include insulin resistance and aberrant adipogenesis, both of which are regulated by hepatic IGF-1. Previous studies demonstrate that prenatal conditions such as uteroplacental insufficiency and maternal malnutrition affect the postnatal hepatic IGF-1 expression and epigenetic profile. However, little is known whether maternal diabetes will have similar consequences on IGF-1. We hypothesized that maternal diabetes in the rat increases postnatal IGF-1 hepatic expression and epigenetic characteristics.

**Methods Used:** To test this hypothesis, pregnant rats were given streptozotocin (STZ) on day 13 of pregnancy. Maternal glucose levels were moderated with insulin injections. Livers were harvested on postnatal days 1 (DOL1) and 21 (DOL21) from pups of both STZ and sham (CON) maternal rats. Real time RT-PCR was used to determine levels of IGF-1 mRNA variants: P1 - produced from IGF-1 promoter 1; P2 - produced from IGF-1 promoter 2; IGF-1A - no exon 5; IGF-1B - includes exon 5. The histone 3 (H3) epigenetic profile of the hepatic IGF-1 gene was determined using chromatin immunoprecipitation with antibodies for lysine 4 dimethylation (K4DMeH3) and trimethylation (K4TMeH3), K9 acetylation H3 (K9AcH3), and K36TMeH3, because these sites are known to be vulnerable to hormonal events.

**Summary of Results:** At DOL21, maternal diabetes significantly decreased mRNA levels of IGF-1 P1 (78% ± 2.8), IGF-1 P2 (67% ± 5.3), and IGF-1 A (74% ± 2.1). Concurrently, maternal diabetes significantly increased K36TMeH3 in the 3′ region and decreased the same modification in 5′ region of the male hepatic IGF-1 gene. Female STZ trended toward the same pattern. K9AcH3 also appeared to be affected in a gender specific manner.

**Conclusions:** Maternal diabetes decreases postnatal hepatic IGF-1 mRNA levels and affects the hepatic IGF-1 epigenetic profile in a gender specific manner. These findings are intriguing because they demonstrate that the epigenetic profile of the hepatic IGF-1 gene is sensitive to disparate prenatal conditions. We speculate that by altering the epigenetic profile of the hepatic IGF-1 gene, maternal diabetes affects IGF-1 gene expression in adulthood.

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**DEVELOPMENTAL MASSAGE THERAPY (DMT) PROMOTES WEIGHT GAIN AND DECREASED ADIPOSITY IN RAT PUPS EXPOSED TO ENVIRONMENTAL STRESSORS DURING EARLY NEONATAL LIFE**

K.D. Gulliver1, S. O’Grady1, S. Haley1, X. Ke1, A. Zabrocki1, R. Lane1, S. Miller, L. Moyer-Mileur1 1University of Utah, Salt Lake City, UT and 2University of Utah, Salt Lake City, UT.

**Purpose of Study:** Preterm infants (<37 wk gestation) are exposed to physical and environmental stressors that increase circulating glucocorticoid (GC) levels. Elevated GC during early life is associated with poor postnatal growth and increased adiposity. Massage therapy lowers GC in humans and animals. We tested the hypothesis that DMT would lower serum GC and improve growth in rat pups exposed to environmental stressors during early neonatal life.

**Methods Used:** Timed pregnant 3-month old S-D rats delivered at term and litters culled to 10 pups (5 M, 5 F). Litters were randomized to five groups: Control (C), Maternal Separation (MS, 60 min period of separation); MS + DMT (10 min of DMT + MS); Neonatal Stress (NS, MS + injection hypertoxia/hyperorxia); and NS + DMT (10 min of DMT + NS). Treatments were given daily on D6-D10 with litters cross-fostered from D6-D21. DMT consisted of 5 minutes of stroking with a camel hair brush and 5 minutes of range of motion to both fore- and hindlimbs. Daily body weight (g), percent body fat (%BF) by DXA, and serum GC by ELISA were measured.

**Summary of Results:** Relative weight gain (%) during intervention (D6-11 was lowest in both NS groups although significantly higher weight gain was observed in NS+DMT than NS pups (P < 0.05). Relative weight gain post intervention (D11-D21) was similar for all groups. At weaning (D21), %BF and serum GC levels were greater in NS and NS+DMT pups versus C or MS groups (P < 0.05)(Table, results for C pups not shown). No correlations were found between serum GC levels and postnatal weight gain or %BF.

**Conclusions:** Our findings demonstrate greater postnatal weight gain and decreased adipose tissue deposition in response to developmental massage therapy during severe environmental stress in neonatal animals.

**Table:**

<table>
<thead>
<tr>
<th>Relative growth, body fat, and serum GC by treatment</th>
<th>MS</th>
<th>MS+DMT</th>
<th>NS</th>
<th>NS+DMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>%WI Gain</td>
<td>61.5 (8.9a)</td>
<td>62.1 (1.3a)</td>
<td>51.6 (4.5)</td>
<td>56.5 (3.2a)</td>
</tr>
<tr>
<td>%BF</td>
<td>4.9 (1.9)</td>
<td>5.2 (1.3)</td>
<td>8.0 (2.0)</td>
<td>7.5 (1.1c)</td>
</tr>
<tr>
<td>Serum GC (ng/dL)</td>
<td>8.3 (4.4)</td>
<td>8.2 (1.6)</td>
<td>7.4 (0.6c)</td>
<td>22.8 (10.5c)</td>
</tr>
</tbody>
</table>

Means (SD); p < 0.05; a > NS, NS+DMT; b > NS; c > MS, MS+DMT; d > NS+DMT

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**INTRATRUNKAL GROWTH RESTRICTION ALTERS BONE MRNA LEVELS OF SEX STEROID AND GLUCOCORTICOID HORMONE RECEPTORS, BUT NOT INSULIN-LIKE GROWTH FACTOR 1 RECEPTOR IN MALE RAT**

A.J. Zabrocki, R. Lane, L. Moyer-Mileur, S. Miller, C. Callaway, X. Yu University of Utah, Salt Lake City, UT.

**Purpose of Study:** Intratruneral Growth Restricted (IUGR) newborns have smaller, weaker, and less mineralized bones, leading to more fractures and osteoporosis as adults. Frequently, IUGR leads to gender specific effects, with
292 MATERNAL ZINC DEFICIENCY AFFECTS POSTNATAL GROWTH AND GLUCOSE HOMEOSTASIS IN RAT PUPS DIFFERENTLY DEPENDING UPON ADEQUACY OF THEIR NUTRIENT INTAKE

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Purpose of Study: The “thrift” phenotype hypothesis suggests that inadequate nutrition during fetal life results in permanent metabolic modifications and increased risk of diabetes in adulthood. The effects of moderate maternal zinc (Zn) deficiency on growth and glucose homeostasis in the offspring and the interaction between maternal Zn deficiency and postnatal nutrition are not well understood.

Methods Used: Bilateral intrauterine artery ligation was preformed on rats on 19th day of gestation. Pups were sacrificed either at birth (P0) or on day 21 (P21). Femurs and tibias were collected and flash frozen. Whole bone mRNA was extracted and real time RT-PCR was performed for levels of GR, AR, IGF-1R, ERα, and ERβ.

Summary of Results: IUGR decreased mRNA levels for Gr(81% of control, P = 0.002) and AR (75% of control, P = 0.05) at P0. At P21 IUGR increased mRNA levels for ERα (147% of control, P = 0.04) and ERβ (216% of control, P = 0.07). There was no significant change in IGF-1R mRNA levels at either age.

Conclusions: We conclude that IUGR decreased Gr and AR mRNA levels in male rat bone at P0, but the decrease was not sustained. IUGR also increased ERα and ERβ mRNA levels by P21. In contrast, IUGR did not influence IGF-1R mRNA levels at any age. We speculate that mRNA levels might contribute to the molecular mechanism underlying the IUGR induced decrease in strength, and mineralization of bone.

293 GLUCOCORTICOID RECEPTOR GENE VARIANT COMPOSITION AND ASSOCIATED HISTONE CODE ARE ALTERED BY NEONATAL STRESS AND ERYTHROPOIETIN IN THE RAT BRAIN

X. Ke1, S. O’Grady1, D. Caprau2, R. McPherson2, R. McKnight1, S. Juul2, R. Lane1 1Univ of Utah, Salt Lake City, UT and 2University of Washington, Seattle, WA.

Purpose of Study: The NICU regularly exposes preterm infants to multiple postnatal stressors. Stress has been shown to affect epigenetic regulation of glucocorticoid receptor (GR). GR is composed of multiple isoforms generated by alternative mRNA splicing. Erythropoietin (Epo) has been shown to be neuroprotective after perinatal hypoxic-ischemia. It is unknown whether Epo can modulate stress-induced epigenetic changes to GR. We hypothesize that neonatal stress-induced alterations to cerebral GR histone code and splice variant composition can be minimized by Epo.

Methods Used: Rat pups were exposed to neonatal stress and given 5000 U/kg Epo s.c. daily for 5 days from postnatal day 3-7. Stress included daily maternal separation, hand-feedings, daily hypoxia/hyperoxia, and cold exposure. Five treatment groups were controls (CC), vehicle-treated controls (CV), Epo-treated controls (CE), vehicle-treated stressed rats (SV), and Epo-treated stressed rats (SE). Brains were harvested on P10. Real-time RT-PCR analysis and Western blots were used to examine changes in mRNA and protein levels. Chromatin immunoprecipitation (ChIP) with five histone H3 markers was used to determine histone code along the GR gene.

Summary of Results: The stress of vehicle and Epo increased total cerebral GR mRNA and protein levels in both genders. Though Epo had no effect on GR protein isoforms in control animals, Epo increased GR alpha protein levels in the stressed male pups. In terms of mRNA, the stress of vehicle and Epo increased exon 1.5, 1.6, 1.7, 1.10, and 3’ end variant GRA mRNA levels in both genders. Increased GRA variants mRNA levels were associated with increased H3me3K9 in both genders towards the 3’ end and decreased H3AcK9 in males only towards the 5’ end.

Conclusions: We conclude that (1) stress of injection increases cerebral GR expression, and that (2) Epo altered GR alpha protein levels in a gender specific manner in stressed animals. Associated changes in GR mRNA variants occurred concurrently with changes in H3 acetylation and methylation. We speculate that the changes in the GR histone code may affect subsequent postnatal GR expression and signaling.

294 DEVELOPMENTAL MASSAGE THERAPY ALTERS THE HEPATIC IGF1 PATHWAY IN A NEONATAL STRESS MODEL

S. Haley, S. O’Grady, K. Gulliver, X. Ke, A. Zabrocki, S. Miller, R. Lane, L. Moyer-Mileur University of Utah, Salt Lake City, UT.

Purpose of Study: Premature infants are exposed to stressful events in the NICU. Neonatal stress impairs postnatal growth. NICU clinical studies and animal models of neonatal stress have demonstrated that developmental massage therapy (DMT) in early life improves weight gain and alters percent body fat. The IGF1 pathway is known to play a vital role in neonatal weight gain. We hypothesize that the molecular events that result from DMT will affect the hepatic IGF1 pathway because the liver is the major site for IGF1 production.

Methods Used: Timed pregnant dams were delivered at term (E21). Litters were culled to 10 pups (5 M, 5 F) and divided into 3 groups: control (C), neonatal stress (NS; maternal separation + injection + hypoxia/hyperoxia) and NS + DMT (10 min of stroking and limb movement). All treatments were given from D6 to D10 and tissue was harvested on D21 of life. Hepatic mRNA levels of growth hormone receptor (GHR), insulin-like growth factor receptor (IGF1R), IGF1, and serum levels of IGF1 were measured.

Summary of Results: DMT alters the IGF1 pathway differently between sexes. DMT in female NS rats results in 26% higher levels of GHR (P = 0.002) and 15% higher levels of IGF-1R (P = 0.14) compared to NS rats with no DMT. DMT in male NS rats results in 30% higher levels of IGF1R compared to NS rats with no DMT (P = 0.004). DMT did not alter levels of circulating or hepatic IGF1 levels for either sex in the NS rat model.
Conclusions: We conclude that DMT alters hepatic mRNA levels of IGF1R and GHR that persists two weeks after DMT. These changes in hepatic mRNA may be the result of altered transcriptional regulation that continues to persist into later stages of life. The increase in GHR is an important finding because GHR mediates IGF1 levels. Despite the increase in GHR, there were no differences in circulating and hepatic IGF1. However, we speculate that there may be tissue specific differences in the IGF1 splice variants.

Methods Used: HGFIN, colony stimulating factor (CSF), IL-6, TNFa, IL-10 and beta-actin mRNA abundance were measured by real time PCR in isolated blood monocytes before and seven days after in vitro transformation to macrophages.

Summary of Results: Dialysis patients exhibited marked upregulation of CSF and IL-6 and significant downregulation of IL-10 in both intact and transformed monocytes. HGFIN expression in intact monocytes was negligible in controls but conspicuously elevated (8.6 fold) in dialysis patients. As expected, in vitro monocyte-macrophage transformation resulted in marked upregulation of HGFIN in cells obtained from both groups but much more so in dialysis patients (17.5 fold higher).

Conclusions: Intact monocytes from dialysis patients exhibit early features of macrophage transformation while still in the circulation (as evidenced by heightened CSF and HGFIN expressions) and an exaggerated response upon transformation. Further studies are needed to determine the role of heightened monocyte/macrophage HGFIN expression in the pathogenesis of CKD-induced vascular-soft tissue calcification and inflammation.

Nephrology and Hypertension
Concurrent Session
1:30 PM
Friday, January 30, 2009

296 UPRREGULATION OF MONOCYTE/MACROPHAGE HEMATOPOIETIC GROWTH FACTOR INDUCIBLE NEUROKININ-1 (HGFIN) EXPRESSION IN END-STAGE RENAL DISEASE
M. Pahl1, N. Vaziri1, J. Yuen1, S. Adler2 1University of California, Irvine, Orange, CA and 2Harbor-UCLA, Torrance, CA.
Purpose of Study: HGFIN is a type 1 transmembrane glycoprotein which is expressed in numerous cell types including osteoclasts, myocytes, retinal pigment epithelium, renal tubules, macrophages, and dendritic cells. It serves as an osteoblast differentiation factor, participates in bone mineralization, and functions as a negative regulator of inflammation in macrophages. Monocyte transformation to tissue macrophages triggers HGFIN expression. CKD is associated with systemic inflammation, arteriosclerosis, bone demineralization, and soft tissue-vascular calcification/osseification. Since HGFIN is involved in inflammation and mineralization, processes which are affected by CKD, we explored its expression in circulating monocytes and monocyte-derived macrophages in a group of 14 hemodialysis-dependent patients and 10 age-matched controls.

Methods Used: HGFIN, colony stimulating factor (CSF), IL-6, TNFa, IL-10 and beta-actin mRNA abundance were measured by real time PCR in isolated blood monocytes before and seven days after in vitro transformation to macrophages.

Summary of Results: Dialysis patients exhibited marked upregulation of CSF and IL-6 and significant downregulation of IL-10 in both intact and transformed monocytes. HGFIN expression in intact monocytes was negligible in controls but conspicuously elevated (8.6 fold) in dialysis patients. As expected, in vitro monocyte-macrophage transformation resulted in marked upregulation of HGFIN in cells obtained from both groups but much more so in dialysis patients (17.5 fold higher).

Conclusions: Intact monocytes from dialysis patients exhibit early features of macrophage transformation while still in the circulation (as evidenced by heightened CSF and HGFIN expressions) and an exaggerated response upon transformation. Further studies are needed to determine the role of heightened monocyte/macrophage HGFIN expression in the pathogenesis of CKD-induced vascular-soft tissue calcification and inflammation.
298

FT061452TM, A NOVEL ANTIOXIDANT, PREVENTS VASCULAR SMOOTH MUSCLE CELL APOPTOSIS THROUGH SUPPRESSION OF OXIDATIVE STRESS AND JNK-MEDIATED INTRINSIC PATHWAY SIGNALING

I. Sinha-Hikim, R. Shen, A. Crum, K. Norris Charles Drew University, Los Angeles, CA.

Purpose of Study: Vascular smooth muscle cell (VSMC) apoptosis plays an important role in atherosclerosis and plaque stability. In earlier studies, we have shown among four antioxidants that include FT061452 TM (F1), FT061453 TM (F2), N-acetyl-cysteine (NAC) and reduced glutathione (GSH), F1 is more efficacious in preventing spermine (Sp) induced VSMC apoptosis. The goal of this study was to elucidate the molecular mechanisms by which these stress reducers, and F1 in particular prevents VSMC apoptosis.

Methods Used: Human VSMC were subjected to one of the following treatments for up to 24 h: Sp (15 μm) only; Sp+NAC (200 μg/mL); Sp+ GSH (200 μg/mL); Sp+ F1 (200 μg/mL); Sp+ F2 (200 μg/mL); and control.

Summary of Results: The cells in Sp-only group showed 31.9±3.9% apoptosis after 24 h of treatment. Concomitant treatments with any of these antioxidants would, in turn, lead to demonstrable vasoconstritory dysfunction. Electron microscopy further revealed normal appearance of these rescued cells. The intracellular GSH levels dropped significantly within 8 h after exposure to spermine. This was further accompanied by activation of JNK and induction of iNOS and 4HNE (biomarkers of oxidative stress), and was associated with activation of the mitochondria-dependent intrinsic pathway signaling, characterized by perturbation of the BAX/BCL-2 rheostat, cytosolic translocation of cytocyte c, and activation of caspase 9 and caspase 3. The protection offered by these antioxidants involved restoration of intracellular GSH levels and suppression of JNK activation, INOS induction, and intrinsic pathway signaling. Among four antioxidants tested, F1 was most efficacious in restoring intracellular GSH levels and BCL-2 expression and preventing cytochrome c release and, in turn, VSMC apoptosis.

Conclusions: F1 is a promising antioxidant in preventing spermine induced VSMC apoptosis through suppression of oxidative stress and JNK-mediated intrinsic pathway signaling. Dietary supplementation of F1 may be of therapeutic value in mitigating stress induced cellular dysfunction.

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ELEVATED ACTIVITY OF MATRIX METALLOPROTEINASE-2 AND -9 IS ASSOCIATED WITH INCREASED STIFFNESS, MEDIAL CALCIFICATION AND VASMOTOR DISFUNCTION OF ARTERIAL VASCULATURE IN PATIENTS WITH END-STAGE KIDNEY DISEASE

J.M. Kim1, H.C. Yang1, E. Chun2, W.A. Gourlay3, A. Levin2, A.W. Chung1
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Purpose of Study: Arterial stiffening and medial calcification contribute to increased cardiovascular mortality in patients with chronic kidney disease (CKD). Matrix metalloproteinase (MMP) -2 and -9 play a crucial role in vascular remodeling and maintaining matrix integrity and structural stability. We hypothesized that in the macro-vasculature of CKD patients, especially those on dialysis (Stage 5), MMP-2 and -9 would be elevated, leading to elastic fiber fragmentation and arterial stiffening. Such abnormal structural changes would, in turn, lead to demonstrable vasoconstritory dysfunction. Electron microscopy further revealed normal appearance of these rescued cells. The intracellular GSH levels dropped significantly within 8 h after exposure to spermine. This was further accompanied by activation of JNK and induction of iNOS and 4HNE (biomarkers of oxidative stress), and was associated with activation of the mitochondria-dependent intrinsic pathway signaling, characterized by perturbation of the BAX/BCL-2 rheostat, cytosolic translocation of cytocyte c, and activation of caspase 9 and caspase 3. The protection offered by these antioxidants involved restoration of intracellular GSH levels and suppression of JNK activation, INOS induction, and intrinsic pathway signaling. Among four antioxidants tested, F1 was most efficacious in restoring intracellular GSH levels and BCL-2 expression and preventing cytochrome c release and, in turn, VSMC apoptosis.

Methods Used: During living donor kidney transplantation, inferior epigastric arteries (EFA) from recipients [non-dialysis (ND-EGA) = 11; dialysis (D-EGA) = 22] were harvested for mechanical, histological, functional, and molecular studies.

Summary of Results: Stiffness coefficient of D-EGA was 30% greater than that of ND-EGA. Movat's staining showed elastic fiber fragmentation and a marked reduction of the external elastic lamina (EEL)/media ratio in D-EGA. Medial calcium/phosphate deposition, demonstrated by von Kossa stain, strongly correlated with the increased stiffness coefficient in D-EGA (r = 0.61, P < 0.05). Both stiffness coefficient and medial calcium/phosphate deposition in D-EGA were negatively correlated with the phenylephrine-induced contraction (r = -0.406, r = -0.443, P < 0.05, respectively). These correlations were absent in ND-EGA. In D-EGA, the expression level and gelatinolytic activity of both MMP-2 and -9 were elevated, and the activity of MMP-2 negatively correlated with the EEL/media ratio (r = -0.60, P < 0.05).

Conclusions: The impaired vasmotor function of EGA from Stage 5 CKD patients correlated with composite measures of arterial stiffening, elastic fiber disorganization, and medial calcification. These findings were correlated with increased levels of MMP-2 expression and activation. Therefore, elevated MMP-2 activity may be the molecular basis for the adverse cardiovascular events in patients with end-stage kidney disease.

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MECHANISMS OF IMPAIRED HDL-MEDIATED REVERSE CHOLESTEROL TRANSPORT IN CHRONIC KIDNEY DISEASE


Purpose of Study: Chronic kidney disease (CKD) is associated with accelerated atherosclerosis which is, in part, due to diminished plasma level and impaired maturation of HDL. In the artery wall and glomerular mesangium, oxidized lipoproteins are engulfed by macrophages via scavenger receptor, SRA-1 and lectin-like oxidized LDL receptor, LOX-1 a process that can lead to foam cell formation. HDL mitigates this process by releasing surplus cholesterol via binding to ABCA1 transporter. Free cholesterol reaching the surface of HDL is promptly esterified by LCAT and sequestered in the core of HDL. The loaded HDL unloads its cholesterol content in the liver via reversible binding with SRB-1 and returns to circulation for recycling. In addition, liver contains an HDL holo-receptor (B chain ATP synthase) which internalizes and degrades HDL. Earlier studies have shown down-regulation of hepatic Apo A1 and LCAT gene expression in CKD.

Methods Used: The effect of CKD on tissue LOX-1, SRA1, ABCA1 and of B chain ATP synthase was explored using rats 8 weeks post 5/6 nephrectomy (CKD) or sham operation.

Summary of Results: The CKD group showed significant reductions in plasma LCAT and HDL/total cholesterol ratio, increased LOX-1 and SRA-1 abundance and elevated stainable lipids and increased ABCA-1 abundance in the kidney and aorta, reflecting physiologic response to increased intracellular cholesterol in these tissues. Liver tissue SR-BI and holo-HDL receptor were unchanged in CKD group.

Conclusions: CKD results in LCAT deficiency and up-regulation of aorta and kidney SRA1 and LOX-1, events that favor atherosclerogenesis and glomerulosclerosis.

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FAVORABLE EFFECTS OF APOA1 MIMETIC PEPTIDE ON HDL ANTI-INFLAMMATORY AND LDL PRO-INFLAMMATORY PROPERTIES IN UREMIC PLASMA

N.D. Vaziri1, H. Morari1, M. Pahl1, M. Navab2
1University of California, Irvine, Orange, CA 2UC Los Angeles, Los Angeles, CA.

Purpose of Study: End-stage renal disease (ESRD) results in accelerated atherosclerosis which is primarily driven by oxidative stress, inflammation and HDL deficiency. In addition to mediating reverse cholesterol transport HDL possesses potent antioxidant-anti-inflammatory properties. Plasma Apo A-1 is reduced and HDL maturation and antioxidant activity are impaired in ESRD. Anti-inflammatory action of HDL is, in part, due to preferential binding of oxidized lipids/sterols by ApoA-1. ApoA-1 administration has been shown to ameliorate atherosclerosis in humans and experimental animals. However, its clinical utility has been curtailed by lack of mass production capability. ApoA-1 mimetic peptides which can be readily prepared on a large scale can elicit HDL properties in humans and experimental animals. We tested the hypothesis that ApoA-1 mimetic peptide, LAF (MW = 2400), can reduce pro-inflammatory properties of LDL and enhance anti-inflammatory properties of HDL in uremic plasma.

Methods Used: Plasma HDL and LDL fractions from 12 ESRD patients were incubated with LAF (0.43 nM) and vehicle and employed in the LDL-induced monocyte chemotactic activity assay using cultured human aortic endothelial cell.

Summary of Results: Compared to the controls, ESRD patients exhibited marked reductions of plasma paraoxonase, glutathione peroxidase, LCAT, ApoA-1, HDL-cholesterol, and HDL antioxidant activity and elevations of
CRP, IL-6 and carbonylated proteins. This was accompanied by increased LDL pro-inflammatory and depressed HDL anti-inflammatory activity. Pre-incubation with L4F lowered LDL pro-inflammatory and enhanced HDL anti-inflammatory activity in the uremic plasma.

**Conclusions:** Oxidative stress and inflammation in ESRD is associated with marked reduction of HDL antioxidant/anti-inflammatory activities which are ameliorated by Apo A-1 mimetic peptide, L4F in vitro. Clinical studies are needed to explore efficacy of L4F therapy in ESRD patients.

### 302
**ELDERLY KIDNEY RECIPIENT OUTCOMES IN TRANSPLANTED PATIENTS**

T. Ly, M. Shangguan, M.S. Sampaio, A. Kadiyala, S. Bunnapradist David Geffen School of Medicine at UCLA, Los Angeles, CA.

**Purpose of Study:** The elderly are the fastest growing group of dialysis patients with increasing numbers on the kidney transplant waitlist. In 2007, over 14% of transplants were performed in patients ≥65 years versus 8.9% in 2000. We propose to examine transplant outcomes and complications among elderly patients (age ≥65 years) transplanted at the University of California, Los Angeles (UCLA).

**Methods Used:** A chart review was conducted on kidney recipients at UCLA from 1998 to 2006. The elderly cohort (n = 100) included solitary kidney recipients. They were compared to a control group of recipients (n = 2767) aged between 18 and 65 years. Outcomes included delayed graft function, graft and patient survival, and duration of initial hospitalization.

**Summary of Results:** See please table.

**Conclusions:** Elderly kidney recipients at UCLA had excellent post-transplant outcomes. Post-transplant complications are comparable between the groups, except for a higher rate of infections in the elderly.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Elderly</th>
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<tr>
<td>Mean age (yr)</td>
<td>69.0</td>
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<tr>
<td>Mean BMI</td>
<td>26.2</td>
<td>26.2</td>
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<tr>
<td>Diabetes pre-transplant (%)</td>
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<td>Malignancy pre-transplant (%)</td>
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<tr>
<td>Cadaveric donor source (%)</td>
<td>74</td>
<td>69</td>
<td>0.03</td>
</tr>
</tbody>
</table>

### 303
**PROINSULIN AND C PEPTIDE ARE ASSOCIATED WITH WORSE KIDNEY FUNCTION IN OLDER ADULTS WITHOUT DIABETES: THE RANCHO BERNARDO STUDY**

S.K. Jassal1, E. Barrett-Connor 1,2 UCSD/V ASDHS, San Diego, CA and 1UCSD, La Jolla, CA.

**Purpose of Study:** Obesity is associated with chronic kidney disease and type 2 diabetes is leading cause of end stage renal disease in the US, but there is conflicting evidence about the relationship between markers of insulin resistance and kidney function, particularly in those without diabetes. We hypothesized that markers of insulin resistance would be associated with lower estimated Glomerular Filtration Rate (eGFR) and higher urine albumin/creatinine ratio (ACR) even in those without diabetes.

**Methods Used:** We report a cross-sectional study of markers of insulin resistance with kidney function by both eGFR and ACR in 1416 community dwelling participants (mean age 75) from the Rancho Bernardo study who attended a clinic visit in 1992-96. Logistic regression was used to assess which markers of insulin resistance were associated with eGFR <60 ml/min/1.73 m2 and ACR ≥30 mg/g.

**Summary of Results:** 217 participants had type 2 diabetes, 511 had eGFR <60, and 191 had ACR ≥30 mg/g. In age adjusted analyses, hemoglobinA1C, fasting insulin, proinsulin, C peptide, and HOMA (Table) were associated with an increased risk of eGFR <60 only in those without diabetes. In age adjusted analyses, systolic blood pressure, fasting glucose, proinsulin, and C peptide were associated with increased risk of ACR ≥30 in those without diabetes while hemoglobinA1C, C peptide and HOMA were associated with ACR ≥30 in those with diabetes.

**Conclusions:** In those without diabetes, only proinsulin and C peptide were associated with increased risk of both eGFR <60 and ACR ≥30. Future prospective studies are warranted.

### 304
**RETORETROSPECTIVE STUDY OF THE EFFECT OF SHORT ACTING VS. LONG ACTING ERYTHROPOIESIS STIMULATING AGENTS ON DIALYSIS ACCESS THROMBOSIS/STENOSIS**

V. Ha, M. Pahl, N.D. Vaziri University of California, Irvine, Orange, CA.

**Purpose of Study:** Vascular access complications are a major cause of morbidity in hemodialysis populations worldwide. Erythropoietin (EPO) has been shown to heighten platelet activity, stimulate vascular smooth muscle cell proliferation and promote vascular remodeling and thrombosis. Administration of EPO results in a marked but transient surge of drug concentration within the vascular access. Pharmacodynamic and receptor binding affinity of short-acting EPO (epoetin alfa) differ from those of long-acting EPO (darbepoetin alfa). These differences can have potential impact on hemodialysis vascular complications.

**Methods Used:** In March, 2005, maintenance EPO therapy at the UCI hemodialysis program was switched from thrice weekly IV epoetin to once weekly IV darbepoetin. The incidence of vascular access thrombosis, stenosis, surgical revision, replacement, and infection were retrospectively analyzed on 56 patients during the one-year period before and after conversion to darbepoetin.

**Summary of Results:** The average hemoglobin concentration (11.9 vs. 11.6, P = 0.024) and equivalent dose of EPO preparations (11,995 Units for epoetin vs. 45.4 mcg for darbepoetin) were similar during the two periods. The incidence of vascular access thrombosis, stenosis, surgical revision, replacement, and infection were retrospectively analyzed on 56 patients during the one-year period before and after conversion to darbepoetin.

**Conclusions:** The incidence of vascular access thrombosis appears to be higher with short -acting EPO than long-acting EPO. This may be due to higher receptor affinity and frequency of EPO concentration surge within the blood access with the former modality.

### 305
**IDENTIFICATION OF OSMOTIC NEPHROSIS AS THE CAUSE OF GADOLINIUM-INDUCED ACUTE KIDNEY INJURY IN HUMANS**

A. Pham 1,2, A. Jin 2, G. Shalh 11University of California, Irvine, Orange, CA and 1UCSD, La Jolla, CA.

**Purpose of Study:** Contrast induced acute kidney injury (CI-AKI) has been reported following administration of gadolinium contrast agents. The pathophysiological mechanisms of CI-AKI, however, remain to be elucidated.

**Methods Used:** We conducted a retrospective analysis of 17 CI-AKI patients who received gadolinium contrast agents from 2004 to 2007. We used angiographic, clinical, and laboratory data to correlate the presence and extent of osmotic nephrosis (ON) with CI-AKI.

**Summary of Results:** Using a strict diagnostic criteria for ON, we found ON in 14/17 CI-AKI patients. ON was associated with a higher incidence of CI-AKI (P = 0.001) and a higher incidence of severe CI-AKI (P = 0.018).

**Conclusions:** Our findings support the hypothesis that ON is a major contributing factor to CI-AKI and may explain the increased risk of CI-AKI following administration of gadolinium contrast agents.
Case Report: Back ground- Gadolinium-based contrast preparations are commonly employed as an alternative to iodinated contrast media for relevant radiographic evaluation of patients with pre-existing kidney disease. This is because gadolinium has been generally considered to be non-nephrotoxic. However, several cases of acute kidney injury have been reported in patients following radiological studies with gadolinium-based contrast media. Osmotic stress has been shown to result in a characteristic form of acute kidney injury known as osmotic nephrosis in patients receiving iodinated radiographic contrast media and other hyper-osmolar preparations. Osmotic nephrosis is histologically characterized by presence of isometric vacuolization and swelling of the cytoplasm of the proximal tubular epithelial cells. To our knowledge, the nature of gadolinium-induced acute kidney injury via osmotic nephrosis in humans has not been previously elucidated. Here we report histological evidence of osmotic nephrosis in a patient who suffered acute renal injury as a result of an magnetic resonance imaging (MRI) procedure with gadodiamide.

Case report and Methods- A 57-year old man with type 2 diabetes, hypertension, and chronic back pain underwent MRI with gadodiamide for evaluation of acute back pain and radiculopathy. During the ensuing two weeks he experienced progressive oliguria, azotemia, hematuria, and mild proteinuria. Renal biopsy revealed extensive swelling and isometric vacuolization of the proximal tubular epithelial cells consistent with osmotic nephrosis. Patient was admitted to the hospital for observation and supportive care. His urine out put increased and renal function steadily improved during the ensuing 10 days.

Conclusions- Use of gadolinium-based contrast media can result in acute kidney injury. The gadolinium-induced acute kidney injury is associated with the prototypical lesions of osmotic nephrosis. These findings point to the role of osmotic stress in the pathogenesis of the gadolinium-induced acute kidney injury.

307 DYSREGULATION OF RENAL MELANOCORTIN 3 RECEPTOR IN HEREDITARY SALTMAN SENSITIVE HYPERTENSION

G. Chandramohan1,4, N. Vaziri2, K. Norris3,4, S. Sinhar1 Harbor-UCLA Medical Center, Torrance, CA; 2Charles Drew University, Los Angeles, CA; 3University of California, Irvine, CA and 4University of California, Los Angeles, CA.

Purpose of Study: Melanocortin 3 receptor (MC3-R) belongs to the family of melanocortin receptors that has high affinity and specificity to gamma melanocyte stimulating hormone (γMSH), a natriuretic peptide, that is known to play a role in the regulation of blood pressure (BP) and sodium homeostasis. Recent studies showing increased expression of MC3-R along with high circulating levels of gamma MSH in normotensive Sprague Dawley rats fed a high salt diet further supports the role of this humoral system in sodium homeostasis. We hypothesize that a potential dysregulation of MC3-R response to dietary salt may contribute to salt retention and hypertension in salt sensitive hypertension.

Methods Used: Dahl sensitive (DSS) and Dahl salt-resistant (DSR) rats were fed high (8%) or low (0.07%) salt diets for 3 weeks. We examined MC3-R expression in the kidneys and γMSH concentration in the plasma of these rats. Also, in another set of DSS rats that were fed a low or high salt diet, blood pressures were monitored by telemetry for 3 days while the animals were receiving intraperitoneal MC3-R agonist (melanotan II; MT II) and MC3-R antagonist (SHU9119).

Summary of Results: As expected consumption of high salt diet did not alter BP in the DSR but significantly increased BP in the DSS. Consumption of high salt diet in DSR rats led to a 5 fold increase in plasma γMSH (3.1±1.4 pg/ml vs. 19.9±1.6 pg/ml, P = 0.01) and a two-fold increase in renal MC3-R protein abundance but failed to change either plasma γMSH or renal MC3-R protein abundance in DSS rats. Administration of MT II led to a significant fall in BP in DSR but not in the DSS rats consuming high salt diet. In contrast, administration of SHU9119 resulted in significant rise in BP in both low and high salt groups.

Conclusions: In contrast to the DSR rats the DSS rats exhibit resistance to BP-lowering action of MC3-R agonist and fail to up-regulate MC3-R expression and gamma MSH synthesis in response to high salt diet. Given the role of gamma MSH- MC3-R system in modulation of sodium homeostasis, the observed abnormality may, in part, contribute to salt retention and hypertension in DSS rats.

Western Student Medical Research Forum Student Scientific Session V
1:30 PM
Friday, January 30, 2009

308 A MULTIFACTORIAL, MEDICAL STUDENT-DRIVEN SOLUTION TO INTESTINAL HELMINTH INFECTION IN A DEVELOPING COMMUNITY

C.J. Wallis1, N. Alexander1, S. Bradwell1, D. El-Zammar1, D. Fang1, S. Finke2, C. Huang2, V. Kapoor2, J. Khangura1, J. Lubin1, F. Petigara1, M. Yan1 University of British Columbia, Vancouver, BC, Canada and 2University of British Columbia, Vancouver, BC, Canada.

Purpose of Study: Intestinal helmint infection is a common affliction worldwide with increased prevalence in the third-world. Here we present a multifactorial approach, designed and implemented by medical students, to reduce the burden of this disease on the student population at Munsel-fing Boarding School in rural northern India.

Methods Used: A multifaceted methodology was employed. Health screens were conducted on the 380 students who attend the school. Following this, a survey was conducted with the student population at Munsel-ling School to assess their hygiene habits focusing on handwashing practices.

Summary of Results: In consultation with the school health worker, principal, local government doctors, and clinical assessment of the children during the health screens, a high prevalence of helmint infection was observed.

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reported. As a result, the entire student population was given deworming medication (albendazole, weight adjusted dosing). The survey showed infrequent handwashing, with almost half the students (47.5%) reporting washing their hands once or fewer per day and the majority reporting that they only ‘sometimes’ wash their hands following defecation and before eating. The vast majority reported only occasional use of soap (85.4%). To address this, handwashing stations (with soap) were constructed adjacent to the toilet block and dining hall and age-appropriate education programs were undertaken. As these activities were undertaken this summer, the efficacy of our project will be assessed next summer with clinical assessment, surveys and interviews to monitor handwashing practices and to assess knowledge of gastrointestinal helmthit and its prevention.

**Conclusions:** Our approach was widely accepted by the local population including children, teachers and staff. As a result, this multifactorial approach, combining clinical assessment, pharmaceutical treatment, educational programs including handwashing technique and handwashing infrastructure development, in collaboration with the Munsel-ling School staff, serves as a model for sustainable solutions to reducing disease burden in developing communities.

**309 HEALTHCARE SELF-MANAGEMENT TOOL FOR PEOPLE LIVING WITH HIV/AIDS AS A CHRONIC ILLNESS AT THE MADISON CLINIC IN SEATTLE, WA**

J. Angel-Padilla University of Washington School of Medicine, Seattle, WA

**Purpose of Study:** HIV has become a chronic illness during the past two decades with the help of better medications and understanding, which means that a new approach to managing patients living with HIV needs to be developed. It has been shown that self-management tools increase medication adherence, patient education and doctor-patient communication for people living with chronic illnesses. The purpose of this project was to develop a self-management tool that would improve healthcare outcomes for people living with HIV by getting patients more involved in their own healthcare and better able to manage their own health needs.

**Methods Used:** A review of the literature was preformed in order to examine the best way to implement a reasonable intervention to support the management of a chronic illness like HIV. A self-management card was conceived to assist the patients with their own health and be a prompt for better patient-provider communication. A group of physicians from the Madison Clinic, which is the largest provider of HIV care in the Northwest, were interviewed in order to provide insight into critical information that should be included in the tool. The physicians and the clinic’s Community Advisory Committee, which consists of patients with HIV from the clinic critiqued and reviewed the card. They determined the final form of the card was a useful tool.

**Summary of Results:** The self-management card includes personal medical information that is pertinent to the care of HIV patients such as other medical conditions, allergies, vaccines, general health maintenance (ie, pap smears, PSA levels, etc.), prescriptions, lipid panels, CD4 counts and viral load levels. The card will be implemented at the Madison Clinic and the effects it has on patient education, chronic illness self-management, and better patient-provider communication will be monitored after a trial period. If the card proves to be helpful and successful at the Madison Clinic it will then be given to patients at other HIV/AIDS providers in the Seattle area.

**Conclusions:** The self-management card can improve healthcare outcomes such as medication adherence, general healthcare maintenance, education, and doctor-patient communication while providing more thorough care over time by getting patients involved in their own health care.

**310 ENDOGENOUS ENDOPHTHALMITIS: A RETROSPECTIVE STUDY**

D. Mayor1, J. Fan2, H. Wilson2 1Loma Linda University, Loma Linda, CA and 2Loma Linda University, Loma Linda, CA

**Purpose of Study:** To give an update on the etiologies, causative organisms and comorbidities of endogenous endophthalmitis.

**Methods Used:** A retrospective review of charts from patients treated for endogenous endophthalmitis at the Loma Linda University Medical Center from January 2002 to July 2008. Etiologies, causative organisms of infection, comorbidities and visual prognoses were tabulated and studied.

**Summary of Results:** Of 22 patients (22 eyes) with endogenous endophthalmitis, two were excluded because of lack of data; 40% (8/20) of the eyes were vitreous culture positive and 35% (7/20) had positive blood cultures. Staphylococcus aureus grew in 50% (4/8) of positive vitreous cultures. All patients were treated with either a pars plana vitrectomy and intravitreal antibiotics or a vitreal tap and intravitreal antibiotics. At presentation the following visual acuity (VA) was recorded: 30% (6/20) had no light perception (NLP), 20% (4/20) had light perception (LP), 20% (4/20) had count finger (CF) or hand motion (HM), 20% (4/20) had greater than or equal to 20/400, 10% (2/20) had between 20/200 and 20/400. The final VA for patients was: 33% (6/18) had NLP; 17% (3/18) had LP; 22% (4/18) had CF or HM; 11% (2/18) had between 20/200 and 20/400, 5% (1/18) had 20/100, 11% (2/18) had better than 20/100 vision, two had no final VA because of death. Thirty-five percent (7/20) later developed retinal detachment. Length of follow up varied from 7 days to 17 months and four patients died during the follow up period. The time from presentation to death was between 21 days to 36 months. Comorbidities were as follows: 65% (13/20) had diabetes mellitus, 40% (8/20) had hypertension, 35% (7/20) had renal disease, 5% (1/20) had coronary artery disease, 5% (1/20) had vascular disease, 5% (1/20) had an autoimmune disease. Two patients had cancer; one had metastatic cancer and bilateral endophthalmitis.

**Conclusions:** Endogenous endophthalmitis continues to carry a poor prognosis despite treatment with antibiotics. In our study the organism most likely to cause culture positive endogenous endophthalmitis is Staphylococcus aureus.

**311 IMPACT OF HCV-INFECTION ON GLOMERULAR FILTRATION RATE (GFR) IN THE FIRST YEAR POST-LIVER TRANSPLANT**

M.M. Asay, R.S. Mangus, J.A. Fridell, A.J. Lutz, A.J. Tector, R.M. Vianna Indiana University, School of Medicine, Indianapolis, IN

**Purpose of Study:** Liver transplant recipients with hepatitis C (HCV) may be predisposed to a more rapid decline in renal function after liver transplantation because of the effect of chronic hepatitis C infection on the kidney. This study evaluates the change in glomerular filtration rate (GFR) in the first year after liver transplantation for recipients infected (HCV(+)) and not infected (HCV(-)) with HCV.

**Methods Used:** The records of 963 adult, deceased donor liver transplants from 2001 to 2008 were reviewed. Renal function was assessed by calculating the baseline and post-transplant GFR using the modification of diet in renal disease equation.

**Summary of Results:** Overall, 75% of recipients experienced a decrease in GFR. 74% (HCV(+)) and 77% (HCV(-)) (P = 0.55). Overall percent change in GFR was -19%, -16% HCV(+) and -23% HCV(-) (P = 0.18). Absolute change in GFR was -13 ml/min/1.73m2 HCV(+) and -17 ml/min/1.73 m2 HCV(-) (P = 0.001).

**Conclusions:** In conclusion, HCV(+) patients do not have a more rapid decline in renal function within 1-year.

**312 P63 EXPRESSION AND DISEASE-SPECIFIC SURVIVAL IN MERKEL CELL CARCINOMA**

J. Malekirad1,2, Garneski1,2, G. Stetsenko1,2, P. Nghiem1,2 1University of Washington School of Medicine, Seattle, WA and 2Seattle Cancer Care Alliance, Seattle, WA

**Purpose of Study:** Merkel cell carcinoma (MCC) is a lethal neuroendocrine skin cancer with an incidence of >1,500 cases in the US and a mortality of 30%. A recent study in an Italian cohort of 47 MCC patients reported strong correlation between the expression of the transcription factor p63 and patient survival, with p63 positive tumors associated with worse prognosis (3-year survival of patients with p63+ MCC tumors of only 14% as compared to 95% of patients with p63- tumors).[1] We sought to confirm this striking finding in an independent population of MCC patients in the USA. If replicable, p63 immunohistochemistry could be applied immediately to clinical practice.

**Methods Used:** 29 formalin-fixed, paraffin-embedded, pathologically confirmed MCC specimens were analyzed. Excellent clinical follow-up
was obtained (average: 20 months). P63 expression was measured using the monoclonal Dakopatts antibody; basal epidermis served as an internal control and an adjacent section stained without primary antibody as the control. Tumors were defined as p63+ if 10% or more of the tumor nuclei stained at all for p63. Disease-specific survival curves were calculated using the Kaplan-Meier method and compared by Log-rank test.

**Summary of Results:** We observed a trend toward worse survival in patients with p63 positive tumors. There were no survivors after three years for p63 positive tumors vs. 61% surviving for p63 negative ones. However, our findings were not statistically significant ($P = 0.16$). As expected, our data demonstrate association between mitotic index and disease-specific survival ($P = 0.01$) and between stage at presentation and survival ($P < 0.0001$).

**Conclusions:** Our data currently do not confirm the role of p63 expression as an independent prognostic marker in Merkel cell carcinoma. Differences between these findings may result from the outcomes measure; the prior study used overall survival while ours uses disease-specific survival. We are currently expanding our study to include 86 additional MCC patients to more definitively determine the clinical utility of the p63 stain.


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**315 IMPACT OF DELAYED RECTAL CANCER SURGERY FOLLOWING NEOADJUVANT CHEMORADIOThERAPY**


**Purpose of Study:** Although combined modality therapy is recommended for the majority of patients diagnosed with locally advanced rectal cancer, the optimal timing of surgery has been debated. This study analyzes the impact of delayed rectal cancer surgery (>8 weeks) following neoadjuvant chemoradiation therapy from January 1998 - June 2006. Main Outcome Measures: Surgical complications, treatment outcome, and survival.

**Summary of Results:** Twenty patients underwent early resection (within 8 weeks) and 18 patients underwent delayed resection (8.1-17.4 weeks) following neoadjuvant chemoradiotherapy. Nineteen (50%) patients received additional postoperative therapy. One (5%) early and 3 (17%) delayed patients had positive pathologic margins ($P = 0.01$). There were no significant differences between both groups in intraoperative complications, surgical morbidity, sphincter-preservation rates, and progression-free or overall survival rates with a median follow-up of 30 months.

**Conclusions:** The timing of rectal cancer surgery following completion of neoadjuvant chemoradiotherapy has been debated. There has been increasing evidence that longer time intervals to surgery are associated with increased complete response rates. Delaying surgery beyond an 8 week interval does not appear to significantly impact surgical morbidity, sphincter-preservation rate, or oncologic outcome.

**314 A STUDY OF HOSPITALIZATION AND SURGERIES AMONG INJECTION DRUG USERS IN VANCouVER**

**B. Maas $^1$, S. Jones $^1$, T. Kerr $^3$, L. Lai $^2$, E. Wood $^2$ 1University of British Columbia, Vancouver, BC, Canada and 2St. Paul’s Hospital, Vancouver, BC, Canada.**

**Purpose of Study:** Injection drug users (IDUs) are at a high risk of many negative health outcomes in addition to HIV and infectious diseases. Hospitalizations are common among IDUs and diagnostic and therapeutic interventions are often necessary. This study sought to characterize the surgical and diagnostic interventions among a cohort of injection drug users at St. Paul’s Hospital (SPH) in Vancouver, BC.

**Methods Used:** The Scientific Evaluation of Supervised Injection (SEOSI) is a prospective cohort study of IDUs in Vancouver. Hospital admissions and procedure records from 2001 to 2007 were compared through confidential linkage to the cohort participants. We studied the incidence of surgical and diagnostic procedures performed on SEOSI participants and examined which departments were consulted to perform surgeries and other interventions.

**Summary of Results:** Of 1028 eligible IDUS, 179 (17%) required a total of 503 admissions to SPH between 2001 and 2007. 156 (31%) of the admissions involved procedures performed by hospital staff, of which 126 (81%) were interventional and 30 (19%) were diagnostic. The most commonly performed interventional procedures were the insertion of central lines (47, 37%), and drainage of wounds (36, 20%). Of the 156 procedures, 45 (36%) were surgical operations requiring use of an operating room. The breakdown of procedures by department was: 49 (31%) Internal Medicine, 33 (21%) Radiology, 20 (12%) Plastic Surgery, 15 (10%) Orthopaedic Surgery, 7 (4%) Gastroenterology, 6 (4%) General Surgery, and 26 (16%) other.

**Conclusions:** IDUs in Vancouver were found to have frequent health complications requiring hospital admission for diagnostic and surgical interventions. Many of these procedures were for medical conditions that might have been preventable. Further studies are needed to determine whether improved access to primary care could prevent hospitalizations and costly medical procedures among IDUs.

**315 ASSOCIATION OF EGO DEFENSE MECHANISMS, DEPRESSION AND COMT GENOTYPING AMONG PARENTS OF CHILDREN WITH PEDIATRIC CANCER**

**D. Otten, T. Beresford, A. Hoffenberg University of Colorado Denver, Denver, CO.**

**Purpose of Study:** This study looks to investigate the association of ego defense mechanisms and depression scores of parents of children with cancer with their genotype for the COMT allele and their cortisol levels. A secondary goal for this study will be the investigation of the association of parents’ ego defense mechanism profiles and their children’s cancer survival three and five years later. The enzyme catecholamine-O-methyltransferase (COMT) degrades the neurotransmitters dopamine, epinephrine, and norepinephrine. A polymorphism of the gene that codes for this enzyme results in differential enzymatic activity, and those with methionine (Met58) alleles have decreased COMT activity. Individuals with this low-activity allele are prone to anxiety, depression, and neuroticism, thereby increasing their cortisol levels. Furthermore, studies have indicated that the maturity of ego-defense adaptation among adult cancer patients not only affected their psychological adjustment but also was associated with increased cancer survival. Therefore, we hypothesize that among parents of children with cancer, the individuals who are less depressed or anxious are more likely to have lower cortisol levels, more likely to have the high-activity COMT allele, and are more likely to have “mature” ego defense mechanisms. We also believe that these parents’ children with cancer will have a longer survival probability than children with cancer whose parents have “immature” adaptation styles.

**Methods Used:** Parents will be administered the Beck Depression Inventory and the Defense Style Questionnaire while their child undergoes chemotherapy infusions. A salivary cortisol and DNA sample will be gathered during this session. Follow up will occur at 3- and 5-years to determine child survival via the Cancer Registry.

**Summary of Results:** The study protocol was submitted to COMIRB, full board. It was reviewed and approval was deferred to a future date, as a few questions needed clarification. Meanwhile, a new research member was identified in the Department of Pediatric Oncology, and new details are under discussion to be incorporated in the protocol application.

**Conclusions:** The results of this study would help the child’s treatment team reach out to at-risk parents, maximizing positive outcomes and minimizing distress in both the parent and the child.

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**316 ASSESSMENT OF RASSF1A ASSOCIATION DOMAIN FAMILY PROTEIN 1 GENE EXPRESSION IN NORMAL AND MALIGNANT HUMAN MAMMARY CELLS**

**J.A. Fawley $^1$, F.P. Hasibuan $^1$, J. Jeong $^2$, R.J. Aragon $^2$, M.L. Baldwin $^2$, V.G. Amaro $^1$, M.E. Reeves $^1$ 1Loma Linda University School of Medicine, Loma Linda, CA and 2Loma Linda VA Healthcare System, Loma Linda, CA.**

**Purpose of Study:** To determine if RASSF1C is up-regulated in tumor versus normal human breast tissue and cell lines.

**Methods Used:** Analysis was carried out in normal and malignant human breast tissue, as well as cell lines. Total RNA from human normal and
malignant mammary tissue were obtained (Clontrec), then quantified by optical density and normalized. The human breast cancer lines T47D, MDA-MB231, and H557T were used, along with the normal human breast cell line AG-1132. All cell lines were expanded and harvested per routine tissue culture methods. RNA was extracted using the Absolutely RNA Miniprep Kit (Qiagen). First-strand cDNA was produced for both the tissue and cell lines using reverse transcriptase. PCR and quantitative real-time PCR were performed to assess expression of RASSF1A and RASSF1C.

**Summary of Results:** Real-time PCR analysis of normal and malignant human breast tissue demonstrated down-regulation of RASSF1A expression by 1.3 fold and up-regulation of RASSF1C expression by 2.9 fold (Table 1).

Real-time PCR analysis of the normal and malignant human breast cell lines demonstrated an up-regulation of RASSF1C as high as 56-fold in the malignant cells as compared to the normal cells (Table 2). Conclusions: Our data shows the up-regulation of RASSF1C, an isoform previously shown to promote tumor growth, in human breast cancer tissue and cell lines. We also show the down-regulation of RASSF1A, a known tumor suppressor, in human breast cancer tissue.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Tumor Breast</th>
<th>Fold Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Breast</td>
<td>RASSF1A</td>
<td>1.3</td>
</tr>
<tr>
<td>Tumor Breast</td>
<td>RASSF1C</td>
<td>2.9</td>
</tr>
</tbody>
</table>

### 317 TOLL-LIKE RECEPTOR-2 DEPENDENT SIGNALING IN PULMONARY ENDOTHELIAL AND EPITHELIAL CELLS IN RESPONSE TO OXIDATIVE STRESS

J. Popper, J. Keech, M. Mulligan University of Washington, Seattle, WA.

**Purpose of Study:** Despite advancements in donor management, organ preservation, and post-operative care following lung transplantation, lung ischemia reperfusion injury continues to affect up to 25% of lung transplant recipients, increasing their risks of acute and chronic rejection, bronchiolitis obliterans and impairing survival outcomes. Toll-like receptor-4, toll-like receptor-2 and the alveolar macrophage have all been implicated as critical factors in the development of lung ischemia reperfusion injury, but the role of toll-like receptors in pulmonary artery endothelial and epithelial cells remains unclear. We sought to determine the role of toll-like receptor-2 and -4 in pulmonary artery endothelial and epithelial cells following hypoxia and reoxygenation.

**Methods Used:** Primary cultures of type II pneumocytes and pulmonary artery endothelial cells were obtained from male long evans rats. Molecular knockdown of each receptor was achieved with short interfering RNA (siRNA). Cells were transfected with toll-like receptor-2 or -4 siRNA in a lipid vector prior to undergoing periods of hypoxia and reoxygenation. At the termination of experiments, media was collected and analyzed for cytokine lipid vector prior to undergoing periods of hypoxia and reoxygenation. At the termination of experiments, media was collected and analyzed for cytokine activation and CINC secretion. The purpose of study was to assess expression of RASSF1A and RASSF1C.

**Summary of Results:** Real-time PCR analysis of normal and malignant human breast tissue demonstrated down-regulation of RASSF1A expression by 1.3 fold and up-regulation of RASSF1C expression by 2.9 fold (Table 1).

Real-time PCR analysis of normal and malignant human breast cell lines demonstrated an up-regulation of RASSF1C as high as 56-fold in the malignant cells as compared to the normal cells (Table 2).

Conclusions: Our data shows the up-regulation of RASSF1C, an isoform previously shown to promote tumor growth, in human breast cancer tissue and cell lines. We also show the down-regulation of RASSF1A, a known tumor suppressor, in human breast cancer tissue.

### 318 PULMONARY FUNCTION TESTING PRE-HEART TRANSPLANT CAN PREDICT OUTCOME

J. Patel, M. Hamilton, J. Kobashigawa David Geffen School of Medicine at UCLA, Los Angeles, CA.

**Purpose of Study:** Significant chronic obstructive pulmonary disease (COPD) is a relative contraindication to heart transplantation. However, the exact criteria for COPD have not been established. Pulmonary function tests (PFTs) reflect the degree of the pulmonary pathology and traditionally, FEV1<70% predicted and an FEV1/FVC ratio<70% describe COPD. We examined whether these pretransplant PFT abnormalities were associated with poor outcomes following heart transplant.

**Methods Used:** Between 1994-2008, 415 patients with complete pre-transplant PFT data were examined. 91 patients had FEV1/FVC<70%, 39 patients had FEV1<50% predicted and the remaining 324 patients as controls. The following outcomes were assessed: 1-year rejection, 5-year survival, 5-year cardiac allograft vasculopathy (CAV), and 5-year non-fatal major adverse cardiac events (NF-MACE; myocardial infarction, heart failure, percutaneous intervention, pacemaker, stroke, new peripheral vascular disease).

**Summary of Results:** Patients with FEV1<50% predicted had no difference in the incidence of rejection, survival, CAV, or NF-MACE compared with patients with higher FEV1. However, patients with FEV1/FVC<70% had significantly lower 5-year survival, lower freedom from NF-MACE and a trend towards lower freedom from CAV (Table). Patients with FEV1/FVC<70% had more pulmonary infections (68% vs. 15%, P = 0.003) and a higher incidence of fatal pulmonary infections (8% vs. 1%, P = 0.001).

**Conclusions:** Pre-transplant FEV1/FVC<70% but not FEV1<50% predicted is a marker for poor outcomes after heart transplantation. This suggests that the FEV1/FVC ratio, but not the FEV1, may be used as a contraindication in the transplant evaluation process.

### 319 OUTCOME OF OLDER REDO HEART TRANSPLANT PATIENTS

M. Yajnik, M. Hamilton, J. Kobashigawa David Geffen School of Medicine at UCLA, Los Angeles, CA.

**Purpose of Study:** Patients who undergo redo heart transplantation when they are more than 1 year after initial heart transplantation have comparable survival compared to de novo heart transplant patients according to the ISHLT registry. As heart transplant centers mature, more of their patients may be in need of redo heart transplantation due to severe cardiac allograft vasculopathy (CAV). The purpose of the current study was to examine whether older redo heart transplant patients >60 years of age have comparable outcome to de novo heart transplant patients.

**Methods Used:** Between 1994 and 2008, we identified 12 redo heart transplant patients who >60 years of age (older redo group, ages 61-68 years). This group was compared to 821 contemporaneous de novo heart transplant patients.

**Summary of Results:** Baseline demographics (percentage of males, CMV status, ischemic time, and donor age) were comparable between the older redo heart transplant patients and controls, except for mean age (65 ± 2 vs. 55 ± 12; P = 0.004). All 12 older redo patients survived >1 year and actuarial 5-year survival was comparable to the control group (66.7% vs. 76.4%, p = NS). First-year freedom from any treated rejection was also comparable.
COMMON IN OBESE MEN WITH HEART FAILURE

Risk factors for obstructive sleep apnea (OSA) due to heavy snoring and nocturnal arousals, obstructive sleep apnea may remain undiagnosed in this population.

The aim is to study the prevalence and gender differences in risk factors for OSA among patients with HF.

Methods Used: We reviewed anthropometric measurements such as weight, neck and waist circumference in 694 consecutive patients who were enrolled in the Clinical Information Manager for HF (CIM-HF) registry (Table 1). We then compared risk factors between both sexes among obese patients were compared using Student t test for continuous variables. P ≤ 0.05 was considered significant (Table 1).

Summary of Results: Both genders have the similar body mass index (BMI), age and systolic blood pressure. Men have larger waist size, NC and NHR and have higher diastolic BP. These findings also persist when the subset of obese HF (BMI >30) patients were examined. (Table 1)

Conclusion: Risk factors for OSA such as NC and NHR are more common among male HF patients. Routinely collecting anthropometric data will increase the detection of OSA and may potentially improve the symptoms among obese chronic HF patients.

### Table 1: Characteristics of Obese Patient Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65.1</td>
<td>63.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>91.5</td>
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<tr>
<td>Height (cm)</td>
<td>178</td>
<td>170</td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td>32.7</td>
<td>31.5</td>
</tr>
<tr>
<td>Neck Circumference (NC)</td>
<td>59.5</td>
<td>57.0</td>
</tr>
<tr>
<td>Neck Height Ratio (NHR)</td>
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<td>0.91</td>
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</table>

### Table 2: Postmenopausal Women with Obstructive Sleep Apnea

<table>
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<th>Characteristic</th>
<th>Overweight</th>
<th>Normal Weight</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>51.2</td>
<td>52.4</td>
<td>0.39</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.6</td>
<td>25.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td>91.3</td>
<td>85.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neck Circumference (cm)</td>
<td>59.3</td>
<td>57.0</td>
<td>0.12</td>
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<td>Neck Height Ratio</td>
<td>0.92</td>
<td>0.91</td>
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</table>

### Table 3: Prevalence of Obstructive Sleep Apnea in Obese Men and Women

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>51</td>
<td>52</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.7</td>
<td>29.5</td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td>91.5</td>
<td>85.4</td>
</tr>
<tr>
<td>Neck Circumference (cm)</td>
<td>59.3</td>
<td>57.0</td>
</tr>
<tr>
<td>Neck Height Ratio</td>
<td>0.92</td>
<td>0.91</td>
</tr>
</tbody>
</table>

### Table 4: Comparison of Obstructive Sleep Apnea Prevalence in Obese Men and Women

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>51</td>
<td>52</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.7</td>
<td>29.5</td>
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<tr>
<td>Waist Circumference (cm)</td>
<td>91.5</td>
<td>85.4</td>
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<tr>
<td>Neck Circumference (cm)</td>
<td>59.3</td>
<td>57.0</td>
</tr>
<tr>
<td>Neck Height Ratio</td>
<td>0.92</td>
<td>0.91</td>
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</table>

### Table 5: Multivariate Analysis of Risk Factors for Obstructive Sleep Apnea

<table>
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<tr>
<th>Characteristic</th>
<th>Odds Ratio (95% CI)</th>
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<tr>
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<tr>
<td>BMI (kg/m²)</td>
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<tr>
<td>Waist Circumference (cm)</td>
<td>1.05 (1.03-1.07)</td>
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<tr>
<td>Neck Circumference (cm)</td>
<td>1.02 (1.01-1.03)</td>
</tr>
<tr>
<td>Neck Height Ratio</td>
<td>1.00 (0.99-1.01)</td>
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### Table 6: Comparison of Obstructive Sleep Apnea Prevalence in Obese Men and Women

<table>
<thead>
<tr>
<th>Characteristic</th>
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<th>Women</th>
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</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>51</td>
<td>52</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.7</td>
<td>29.5</td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td>91.5</td>
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</tr>
<tr>
<td>Neck Circumference (cm)</td>
<td>59.3</td>
<td>57.0</td>
</tr>
<tr>
<td>Neck Height Ratio</td>
<td>0.92</td>
<td>0.91</td>
</tr>
</tbody>
</table>

### Table 7: Comparison of Obstructive Sleep Apnea Prevalence in Obese Men and Women

<table>
<thead>
<tr>
<th>Characteristic</th>
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<th>Women</th>
</tr>
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<tbody>
<tr>
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</tr>
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<td>59.3</td>
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</tr>
<tr>
<td>Neck Height Ratio</td>
<td>0.92</td>
<td>0.91</td>
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323 BETA BLOCKER THERAPY IS WELL TOLERATED IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND CHRONIC HEART FAILURE: CLINICAL INFORMATION MANAGER FOR HEART FAILURE REGISTRY ANALYSIS

R. Bell1, L. Houston-Feenstra2, C. Fuller3, D.K. Petersen2, J.R. Chiong2
1Loma Linda University, Loma Linda, CA and 2Loma Linda University Medical Center, Loma Linda, CA.

Purpose of Study: The use of Beta-blocker therapy remains controversial in patients with Chronic Obstructive Pulmonary Disease (COPD) associated with the belief that use of this therapy may result in worsening symptoms of bronchospasm. However, development of new types of beta-blockers and reports of these new drugs being well tolerated in patients with both COPD and chronic heart failure (CHF) suggests that the benefit of this therapy may outweigh long held concerns over worsening of COPD symptoms. Beta-blockade has been shown to reduce mortality in patients with CHF; our experience has shown that with carefully managed titration in a dedicated CHF program, patients with both COPD and CHF will benefit from this therapy. However, the effects and safety of ongoing beta-blocker therapy in patients with CHF and COPD is not well documented in the literature. This study was designed to evaluate the use of non-selective beta-blocker therapy in patients with both CHF and COPD as part of the Clinical Information Manager for Heart Failure (CIM-HF) registry.

Methods Used: Designed as a prospective observational study, we evaluated the proportion of beta-blocker use in patients with different stages of COPD. We prospectively reviewed data from 880 patients followed in our heart failure program. 314 patients had pulmonary function tests (PFT) done as part of a workup for complaints of dyspnea.

Summary of Results: Of the 314 patients with PFT data: 94 patients had normal FEV1, COPD was documented in 220 patients using American Thoracic Society (ATS) guidelines, 116 patients had mild COPD (FEV1 60-79%), 73 patients had moderate COPD (FEV1 40-59%) and 31 had severe COPD (FEV1 <40%). All patients with COPD demonstrated no increase in shortness of breath or changes in airway mechanics following long term, upward titration of beta-blockers.

Conclusions: Patients with both CHF and COPD tolerated long-term use of beta-blocker therapy with no worsening of symptoms related to COPD. This study suggests that beta-blocker therapy can be safely achieved in patients with CHF and COPD.

324 RECURRENT SYNCOPE CAUSED BY PHYSICAL AND EMOTIONAL STRESS

B. Farhang1, T. Marker2
1Western University COMP, Pomona, CA and 2Good Samaritan Regional Medical Center, Corvalis, OR.

Case Report: Syncope is one of the most common medical complaints in clinical practice and is defined as a transient loss of consciousness usually leading to falling. Its onset is rapid as is its recovery. The overall mechanism is thought to be transient global cerebral hypoperfusion due to either arrhythmias or neurocardiogenic causes. Neurocardiogenic syncope (NCS) is thought to be transient global cerebral hypoperfusion due to either arrhythmias or neurocardiogenic causes. Neurocardiogenic syncope (NCS) is hypothesized that measures of peripheral hemodynamics and perfusion, such as ankle-brachial index (ABI), laser-Doppler imaging flux ratio, post-exercise muscle reoxygenation time, and body mass index (BMI) should be related to and predictive of functional walking performance.

Methods Used: Seven male veteran subjects (mean age 64 yr, mean ABI 0.53) were tested during three clinical visits. The Walking Impairment Questionnaire, International Physical Activity Questionnaire, maximal walking distance, 6-minute walk distance, and maximal exercise times during treadmill and calf exercise constituted the functional variables which were limited by calf claudication symptoms. These were correlated with the physiological variables of ABI, flux ratio (skin perfusion reserve), and recovery times of relative HbO2 calf tissue saturation (StO2) after treadmill and calf exercise tests.

Summary of Results: Higher BMI and longer calf exercise StO2 recovery time were associated with greater walking impairment (r = 0.71 and 0.69). Higher ABI correlated with longer treadmill exercise time (r = 0.67). Lower treadmill StO2 recovery time correlated with higher reported physical activity and longer 6-minute walk distance (r = 0.90 and 0.74). Additionally, treadmill StO2 recovery time correlated with different functional variables from calf StO2 recovery time, implying that, despite similar calf claudication symptoms, the nature of muscle desaturation differs between treadmill and calf exercise.

Conclusions: Significant relationships were indeed found between some physiological parameters and functional variables.
327 MATERNAL PROTEIN DEPRIVATION AND THE EPIGENETIC ORIGIN OF HYPERTENSION: FETAL MOUSE KIDNEY’S RENIN-ANGIOTENSIN SYSTEM

E. Jang1,2, R. Goya2, A. Mittal1, T. Wright1,2, A. Gallif1,2, L.D. Longo1
1Loma Linda University, Loma Linda, CA and 2Loma Linda University, Loma Linda, CA.

Purpose of Study: To examine the effects of maternal protein deprivation on the gene expression of renin in fetal mice kidneys and the developmental programming of hypertension in the offspring.

Methods Used: Pregnant mice were fed either a regular diet (20% and 18% protein) or an isocaloric protein deprived diet (10%, 9%, and 6% protein). One group of mothers was sacrificed at gestational age 17.5 days and fetal organs were harvested for studies of gene expression. The remaining group of mothers was allowed to give birth to pups for blood pressure and weight measurements. Blood pressures were measured using the non-invasive tail cuff method. Weights were measured weekly at birth and blood pressures were measured weekly beginning at age 4 weeks. Protein analysis was done via Western immunoblot assay. Messenger RNA levels were detected by performing reverse transcription to produce cDNA, and then performing ANOVA, and Student T-test and ANOVA, P < 0.05 was considered significant.

Summary of Results: While renin protein levels were not significantly altered in fetal kidneys with maternal protein deprivation, renin mRNA levels were significantly increased (fold increase 11). Furthermore, a significant reduction in birth weight was observed in pups with maternal protein deprivation. These pups showed faster growth rate and achieved normal weight rapidly. They also showed significant blood pressure increase at 12 weeks in females and 16 weeks in males.

Conclusions: Our findings suggest that maternal protein deprivation leads to increased renin message levels from the gene, but a regulatory system between the mRNA and protein levels hinders mRNA translation to protein. This agrees with our blood pressure results, which show elevation only after 12 (females) and 16 (males) weeks of age. Further research is being carried out to look at the possibility of involved microRNAs, which may decrease mRNA stability, and histone modification, which may be the cause of the increased mRNA levels. These findings will be discussed at the meeting.

Western Student Medical Research Forum
Student Scientific Session VII
1:30 PM
Friday, January 30, 2009

328 PROBLEM BASED LEARNING WITH SUPPLEMENTAL INTERACTIVE MEDICAL MULTIMEDIA (PBL-SIMM)

D. Mickelson, G. LiMarzi, B. Ross UW Medicine, Seattle, WA.

Purpose of Study: Problem-based learning (PBL) is an experiential instructional approach that aims to foster the observational, communication, and critical thinking skills of students. Currently, PBL is administered in paper format by a tutor to a small group of students who read, research, and discuss the evolving vignette. Simulation training has been shown as an effective teaching technique, and computers provide an efficient medium for the delivery of rich content. This project combines the effective aspects of both simulation and PBL methodologies while exploiting the added educational benefit of digital multimedia to better achieve the PBL objectives.

Methods Used: Review of literature confirms that multimedia enhances content delivery, and simulation-based education is increasingly regarded as an innovative training component for education. Surveying PBL faculty and students identified shortcomings in the current method, as well as the weakness of presenting an issue by merely written or oral means. Analysis of these findings served to catalyze collaboration with ISIS simulation experts and medical content specialists to develop a novel educational approach - Problem Based Learning with Supplemental Interactive Medical Multimedia (PBL-SIMM).

Summary of Results: PBL-SIMM aims to enrich the current technique by adding a computerized ‘interactive chart’ that serves as a gateway to audio, video, images, and documents vital to the clinical case. It contains an integrated patient simulation that emphasizes teamwork and communication. ‘Fred’, a prototype case, involves the diagnosis and treatment of DVT and PE. Fred’s case is enhanced via radiographic images and film, interactive lab results, integrated medical costs, audio from consulting doctors, and video footage of the patient - all delivered in a dynamic virtual patient chart. The case concludes with a collaborative real time high fidelity mannequin simulation.

Conclusions: Current PBL strategies can be enriched in the areas of medical content delivery, interactivity, and teamwork through a combined use of technology, simulation, and multimedia. Still in development, PBL-SIMM has a sound framework and modern approach to interactive group learning. Once complete, a study will be conducted to compare the effectiveness of this new model to the traditional pen-and-paper PBL.

329 REDESIGNING CLINIC OPERATIONS TO IMPROVE DEPRESSION CARE IN PUBLIC PRIMARY CARE SETTINGS

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Purpose of Study: Previous research has demonstrated that quality of depression care can be improved in primary care clinics. However, most of the interventions that achieve improvement are targeted to public primary care clinics that serve predominant uninsured and multiethnic populations. We propose a more feasible intervention that focuses on systems changes, provider education as well as patient tracking and screening tools.

Methods Used: Subjects from the Mid-Valley family and general medicine clinics were screened using the Patient Health Questionnaire 2 (PHQ-2) depression assessment; those who scored positive were included in the study (N = 229). The family medicine patients were assigned to the intervention group while the general medicine patients were assigned to the control group. Patients were interviewed and their depressive symptoms were evaluated using the PHQ-9 depression index at baseline, 7 months, 18 months, and 24 months. Those with a PHQ-9 score >= 10 were identified as depressed. Prevalence of depression was evaluated at each time point for each group using Chi-Square tests.

Summary of Results: At baseline the intervention and control groups were not significantly different with regards to prevalence of depression (P = 0.16). However, at 7 months and 18 months the intervention group had a lower prevalence of depression (P < 0.05). At 24 months the groups were again not significantly different (P = 0.50). Analysis using ANOVA indicated a significant main effect for treatment group (P = 0.001) and time (P < 0.001), but no significant interaction effect (P = 0.72).

Conclusions: A depression intervention for public primary care settings may decrease the time needed for depression treatment. The ability to rapidly treat depressive symptoms would have a major impact on patients’ lives and general health.

330 COMMUNITY INTERVENTIONS TO ADDRESS CHILDHOOD OBESITY

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Purpose of Study: Gillette is a small city in Wyoming. The schools adopted a Healthy Schools program several years ago to fight the problem of childhood obesity. Although the project has been successful in the schools, there are other organizations that have not adopted the same goals; as a result the outcomes have been less impressive than they hoped. The purpose of this project was to create a forum where community members could recognize the benefits of coordination and cooperation in dealing with chronic disease, and to discuss best practices in their battle against childhood obesity.

Methods Used: A literature review was performed to learn about the best ways to treat childhood obesity, focusing on how providers can manage chronic diseases. Next, key leaders in the community were contacted to learn about their efforts and any problems. Leaders included representatives from Healthy Schools, the Parks Department, and the hospital’s nutrition department. It was found that some groups are addressing the problem of childhood obesity but still find challenges, while others do not have a plan.
Community members were then invited to a lunch meeting that served as a forum for discussion. Community members were educated about the problems surrounding childhood obesity; encouraged to discuss strategies for dealing with chronic health problems; and told about the importance of coordination between providers treating chronic diseases.

**Summary of Results:** Those who attended the forum engaged in discussion that focused on strategies for treating childhood obesity, how they could better coordinate, and how they might want to proceed. They agreed that coordination of efforts was an important goal. The forum generated concrete ideas that include hosting a seminar or booth at the city health fair; producing a DVD that could be shown to parents for education; and including members of the community through events centered on childhood obesity.

**Conclusions:** Childhood obesity is a problem in Campbell County. According to the literature, coordination among care providers is important in solving the problem. The forum was a way for leaders in Campbell County to learn about these ideas and discuss how they will use them. Community leaders believe that better cooperation will lead to greater results in terms. They found the forum to be useful and agreed that it would be helpful to meet again.

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**331 DEVELOPMENT OF EDUMED: A HEALTH EDUCATION & MEDICAL EXPOSURE PROGRAM IN MOSCOW, ID**

D.J. Perry University of Washington, Seattle, WA.

**Purpose of Study:** Moscow, Idaho is considered an underserved community, and has a higher than average proportion of the population below the poverty line. These settings have been shown to affect community health. An assessment of local health education resources prompted the complete design and implementation of a formal community education program to inform the public about various health topics.

**Methods Used:** School leaders and local physicians were contacted to determine what health education resources were already available. An extensive literature search was completed regarding the most effective methods to educate youth about health information. A comprehensive program was designed to be incorporated into an existing community outreach organization in the local WWAMI medical program and was named EduMed. Guidelines and materials were developed to assist volunteer medical & pre-professional students organize and conduct hands-on presentations. A blog, brochures, and flyers were created and distributed to introduce EduMed. Interactive presentations were developed covering recommended health topics for youth ages 4-18. All materials, on DVD and hard copy, were organized into binders and presented to Community Outreach Coordinators, WWAMI leadership, the school district, and local physicians.

**Summary of Results:** All EduMed organization materials were developed. Four binders were distributed containing all of the following: 13 program documents, registration flyers, contact lists, evaluation forms, inventory lists and 12 presentations. An internet blog and email were created. 80 flyers were distributed explaining EduMed and WWAMI. Agreements were made with local health education leadership to provide resources and ensure perpetuation of EduMed. EduMed was presented to all principals and health teachers in Moscow School District. Two EduMed Coordinators were elected from the Idaho WWAMI class of 2008 and initiated the program on Sep 1, 2008.

**Conclusions:** Moscow, Idaho now has a well-organized health education program in operation, which utilizes available resources to educate youth. The School District is using the program and requested permission to incorporate EduMed materials into the school district curriculum. The effectiveness of this program will be determined as it is utilized and evaluated. EduMed is now a valuable asset that will be beneficial to all involved.

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**332 DEVELOPMENT OF A PEDIATRIC CARDIAC SURGERY TRAINEE CURRICULUM: BC CHILDREN’S HOSPITAL AND FUDAN UNIVERSITY CHILDREN’S HOSPITAL CARDIAC SCIENCES PARTNERSHIP**

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**Purpose of Study:** Develop a pediatric cardiac surgery curriculum for trainees at Fudan University Children’s Hospital in Shanghai, China. This resource was developed by the Pediatric Cardiac Sciences team at British Columbia’s Children’s Hospital. The terms of the partnership were teaching, education, surgical mentoring, skills enhancement and the development of a cardiac sciences teaching curriculum.

**Methods Used:** A curriculum was amalgamated utilizing guidelines from accredited training bodies. Subtopics for the curriculum included: pediatric cardiology, pediatric surgical cardiology, surgical cardiology, perfusion, echocardiography, cardiac catheterization, anesthesia, critical cardiac care, peri-operative nursing and critical care nursing. Translation was also performed.

**Summary of Results:** A 127-page pediatric cardiac surgery curriculum complete with addendum section (cardiac trainee exam, nursing trainee exam, teaching materials). Translation into simplified Chinese was also performed for the benefit of the trainees. The curriculum has been made available through Fudan University’s Pediatric Cardiac Surgery training website. Despite the unknown environment challenges and the complexity of the cases, a success rate of 97% was obtained. Quality assurance discussions have occurred, leading to the establishment of a computerized database system, allowing tracking of their mortality and complexity following North American standards. The Chinese cardiac program did 570 cases in 2006, 438 being open heart cases and 96 of them complex cases, with a total mortality of 1%. In 2007, there were a total of 743 cases, with 563 open.

**Conclusions:** The goal of the pediatric cardiac surgery training curriculum would be to bring universal standards to a country which does not have formal guidelines when it comes to training their medical personnel. The hope would be that through collaborative efforts from the Centre for International Child Health, this curriculum would serve as a template for an international, standardized curriculum for pediatric cardiac surgery trainee programs that would be available worldwide.

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**333 INCREASING AWARENESS OF CA-MRSA AND HSV-1 IN EUREKA, MONTANA TO PREVENT INFECTIONS IS STUDENT-ATHLETES**

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**Purpose of Study:** Eureka is a rural town in northwest Montana. Like many small towns, school related activities are a uniting force for the community and a good opportunity for students to learn important life skills. Recently several student athletes have seen their seasons cut short due to skin infections acquired while competing in high school sports. A community intervention plan was developed to improve awareness for those athletes, coaches, parents, and administrators and provide the school with strategies designed to prevent future infections in their student athletes.

**Methods Used:** Current literature concerning Community Acquired Methicillin Resistant Staphylococcus Aureus (CA-MRSA) and Herpes Simplex - 1 Virus infections in student-athletes was reviewed. Governing bodies (NCAA and NFHS) were also consulted and appropriate protocols were obtained. A guideline, targeted at student-athletes and parents, was designed to improving awareness about transmission, prevention, and identification of CA-MRSA and HSV infections. The Eureka Athletic Department was informed on steps they can take to help insure the safety of their students.

**Summary of Results:** Guidelines and protocols designed by National Federation of High Schools were obtained and presented to the Athletic Department and plans to improve student health were made. Plans included making steps towards improving basic hygiene and sanitation. The coaches were educated on these infections and briefed on the NFHS guidelines. A plan to train all athletic personnel on basic wound care was discussed. Also, the basic guidelines on infections were distributed to all parents at preseason meetings and to students at annual, preseason sports physicals by local health providers.

**Conclusions:** Skin infections in the community are becoming a severe problem since the emergence of MRSA. These infections can infect healthy individuals and direct contact, such as between members of wrestling or football teams, increases transmission rate of these organisms. Herpes viruses are also spread easily between wrestlers and can spread to opposing teams, resulting in state wide epidemics. Improving early recognition, by coaches, parents, and students, will help improve outcomes and installing prevention strategies will help stop infections before they start.
334 COMMUNITY AND PATIENT EDUCATION ON PREVENTION OF METHICILLIN-RESISTANT STAPHYLOCCUS AUREUS SKIN INFECTIONS IN FAIRBANKS, ALASKA

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Purpose of Study: Methicillin-resistant S. aureus skin infections are a large problem within the surrounding communities of Fairbanks, Alaska; and if not treated can lead to systemic disease. Outbreaks of this infection in rural villages have occurred in the past. Prevention of these types of infection is easy when proper protocol is followed. In the rural villages, lack of water and supplies makes cleaning and washing difficult. Handouts were created to teach the community about five easy ways to prevent spread of skin infections, with or without supplies. Also on the handouts were four ways to prevent spread if you have an active infection. The main purposes of the handouts were to give the important points of prevention and open up the lines of communication between patients and physicians on the subject.

Methods Used: Discussions were held with the clinic physicians and physician assistants to identify the most active problem in the community. The spread of MRSA in the community lead to the need for more education on the subject. The most important aspects of MRSA prevention were identified through discussion with the wound care specialist. Handouts were given in the waiting lobby along with a voluntary anonymous feedback sheet for patients to report on the usefulness of the education material. Everyone received a handout for awareness, and more were left with patients who have a diagnosed case of MRSA. A question and answer session was held in the waiting lobby after patients and family members reviewed the material.

Summary of Results: Over fifty handouts were given, and eleven feedback sheets were received. Physicians and physician assistants reported questions continuing in the clinic after the handouts were given out, effectively opening patient physician communication about the subject.

Conclusions: The handouts were created to provide the community with some examples of what they can do to protect their families and themselves. The handouts also served to open the lines of communication between provider and patient. Many patients continued to ask questions after reading the material. They were interested in understanding more aspects of MRSA skin infections than those that were discussed in the handout. This was a positive outcome for the project.

335 PREVENTING FALLS OF ELDERLY FORT BENTON, MONTANA RESIDENTS: A MULTIDISCIPLINARY APPROACH

A.M. Jayne-Jensen University of Washington, Seattle, WA.

Purpose of Study: Fort Benton, Montana, like many rural communities in the United States, it is becoming more important to train bilingual physicians. Bilingual physicians have better relationships with their patients, and are actually linked to better health outcomes. To this end, an investigation was conducted on behalf of the UW SOM to evaluate whether there are sufficient community resources and interest to create a Spanish immersion program in Brewster, Washington.

Methods Used: A literature review was conducted to find models for Spanish immersion programs and to find evidence supporting the training of bilingual physicians. In addition, community leaders were interviewed and a community assessment performed to determine the resources Brewster offers. Finally, informal interviews were conducted with multiple community members to assess interest.

Summary of Results: Brewster is an ideal community for a Spanish immersion program. There is a strong Hispanic community: Family Health Centers Clinic reports 70-80% of their patients as Hispanic, about the same as the general population. Furthermore, there are several summer youth programs that would provide good opportunities for visiting student involvement. Students would have the opportunity to learn Spanish while being immersed in the local Hispanic migrant culture. Ideally, a student could work half days in the clinic at Family Health Centers and spend the rest of the time working in the community.

Conclusions: Creating a Spanish immersion program is obviously more challenging in Washington than Mexico. There are fewer opportunities to practice Spanish and the student will have to be self-motivated and seek out opportunities to practice their language skills. The program should run at least 6 weeks to allow the student to get to know the community and to maximize opportunities for language acquisition. Additional inquiries should be made to find host families for students and other opportunities in the community such as visits to migrant camps, tours of local fruit factories or any other volunteer opportunities for cultural and language immersion.

336 SPANISH IMMERSION PROGRAM IN BREWSTER, WASHINGTON: A COMMUNITY ASSESSMENT

E. Uno University of Washington School of Medicine, Seattle, WA.

Purpose of Study: Given the rapidly growing Hispanic population in the United States, it is becoming more important to train bilingual physicians. Bilingual physicians have better relationships with their patients, and are actually linked to better health outcomes. To this end, an investigation was conducted on behalf of the UW SOM to evaluate whether there are sufficient community resources and interest to create a Spanish immersion program in Brewster, Washington.

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337 HPV VACCINE EDUCATION IN MCCALL, IDAHO

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Purpose of Study: Human papillomavirus (HPV) is the most common sexually transmitted infection in the U.S., and is associated with the development of cervical cancer and genital warts. With a prevalence of 24% to 44%, sexually active young adults between the ages of 15-25 years are at a greater risk for HPV infection. In June 2006, the FDA approved Gardasil, a vaccine against 4 types of HPV, which causes 70% of cervical cancers and 90% of genital warts. The vaccine is recommended for girls before they become sexually active or between the ages 11-26 years old. Studies indicate that Gardasil is 100% effective at preventing cervical, vulvar, and vaginal precancers and warts.

McCall is a small town in Idaho. There are 2,567 year round residents, with roughly 20% of the population between 10-24 years old. This population is at greatest risk for HPV infection and could greatly benefit from the vaccine. McCall also serves as a health resource for many neighboring small towns, thus the number of young women that could benefit from the vaccine is much greater than estimated above.

Methods Used: A community assessment and discussions with local doctors were used to determine the most effective way to educate students about the HPV vaccine. Additionally, a literature review was done to determine current knowledge about HPV and the vaccine. A 20-minute
educational presentation was designed for high school students. Brochures by
the CDC about the vaccine were produced for students to give to their parents
or caregivers.

**Summary of Results:** Two sophomore health classes were educated about
HPV and the vaccine. Students were also provided with information about
where they can receive the vaccine and the cost of the vaccine. Common
misconceptions and questions that the students had were addressed after the
presentation. Overall, students were attentive and eager to answer and ask
questions. Each student was given an informational brochure for his or her
parents.

**Conclusions:** The presentations were a good start toward increasing
education about the HPV vaccine in McCall. Students who had not received
the vaccine were interested in receiving it. In the future it would be
advantageous to do the presentation with students in the junior high and high
school. Additionally, parent education about vaccinating their child is a
critical step toward HPV prevention.

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**MODIFYING AN EXISTING PUBLIC EDUCATION CAMPAIGN TO PROMOTE CARBON MONOXIDE SAFETY IN CARBON COUNTY, MT**

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**Purpose of Study:** Domestic carbon monoxide (CO) poisoning remains a
significant threat to homes in the US, and poisoning strikes those in rural
communities at a disproportionate rate. A resort near Red Lodge, MT, was the
site of a notable carbon monoxide poisoning accident several years ago;
although the notoriety of this incident, CO poisoning remains a recurrent
problem in the community. A campaign to educate the public about CO and
encourage safe appliance operation and use of CO detectors was put into
place.

**Methods Used:** Little literature exists on the efficacy of CO education
campaigns; smoke detector campaigns were researched as a model. Most
efforts for smoke detector campaigns include media-based education; the
local fire department uses a yearly campaign in the fall to promote smoke
detector alarm use and battery changes. Using this extant program of radio
and newspaper advertisements, an addendum of materials was produced to
courage citizens to keep their gas appliances maintained, change batteries
and purchase CO detectors. In addition, a local hardware store will
generously offer a discount on new detectors the week of the campaign
and the fire department’s free battery program will be expanded to include
those for CO detectors.

**Summary of Results:** A series of radio PSAs and a newspaper
advertisement for print in the county weekly were produced. These ads
were composed of educational information for the public concerning the
prevalence, danger, and prevention of domestic carbon monoxide poisoning.
Response from the public will be measured by the number of people
inquiring to the fire station for batteries and by tallying numbers of CO
detectors sold at the local hardware store.

**Conclusions:** Working with existing smoke detector safety campaigns and
the local fire department proved a convenient way to introduce public
education for CO safety. Measurement of the immediate effectiveness will be
only indirect, through measurement of sales of CO detectors and rates of
inquiry for free batteries, but long term impact of the campaign may be
judged against future rates of CO poisoning. Some existing smoke detector
literature suggests public campaigns increase rates of detector ownership but
do not necessarily save lives; it remains to be seen whether CO poisoning
remains a continuing problem in Red Lodge following this effort.

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**INCREASING VEGETABLE CONSUMPTION OF LOW INCOME FAMILIES THROUGH DISTRIBUTION OF AN EDUCATIONAL COOKBOOK IN CONJUNCTION WITH FREE PRODUCE IN THE METHOW VALLEY**

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University of Washington, Seattle, WA.

**Purpose of Study:** The Methow Valley is a rural community in North
Central Washington. Many of its residents are from low income households
with little access to fresh fruits and vegetables. The Red Shed Produce
program is a new service in the Methow Valley which provides organic
vegetables to low income individuals. The primary purpose of the project
described here is to increase the consumption of fresh vegetables among low
income individuals in the Methow Valley. Another objective is to expand
the recipients’ knowledge of fresh produce so that they feel more comfortable
with the handling and preparing of vegetables. This intervention also aims to
make the target individuals’ attitudes towards eating vegetables more
positive.

**Methods Used:** Two strategies were selected from a survey of the
community and a literature review. The first strategy was the development
of an educational cookbook with basic cooking techniques, recipes for each of
the vegetables distributed, cooking and storage tips, and information on the
health benefits of eating vegetables. The educational cookbooks were
distributed free of charge to mothers at Women, Infants, and Children (WIC)
apPOINTMENTS and the local food bank. The second strategy was the use of
tasting samples of recipes included in the cookbook at both locations.

**Summary of Results:** Fifty educational cookbooks were distributed along
with fresh vegetables and tasting samples were tried by approximately half of
the recipients.

**Conclusions:** From the literature review and the feedback from the
community, it appears that using either distribution of free produce or
education alone is not effective. A past intervention in the Methow Valley
handed out farmer’s market coupons to mothers in the WIC program, but
some of them refused the coupons stating that they didn’t eat vegetables.
Other studies describe interventions in which educational materials and
recipes were distributed, but the cost of the vegetables prevented an increase
in vegetable consumption (Birmingham, et al. 2004). In contrast, the
intervention described here used the distribution of free vegetables, plus
educational materials, and tasting samples. The combination of strategies was
well received by the community and the recipients appeared enthused about
eating the vegetables.

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**ZOONOTIC DISEASE EDUCATION IN THE REPUBLIC OF PALAU**

J. Totten  
University of Washington School of Medicine, Seattle, WA.

**Purpose of Study:** The Republic of Palau is a developing island country
in Micronesia. Large feral and domestic animal populations may have
contributed to recent zoonotic and vector-borne (VB) disease outbreaks of
leptospirosis and scrub typhus. However, neither pet owners nor people who
work with animals receive significant training on zoonoses or infection
control practices. The main goal of this project was to improve zoonotic and
VB disease prevention through a multi-faceted intervention.

**Methods Used:** Local needs in zoonoses prevention and control were
identified by meeting with concerned local parties. Local health professionals
and the veterinarian were then surveyed to identify diseases of local
importance and summaries were created and distributed for the 17 identified
diseases. Three separate presentations were created and given to the local
youth, Koror State Animal Shelter (KSAS) staff, and the Koror State
Sanitation workers on appropriate information concerning hygiene, infec-
tious disease, zoonoses, VB disease, and personal protective measures. An
infection control plan and accompanying quiz were developed for the KSAS
which included new reporting procedures to improve KSAS and hospital
communication. A practice session on proper PPM was also conducted at the
KSAS.

**Summary of Results:** Educational presentations were given to approxi-
mately 60 children, 7 KSAS staff, and 8 state sanitation workers through
8 different sessions. Summaries of 17 diseases were given to the KSAS and
distributed at the KSAS.

**Conclusions:** Zoonoses and VB diseases are neglected issues in Palau and
there is still progress to be made. However, this project appeared successful in
explaining their importance and encouraged at least temporary improvements
in prevention and awareness of zoonoses and VB illnesses.
341 STUDENT-DRIVEN DEVELOPMENT OF A GLOBAL HEALTH CURRICULUM FOR MEDICAL UNDERGRADUATE TRAINING


Purpose of Study: An increasing number of universities are adopting policies to reflect an emphasis on global citizenship and service. At the same time, prospective and current medical students are demanding the tools to understand and address today’s most pressing global issues, including global health. Medical schools across Canada have struggled to systematically integrate global health training into undergraduate medical curriculum. This study identifies the key components of an innovative, student-driven model for global health curriculum development in medical undergraduate training at the University of British Columbia (UBC).

Methods Used: We interviewed medical student and faculty representatives from the UBC Students’ Global Health Initiative (GHI) about the links between key GHI activities and global health curriculum development. We evaluated responses qualitatively for their strategic importance in student-driven development of global health curriculum.

Summary of Results: Interviews revealed that GHI offers a multifaceted, inter-professional program that uses basic global health training for medical students as a vehicle for student-driven curriculum development. GHI combines a monthly skills-based workshop series with three student-led international projects, each designed to generate components that promote the development and implementation of global health curriculum at UBC. Key activities from the last year of GHI programming include: A) Quantification of medical student demand for improved global health training; B) Development of curriculum components, including 5 problem-based learning cases, 4 video modules, and an image bank with more than 400 photos; C) Iterative development of consensus learning objectives, in line with national competency frameworks and in partnership with the U21 Global Initiative; D) Widespread advocacy and engagement of students, faculty and community, including monthly skills-based workshops, 22 submitted conference abstracts and additional presentations planned for 8 academic and community forums.

Conclusions: This study demonstrates how concerted student mobilization can be an effective instrument for curriculum development to improve global health training in Canadian medical schools.

342 A MODEL FOR INTERNATIONAL HEALTHCARE PROMOTION BASED ON STUDENT LEADERSHIP, SUSTAINABILITY, AND COLLABORATION


Purpose of Study: To introduce a sustainable healthcare promotion program to an underserved international community through student leadership

Methods Used: The health care promotion model is led by students and consists of several integral steps: 1) Prior to departure, educate student leaders on common health problems in the local community and initiate partnerships with leaders in other faculties’ thus expanding the scope of knowledge of the health care team; 2) on site, develop a strong rapport with the local community; 3) combine local community input and Canadian healthcare expertise in conducting a needs assessment of the target community; 4) devise timely and realistic solutions to prioritized needs; 5) collaborate with and actively engage local community members in implementing these solutions; and 6) periodically re-evaluate the community’s changing needs and modify the plan of action.

Summary of Results: This strategy has been successful for the University of British Columbia’s (UBC) Global Health Initiative (GHI) in Honduras, Uganda and India. This abstract focuses on the Split Valley India project. Using the model outlined above, UBC students established a connection with community leaders and conducted a needs assessment of the Munsel-Ling school; identified the major health problems affecting 377 students; sponsored the construction of a healthcare center, toilet blocks and a greenhouse; trained and salaried two healthcare workers; developed an annual health screening program and student health records; initiated treatment programs for anemia, worms, scabies and lice; developed hand-washing and tooth-brushing stations; and devised hygiene education modules to be integrated in the testable curriculum. These projects were initiated through collaboration between the local community and GHI’s student leaders and rely on community involvement for their implementation and sustainability.

Conclusions: This successful student-led model of healthcare assessment, provision, and education provides a framework that can be utilized by student leaders to accurately evaluate and fulfill the needs of other underserved international communities.

343 IMPROVING LIFESTYLE CHOICES IN PALAUAN DIABETICS AND HYPERTENSIVES

J.M. Adams University of Washington School of Medicine, Seattle, WA.

Purpose of Study: To improve diet/exercise choices among residents of Ngerdau and Peleliu states, Palau, through educational presentations. Both are outlying states and lack reliable access to Belau National Hospital (BNH) on the central island. The Palauan government reports diabetes and hypertension (HTN) comprise 46.5% of Palauan NCD. 62% of females and 58% of males are obese and at risk for both diseases. Previous studies (2, 3, 5, 6, 7, 8) indicate the potential for education to impact diabetes and hypertension in the Pacific.

Methods Used: Based on discussions with local leaders, a group presentation was held in Ngerdau and 1-on-1 presentations in a local clinic on Peleliu. The presentation covered physiology, risk factors and complications of diabetes and HTN. Guidelines for diet, exercise and diabetes management were handed out, with copies provided to the Ngerdau dietician for future use. Blood pressure and body mass index screening was provided. On Peleliu, individual sessions were held on diet and exercise, emphasizing options specific to the locale. All written materials were translated into Palaunau, and an interpreter was present for the oral presentations.

Summary of Results: On Ngerdau, 27 Palauans attended the presentation and underwent BP and BMI screening. Several at-risk individuals were identified and encouraged to follow up at BNH. All participants took copies of the handouts, and many expressed gratitude for the information and for the health screening. On Peleliu, 10 residents participated in educational sessions, and took home the printed materials. They expressed appreciation that the author was able to schedule sessions at their convenience. The combination of a formal presentation, printed handouts and BP/BMI screening was an effective educational strategy. Many residents said they came only for the screenings, but that the checks led them to stay to learn more. The use of a translator ensured understanding but slowed the presentation; predominantly visual portions were the most effective in reaching the audience. Many participants said the state Governor’s involvement was the deciding factor in their attendance.

Conclusions: The project successfully brought information about healthy lifestyle choices to many at-risk residents of Palau. Long-term lifestyle changes, however, will require ongoing efforts by local health leaders.

344 PROMOTING BIRTH SPACING IN ANTSIRABE, MADAGASCAR

J. Hurst University of Washington School of Medicine, Seattle, WA.

Purpose of Study: Birth intervals of less than two years are associated with poor maternal and infant health outcomes compared with longer birth intervals of 3 to 5 years. On average, women in Madagascar have 5.7 children spaced 31 months apart. At Hopitaly Loterona Andranomadio (HLA), a 130-bed hospital in Antsirabe, short birth intervals contribute to high maternal and
infant mortality rates. The purpose of this project was to promote birth intervals of 3 to 5 years at HLA and in the community.

**Methods Used:** Educational material was developed after working with the HLA family planning clinic director and maternity staff. On an institutional level, opportunities for birth spacing counselling were identified. On a community level, education was provided at a church conference for women.

**Summary of Results:** At HLA, birth spacing counselling was integrated into maternity care, including prenatal consultations, postpartum counselling, and vaccination clinics. Midwives provided counselling to 44 women and distributed 46 brochures promoting increased birth intervals. An additional 1475 brochures were left at HLA for distribution during future counselling. At the conference, 223 women attended presentations about the benefits of birth spacing and family planning and 845 received brochures.

**Conclusions:** This project was well-received and supported by the family planning director, midwives, and other hospital staff. Postpartum, pregnant, and community women displayed interest in learning about birth spacing and family planning methods. This combination of hospital support and community interest will hopefully lead to continued promotion of birth spacing, increased family planning use, and decreased mortality rates at HLA.

**345 MENTORSHIP WITH THE AFRICAN HEARTS COMMUNITY ORGANIZATION WITHIN A CANADIAN GLOBAL HEALTH INITIATIVE**


**Purpose of Study:** The African Hearts Community Organization (The Bakuli Boys Brigade) is a community-based organization for males 6-19. Founded in 2001 by street youth in Kampala, a brotherhood was formed to improve their lives. Currently with 64 members, the group empowers youth to be self-reliant, overcome stigmas and reach their potential. The organization strives to create a safe and stable environment for street youth and think of each other as family. A band was formed and performances assist with education. Canadian university students participating in Brighter Smiles Global Health Initiative were able to: attend performances, tutor academics, engage in sports, teach life skills, and provide mentorship to the boys. Impressed by the boys’ motivation and interest in pursuing careers and education, a mentoring program was initiated. The purpose was two-fold: 1) To provide mentorship and support the youth on overseas visits and by email contact throughout the year 2) To obtain funding for an annual educational grant from the university’s pediatrics residency program.

**Methods Used:** University students on overseas projects fostered a relationship and provided mentorship to the boys. Students offered support by: attending performances, tutoring, and providing mentorship. Video interviews and performances were recorded. Health issues were addressed in sessions facilitated by a doctor. Educational funding was pursued.

**Summary of Results:** Since 2006 over 20 university students on projects in Uganda have assisted the boys. Canadian students were impressed with their talents - playing music, singing and performing acrobatics. The boys received repeat visits from students to provide encouragement and mentoring. An education scholarship was set up on behalf of the UBC Pediatric Residency Program. The video produced contains heart-warming musical performances and compelling stories and will promote new funding.

**Conclusions:** The relationship developed between UBC students and The African Hearts Community Organization fostered a meaningful mentorship program. A quality promotional video was produced. Tutoring classes continue to expand. An annual scholarship fund initiated by the residency program supports these worthy young men in their career dreams and education.

**346 HOW DOES PARTICIPATING IN AN INTERNATIONAL TRIP AFFECT STUDENTS’ GLOBAL HEALTH KNOWLEDGE?**

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**Purpose of Study:** To determine the impact of participation in a student-driven international project on students’ levels of knowledge and awareness in several topic areas.

**Methods Used:** Post-experience written survey data were collected from all 30 UBC Students’ Global Health Initiative (GHI) trip participants. Self-reported prior- and post-trip knowledge were compared for five response variables: cross-cultural communication, project development, project sustainability, community collaboration/local empowerment, and overall global health knowledge. Additionally, student involvement in project dissemination and mentorship was assessed through quantitative survey responses and by comparing the number of applications for 2009 GHI projects with the number of applications received for the 2008 projects.

**Summary of Results:** Quantitative Results:

- On average, students reported a 51% increase in knowledge of cross-cultural communication, and a 117% increase in project development skills.
- Large increases in knowledge of project sustainability (117%) and community collaboration and local empowerment (104%) were also reported.

**Conclusions:** The GHI projects achieved their main objective, which is to increase student knowledge and skills in the field of global health. Additionally, levels of student commitment to knowledge transfer, mentorship, and project development remain high.

**347 REDUCING CERVICAL CANCER IN MADAGASCAR: AN EDUCATIONAL CAMPAIGN AND SCREENING PROGRAM USING VISUAL INSPECTION WITH ACETIC ACID**

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**Purpose of Study:** Cervical cancer is the leading cause of cancer-related mortality in women in Madagascar. Despite this, there was no screening offered at Andranomadio Lutheran Hospital (HLA) in Antsirabe, Madagascar. Therefore, a screening program and educational campaign about cervical cancer was set up in collaboration with HLA staff.

**Methods Used:** A documented screening method for low-resource settings is visual inspection of the cervix with 3-5% acetic acid (VIA). Training was provided to hospital staff with online manuals and by an American OB/GYN. A nurse informed women of the screening’s availability during their visit to HLA’s Family Planning Clinic. Testing was free of charge during the first two weeks and offered for a fee after that. A handout was also developed about the benefits of screening and distributed over two days to women at a church conference, along with short presentations given by a trained layperson.

**Summary of Results:** During the initial testing period, 43 women were screened using VIA. Of these, 37 women tested negative and were recommended for a second screening in 5 years. Six were positive and were treated at the same visit according to HLA protocol. An additional six tests were VIA negative, but were referred to a HLA physician due to findings outside the screener’s training. During the educational campaign, 598 handouts were distributed and 466 presentations were given to groups of 2-10 women. An additional 280 handouts were left at HLA for later distribution.

**Conclusions:** The project met the goals of increasing awareness of cervical cancer and starting a pilot screening program. HLA staff were trained to administer the test and interpret the results. After the departure of the author, HLA staff reported the testing continued. The educational campaign reached women with little exposure to health services, many later stating an interest in
obtaining the screening. Further work is needed to increase the treatment and diagnostic options available to VIA positive women, including cryotherapy and colposcopy.

**348**

**HEALTH PROMOTION IN RURAL HONDURAS: ENGAGING WOMEN IN ORDER TO IMPROVE THE HEALTH OF COMMUNITIES**


**Purpose of Study:** Honduras is one of the least developed countries in Latin America. Due to the mountainous geography and lack of infrastructure, the health needs of many rural communities are underserved. PRODIM, a Honduran NGO was founded in 1989 to improve access to basic health education and medications. During July 2008, UBC students partnered with PRODIM in two rural Honduran communities to achieve the following objectives: 1) Conduct a nutrition, sanitation and reproductive health survey; 2) Provide education about sanitation and reproductive health.

**Methods Used:** With the help of translators, students interviewed 90 women in their homes about their knowledge of nutrition; availability of nutritious foods; available water treatment and sanitation resources; incidence of diarrheal disease within their families; and knowledge and usage of family planning methods. Women responded quantitatively and qualitatively, and were paid 20 Lempiras (US $0.75) for their participation. Based on the women’s responses, education sessions on hand-washing, and reproductive health topics were given.

**Summary of Results:** Improved sanitation and diarrheal disease were not major concerns within families, and incidence of diarrheal illness was much lower than expected due to a treated water source. Some women were familiar with family planning methods, but many were not, or did not know how to access them. Many women had heard of HIV/AIDS yet were unfamiliar with how to prevent sexual transmission. The majority of women expressed a desire to learn more about reproductive health topics. Women identified health concerns within their communities that were not formally included in the survey such as respiratory illnesses, alcoholism, and family violence.

**Conclusions:** Interviewing women provided information about the health needs of communities. Men were often absent working in other regions, thus women were more familiar with community health needs. Additionally, women were more likely to be in contact with health providers as they generally sought treatment in neighbouring communities with health centres when a family member was ill. Women were eager to learn more about health topics. Engaging women in health education and promotion may provide a successful means of improving the health of the greater community in UBC’s partnership in Honduras.

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**SEXUAL HEALTH EDUCATION TO HIGH SCHOOL STUDENTS IN SOUTHERN INDIA**

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**Purpose of Study:** Recent estimates indicate 2.5 million people in India are infected with Human Immunodeficiency Virus (HIV). The nationwide incidence of adults living with the infection is 0.36%. Despite the substantial number of Indians living with the infection, knowledge regarding HIV and other sexually transmitted infections (STIs) is lacking. Additionally, for Indian females, menstrual health issues are not generally addressed.

Education about sex and sexually transmitted diseases is uncommon in southern India. It is problematic that, even though resources such as hospitals, physicians, medications, and condoms are readily available, the population of Namakkal in the southern state of Tamil Nadu lacks a thorough education about HIV risk and spread. The purpose of the project was to educate 10-12th grade students about the spread of STIs, how to take protective measures, and assist students in accessing health care.

**Methods Used:** Five government schools were selected in the district of Namakkal in the state of Tamil Nadu to take part in the educational program. Of the five schools, two were all-male, two all-female, and one mixed gender. Sessions were single sex and students in the 10th -12th grades participated (ages 14-18). Each session ran approximately 2 hours. In total, 15 sessions were conducted. Each session focused on HIV transmission, myths and stigma surrounding HIV, and sexually transmitted infections; for the all-female sessions, the topic of menstrual hygiene was addressed. The information was conveyed through pictures and words written in the local Tamil language.

**Summary of Results:** In total, 3,274 students attended the education sessions. Four students were later seen at the clinic for HIV testing and STI treatment.

**Conclusions:** This project was an effective tool to educate a susceptible population about sexual behaviors and risks. Previous studies in the same district show that knowledge about HIV increases and stigma decreases after an educational session. While the project could be improved by conducting sessions for a smaller group of students and spanning a school year, even a brief educational session does increase awareness in a previously neglected group. STIs are significant barriers to personal and community development, and protecting youth through education is crucial to improving health globally.

**350**

**RAISING BREAST CANCER AWARENESS IN RURAL PERU**

M. Johnston University of Washington, Seattle, WA.

**Purpose of Study:** Seventy-five percent of women with breast cancer in Peru are diagnosed at clinical stages II or III. Although self-breast exams have come under recent scrutiny, there is evidence that they can reduce cancer mortality in resource limited areas. The following project takes place in an orphanage near two small communities in central Peru to increase awareness regarding breast cancer and early detection, to provide clinical breast exams, and to teach self-breast exams, two presentations were performed, one with the employees of the orphanage and another with women from the communities.

**Methods Used:** The director of the orphanage was consulted regarding the breast cancer presentations. Fifteen employees and older children were gathered for the presentation. All received a breast exam and were taught how to do a self-breast exam. As for the presentation for the communities, 100 flyers were distributed and people were contacted door-to-door. Twelve women came to the presentation and were provided a clinical breast exam and taught self-breast exams. Although no suspicious lumps were found, information regarding where to seek health care was given to the women.

**Summary of Results:** In total, 27 women attended the presentations, received clinical breast exams and were taught self-breast exams. They expressed understanding of the importance of the exam and relayed that they would do the exam once a month.

**Conclusions:** The project was a small, short intervention in a resource-limited setting. The project was successful in raising awareness regarding breast cancer, early detection, teaching self-breast exams, and in providing clinical breast exams. Further projects may focus on gathering accurate data regarding breast cancer incidence and mortality.

**351**

**PROMOTING CULTURALLY RELEVANT AWARENESS ABOUT THE BENEFITS OF KANGAROO MOTHER CARE TO MOTHERS OF LOW BIRTH WEIGHT PRETERM NEONATES IN KUMASI, GHANA**

M.N. Owuoka University of Washington School of Medicine, Seattle, WA.

**Purpose of Study:** Kangaroo Mother Care (KMC) was inaugurated in Ghana at six Kumasi regional hospitals in March of 2007 with the aim of decongesting overcrowded wards, decreasing nosocomial infections, and providing a low cost alternative in light of limited resources and funds. Successful adaptation of KMC by mothers is crucial in terms of reaping the advantages of the method as well as decreasing preterm related mortality. A community project was devised to gather ideas for a Twi slogan as well as design suggestions for an educational campaign on KMC.

**Methods Used:** A focus group of mothers learning KMC in the neonatal unit was conducted in order to gather opinions on images they would be most receptive to. Twenty five Doctors, nurses, midwives, health profession students, and KMC mothers from four sites were interviewed in order to gather suggestions for a slogan in Twi that will convey the message of KMC. Final drafts for the poster were edited by the healthcare team responsible for providing training and implementing KMC at regional hospitals in Kumasi.

**Summary of Results:** A total of seven phrases were suggested and ultimately “Fa No Woba Tare Woba”[put your baby close to your chest] was selected to embody the concept of KMC. Eight posters were distributed to
three hospital sites that have the largest number of preterms undergoing KMC. Educational inserts were added to 35 child health record books that will be distributed to KMC mothers upon discharge from the hospital. 

Conclusions: The slogan and new posters were well received by mothers and staff. Original copies of the inserts were left with the head district KMC nurse in order to produce more copies as needed for the child health record books at all six regional hospitals.

A better understanding of these postpartum practices and toas will help medical providers better understand the psychosomatic disorders faced by some Cambodian American women. Clarifying toas will assist the provider with: taking a better history of the patient, treating the patient, and providing culturally sensitive care.

Methods Used: 1. A critical review of the literature of toas was done.

2. Transcripts from a previous study were reviewed. In this study, Cambodian women who were treated for cervical and uterus pain were interviewed about toas. Quotes from data will be extracted to illustrate the different types of toas.

Several groups will be interviewed to assess current postpartum practices, presenting syndromes in clinic, and the understanding of toas by physicians.

3. Cambodian medical interpreters at Harborview Medical Center, 8 to 10 physicians who care for Cambodian women, 6-8 Cambodian community leaders

4. Grounded theory will be used to find any common threads. Hypotheses emerge defining toas and clarify the meaning according to a younger generation. Information will then be contrasted with information we have concerning older Cambodian immigrants and their perception of toas to illustrate the evolution of cultural concepts over time and generations.

Summary of Results: Inquiry will continue until December of 2008. Preliminary results suggest that while younger Cambodian women have heard of these post-partum traditions, most of them do not follow them closely because they believe that medicine from Western doctors helps them to restore their nerves and vessels quickly. The few women who did follow traditions did so on the accord of their mother-in-law or an elder. Many of these traditions were adapted: rather than mother-roasting on a cot, many women used hot water bottles and electric blankets to keep themselves warm.

353 CAMBODIAN PERINATAL CULTURE BOUND SYNDROME (TOAS): INFORMATION FOR MEDICAL PROVIDERS ABOUT TOAS IN FEMALE CAMBODIAN IMMIGRANTS

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Purpose of Study: Cambodians call the postpartum period sor sai kchey alluding to a period of fragile health lasting from one to three months. A number of traditions during sor sai kchey are practiced in order to prevent “toas” which are manifested psychosomatic disorders. These practices are observed in this period to encourage the growth of new blood vessels and restore the heat lost during childbirth.

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354 AN EFFECTIVE MODEL FOR THE INTRODUCTION OF CLINICAL RESEARCH TO MEDICAL AND PARAMEDICAL STUDENTS IN A DEVELOPING COUNTRY


Purpose of Study: In 2005, MU invited UBC to introduce Brighter Smiles, a dental service/education/research program, to Uganda. Medical trainees deliver the preventive oral health program of fluoride varnish, education and daily in-school tooth brushing to rural and remote communities. The MU program has evolved into a Community Based Education and Service (COBES) program with medical trainees spending a month yearly in 18 under-served communities: Yr 1, work with local health care providers; Yr 2, conduct a needs assessment; Yr 3, design and evaluate feasibility of a research or intervention project; Yr 4, complete the study. Our goal was to instruct MU medical trainees in practical research to support the COBES program.

Methods Used: In collaboration with lecturers from MU’s Child Health and Development Centre, a 1-week course on medical research was delivered. Days 1-4 consisted of presentations on literature review, research design, ethics, questionnaire design, proposal writing, data collection, statistical analysis and interpretation, budget, and publication; team discussions; and independent proposal development. UBC students randomly joined one of the 18 MU teams. On Day 5, teams presented project proposals in oral and written format.

Summary of Results: 150 medical, dental, nursing, medical radiology and pharmacy students attended the classes. UBC students enthusiastically joined MU teams, building relationships with potential for long term collaboration. Each group developed a study design. Common topics were malaria, HIV, acute diarrhea, and waste disposal. Overnight review of several proposals during the development process, resulted in much stronger proposals than anticipated. MU faculty were provided with materials to deliver a 10-hour course “Getting Started in Medical Research”. After returning to Canada, review and feedback were given to several of the groups.

Conclusions: The major outcome of the interactive process was focused and feasible studies with concrete outcome measures. Both UBC and MU students had a better understanding of the proposal development process. UBC and MU teams gained a better understanding of medical issues in Uganda, and of obstacles to conducting research in rural Ugandan communities.
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PICTURE OF SELF-INFLICTED INJURY IN LA COUNTY

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Purpose of Study: Self-Inflicted Injury, including suicide, is a leading medical and social challenge in the US. Few studies have looked at the incidence of Self-Inflicted Injury among demographics. This study examines the incidence of self-inflicted injury in LA County based on the individual Service Planning Areas (SPAs). The study addresses whether the rates of self-inflicted injury vary among the SPAs, which are demographically diverse, in an effort to identify any clustering of injuries. The objectives of the study 1) To compare the incidence of SII in Los Angeles County across Service Planning Areas (SPAs); 2) Compare length of hospital stay among SII patients across SPAS; 3) Compare ER utilization as primary source of care as well as the length of hospital stay among SII patients SAPs. The study addresses whether the rates of self-inflicted injury vary among the SPAs, which are demographically diverse, in an effort to identify any clustering of injuries. The study also looks at the extent to which such patients utilize the Emergency Departments as their primary source of care and the length of hospital stay in such patients.

Methods Used: Retrospective analysis of Office of Statewide Health Planning and Development (OSHPD), a public database that contains a summary of all the hospital discharges in California.

Summary of Results: When analyzing the eight SPAs of LA County SPA 1 had a significantly higher incidence of self-inflicted injury, while SPA 6 had a significantly lower incidence than the average for LA County.

Conclusions: The results were surprising since SPA 6 has the lowest incidence of self-inflicted injury in LA County while it is one most underserved areas of the county. We are continuing to examine the various factors that may account for this finding.

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GEOGRAPHIC DISTRIBUTION AND SUPPLY OF FAMILY PHYSICIANS IN IDAHO

M. Flores, T.E. Norris
University of Washington, Seattle, WA.

Purpose of Study: Several national and state studies examining the U.S. physician workforce have predicted current and future shortages. Current trends indicate that primary care physicians in particular are predicted to experience serious shortages. The state of Idaho is not immune to these trends and reports suggest severe future physician shortages, especially for family physicians. Due to their broad scope of practice family physicians play an important role in helping meet the basic healthcare needs of the state especially in rural communities. There is a lack of current data characterizing physician supply or distribution in Idaho relative to the population. The purpose of this study is to provide specific data on the number and geographical distribution of family physicians practicing in the state of Idaho.

Methods Used: Family physicians or their office managers were questioned about their specialties, geographical location, and hours spent in direct patient care. Data was compared to national averages provided by the American Medical Association.

Summary of Results: Results showed an overall shortage of 54.45 full-time equivalent family physicians for the state. Family physicians were also found to be misallocated throughout the state with some counties having an oversupply while several counties are experiencing large shortages.

Conclusions: By better understanding these shortages and maldistributions at state and county levels, more effective strategies can be developed for meeting primary health care needs.

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FACTORS ASSOCIATED WITH PREGNANCY INTENTION IN LATINA MOTHERS

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1Charles Drew University of Medicine and Science, Los Angeles, CA and 2David Geffen School of Medicine at UCLA, Los Angeles, CA.

Purpose of Study: Among Latinas 25%-60% of pregnancies are unintended. Our goal was to determine which characteristics are associated with pregnancy intention in pregnant Latina women attending clinics in Los Angeles County.

Methods Used: A cross section analysis of data collected from a longitudinal study of adult pregnant Latinas attending 2 non-profit obstetrics clinics in Los Angeles, who were at least 12 weeks pregnant, and intended to live in Los Angeles for first year of their child’s life. The main outcome of intentionality of their current pregnancy was categorized as: intended, unwanted, and unplanned (became pregnant while using a contraceptive method). Predictor values were selected from the literature. A logistic regression model was created for each outcome to determine odds ratios for predictor values.

Summary of Results: Women classified as having an unplanned pregnancy had a higher adjusted odds of access to community services (2.49 [1.08-5.72]) and history of IPV (2.53 [1.05-6.10]). Those classified as having an intended pregnancy showed trends with lower odds of being born in the U.S. (0.37 [0.14-1.02]) and experiencing IPV (0.48 [0.22-1.07]) but these results were not significant. No predictor variables were significantly associated with unwanted pregnancy in the logistic regression model.

Conclusions: Latina women experiencing unplanned pregnancy access community services more, thus having greater opportunities to be asked about pregnancy intention and determine factors, such as IPV, that may prevent them from maintaining their reproductive choices, such as intentionality of pregnancy. More studies are needed to characterize unwanted and intended pregnancy in this population.

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WEB-BASED VISUALIZATION AND PROBLEM SOLVING AS INTERVENTIONS FOR MEDICAL STUDENT BURNOUT

N.E. Haddad
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Purpose of Study: Burnout is prevalent in medical students and has implications for health, professional development, attrition from school, and the quality of patient care they will provide later as physicians. Difficulties in intervening to reduce burnout relate to the intensive workload and limited free-time that medical school imposes. Thus, this study was developed as a web-based self-administered stress reduction intervention offered to 674 students in all four years of medical school. A web-based intervention offers flexibility, ease in access, confidentiality, and cost effectiveness. The purpose of this study is to assess whether relaxation training or cognitive behavioral therapy (CBT), administered via a website, can reduce burnout amongst medical students.

Methods Used: This study is a web-based randomized placebo control trial of 150 medical students, who will be randomized into one of three groups: 1) Relaxation intervention 2) CBT intervention 3) Control. The relaxation group will utilize two visualization mp3s and the CBT Group a CBT worksheet. Both intervention groups will be asked to utilize their intervention for 10 minutes, 3x per week for 3 months. A qualifying score on the Maslach Burnout Inventory (MBI) will determine eligibility for the study. Secondary outcomes will be assessed using a locus of control (LOC) scale and distress thermometer. The data in all groups will undergo an intent-to-treat analysis and be analyzed using repeat measures of ANOVA.

Summary of Results: The hypothesis is that students in both intervention groups will experience at least a 30% reduction in scores on the MBI at three months as compared to control, with dose-response effect. The CBT intervention will be more effective than the relaxation intervention. Secondary hypotheses are 1) That students who have an internal LOC will utilize these interventions more frequently and show greater stress reduction than students who have an external LOC and 2) The distress thermometer may be an easier way to assess stress/burnout and will have a significant correlation with scores on the MBI.
Conclusions: A web-based stress reduction intervention is more effective than placebo, practical and cost-effective to administer, and helpful in reducing medical student burnout. Levels of control may predict which students will benefit most from this type of intervention.

359 CASE FINDING BASED ON FAMILY HISTORY AND SCREENING OF HIGH-RISK FIRST DEGREE RELATIVES FOR OBSTRUCTIVE SLEEP APNEA: A PILOT STUDY
R. Shirvastava, S.M. Tuson, G. Singh, M. Saadat San Joaquin General Hospital, French Camp, CA.

Purpose of Study: Family history is routinely obtained in the evaluation of sleep disorders. In general, the purpose of this information is to assess the pre-test probability of the sleep disorders in the patient being evaluated. However, this information can be effectively used for new case finding and timely intervention.

Methods Used: An estimated 80% of obstructive sleep apnea (OSA) continues to be undiagnosed in the United States. Untreated OSA has been shown to be associated with an increased risk of motor vehicle crashes, hypertension, cardiovascular disease and heart failure. Risk factors for OSA such as obesity and craniofacial abnormalities can be inherited and predispose a person to OSA. Clinical screening of family members may facilitate the early recognition of OSAH. In a pilot study we reviewed the medical records of seventy (n = 70) patients. The family history section of the history and physical examination report was specifically reviewed. History of snoring, daytime sleepiness or insomnia was noted to be documented in 29 patients. A follow up phone call was made to the patients regarding the whereabouts of the family member with symptoms. A total of 36 family members were located after consideration of the dead and unable to contact people. Berlin Questionnaire (BQ), a validated survey instrument was then completed for the available family members (n = 17) by telephone interview. A copy of the BQ was mailed to the ones who could not be contacted by telephone (n = 19). Only 5 people returned the BQ. Based on the aggregate data 8 people were found to be at risk for OSA.

Summary of Results: Forty one percent patients reported at least one or more symptomatic family member. Many family members could not be contacted mainly due to social reasons or lack of contact information. A total of 22 people participated in the survey. Thirty six percent of the people (8/22) were at risk for sleep disordered breathing based on the results of Berlin Questionnaire. They were advised to seek further evaluation.

Conclusions: Our small pilot study underscores the importance of following up the information obtained through the family history. It is likely to result in early case finding and intervention.

360 UPREGULATION AND DIFFERENTIATION OF hMSCs WITH EPINEPHRINE TO ENHANCE WOUND REPAIR
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Purpose of Study: Skin repair is the physiological process of regenerating dermal and epidermal tissues that have undergone injury. The repair process is complex, and susceptible to interruption leading to chronic non-healing wounds. Recent research has shown that hematopoietic stem cell (HSCs), found in the human bone marrow, express adrenergic receptors. Activation of these adrenergic receptors with catecholamines leads to increased HSC mobilization, proliferation and migration, as well as enhanced wound healing in NOD-SCID mice. We hypothesized that treating another type of bone marrow cell; the human mesenchymal stem cells (hMSCs), with catecholamines would likewise, lead to increased hMSCs mobilization, differentiation into keratinocytes, and increased cell migration, which could all lead to improved wound healing. We also hypothesized that treatment of hMSCs with epinephrine may lead to differentiation of hMSCs into keratinocytes.

Methods Used: hMSCs were isolated from adult human bone marrow and cultured in vitro. hMSCs at passage 3-5 were divided into 4 groups and treated with either 1 nM, 10 nM, 1 μM epinephrine (epi), and no epi. mRNA and protein were isolated after 48 hrs of treatment, and expression levels of different adrenergic receptors was determined by real time RT-PCR and Western blotting. For the differentiation assays, cells were also divided into the same 4 groups and treated for 3 wks. Differentiation was determined by staining and microscopy observation.

Summary of Results: hMSCs were shown to express adrenergic receptors. Furthermore, there is an increase in expression of adrenergic receptors ν2α, ν2β, a1B, in the epinephrine treated hMSCs, revealed by both real time RT-PCR and western blotting (P < 0.05, n = 12). These results show that hMSCs have the ability to respond to epinephrine. Stress (acute and chronic epidermal/dermal injury) is associated with high levels of circulating and local epinephrine and other catecholamines. We speculate that interaction of endogenous epinephrine and locally injected hMSCs into the wound area could potentially lead to increased engraftment and enhanced wound repair.

Conclusions: Conclusions: hMSCs express adrenergic receptors and epinephrine modulates the expression of these receptors in hMSCs. Assessment of differentiation and migration of epinephrine treated hMSCs are ongoing.

361 DEVELOPMENT OF PROTOCOLS AND STUDY DESIGN FOR AN INTENSIVE LIFESTYLE INTERVENTION PROVIDED TO HIGH RISK PREGNANT AMERICAN INDIAN WOMEN
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Purpose of Study: According to the American Diabetes Association (ADA), Gestational Diabetes (GDM) is defined as diabetes or glucose intolerance during pregnancy. GDM affects 4% of all pregnancies in the USA making it the second leading complication of pregnant mothers. Currently, GDM is on the rise within the American Indian community because of increased obesity in youth and young adulthood. If not treated, GDM can lead to numerous negative outcomes that affect both the mother and fetus including: increased risk for cesarean delivery, spontaneous abortion, infant macrosomia (>4500 grams), neonatal hypoglycemia, infant shoulder dislocation during delivery, and an increased risk in the offspring for developing obesity and DM2 later in life. Recent research has demonstrated that early detection, physical activity, and controlled energy intake may help prevent these negative outcomes. The purpose of this study was to collaborate with NIH/NIDDK staff to develop a research protocol for an interventional study to test the hypothesis that an intensive lifestyle intervention, provided to high risk pregnant American Indian women, can moderate elevations in plasma glucose associated with gestational diabetes and can encourage appropriate fetal and infant growth.

Methods Used: A comprehensive literature review was conducted to learn more about GDM, risk factors, outcomes, treatment, and current research focus. Participation as a team member of the protocol development group began upon completion of NIH protocol development training.

Summary of Results: Project protocol was completed August 1st 2008.

Conclusions: Project protocol was submitted for NIH review and pending approval the study will be implemented at the Phoenix Indian Medical Center.

362 THE DESIGN AND INTEGRATION OF A NOVEL ONLINE PROBLEM-BASED LEARNING RESOURCE TO ENHANCE UNDERGRADUATE MEDICAL EDUCATION
S. Moosaviasl1, M. Butterfield1, K. Chu1, K. Clarke1, T. Fraser1, K. Koh1, W. Wong2, J. Masterson1,2, L. Goldenberg1,2, C. Paterson1,2 1University of British Columbia, Vancouver, BC, Canada and 2BC Children’s Hospital, Vancouver, BC, Canada.

Purpose of Study: To bridge the gap between pre-clinical knowledge and the diagnostic approach to common genitourinary conditions, the University of British Columbia (UBC) Department of Urologic Sciences created an online library of Problem-Based Learning (PBL) modules. The cases were published on Diagnosis X server as a collaborative project between UBC, the Molson Medical Informatics Institute and McGill University. Diagnosis X was launched to provide learners from all UBC distributed medical sites with a variety of easily accessible cases.

Methods Used: Cases were written by medical students and reviewed by urology residents and faculty members. Using the comprehensive template of Diagnosis X, the students authored cases that simulate the patient encounter in real life. Cases were developed in a pedagogical manner to provide a systematic review of clinical presentations, patient assessment and treatment
363 ROLE OF ALCOHOL MISUSE ON DEPRESSION SYMPTOMS, OUTCOMES AMONG MALE, FEMALE ED PATIENTS

L. Downing1,2, S. Bazargan-Hejazi1,2 1Charles Drew University of Medicine & Science, Los Angeles, CA and 2David Geffen School of Medicine, UCLA, Los Angeles, CA.

Purpose of Study: To examine the association between alcohol misuse and depression as it varies among male and female patients.


Summary of Results: In this study, 41% of men and 35% of women reported greater depression, and 34.1% of men and 9.2% of women reported alcohol misuse. Alcohol misuse, stress, and education level were all correlated with greater depression in men whereas age was most significant for women. In men, stress was associated with a 3.5-fold increase in the odds of reporting greater depression (OR = 2.84, 95% CI = 1.56-5.15, P ≤ 0.01). Men that misuse alcohol were 2.5 times more likely to report greater depression (OR = 2.47, 95% CI = 1.37-4.45, P ≤ 0.05). Men that did not complete high school were almost twice as likely to report greater depression (OR = 1.80, 95% CI = 1.05-3.07, P ≤ 0.05). In women, a 10-year increase in age was associated with a 36% increase in the odds of depression (OR = 1.55, 95% CI = 1.12-2.13, P ≤ 0.05).

Conclusions: The findings of this study have implications for mental health and potentially for other health outcomes including the detection, identification, and treatment needs associated with alcohol misuse.

364 EFFECTS OF HAVING A CHILD WITH A SEVERE MENTAL ILLNESS ON MOTHERS

E.R. Frost UCHSC, Aurora, CO.

Purpose of Study: This study is a qualitative inquiry into the effects of having a child with a severe mental illness on mothers. Based on casual observation, these mothers seem to have a great deal of challenges in their lives as a result of their child’s illness. Because there is a relative paucity of information in the literature on the subject, this study will cast a wide net to assess qualitatively how their child’s illness affects their day to day lives.

Methods Used: Using a database of children currently under treatment for schizophrenia, mothers of patients will be contacted and invited to participate in the study. Should they be inclined to participate, they will be provided with a physical copy of informed consent which they will return and schedule a follow up time to conduct a phone survey. The survey will contain between forty five and fifty questions, including demographic information, evaluating the effects of their child’s illness on their day to day life. The main topics to be evaluated are social, financial, and violence in the home. Within the umbrella of social effects are included questions about their social resources outside the home as well as their current significant other (if applicable) in addition to any other family members living at home.

Summary of Results: The data will obtained should hopefully shed light on the challenges that these women face raising a child with a severe mental illness.

Conclusions: Once there is a better understanding of how these families are affected, hopefully an efficient treatment plan for the whole family can be developed. This treatment may range anywhere from social support networks, to additional funding for financial setbacks, to marriage counseling, to psychotherapy and diagnosis for the mothers themselves. The whole point of this study is to find where to focus our efforts.

Cardiovascular III
Concurrent Session
8:30 AM
Saturday, January 31, 2009

365 PREMATURE AORTIC ATHEROSCLEROSIS IS MORE COMMON THAN CAROTID ATHEROSCLEROSIS IN SYSTEMIC LUPUS ERYTHEMATOSUS

J. Jost, J. Sharrar, C. Roldan University of New Mexico HSC, Albuquerque, NM.

Purpose of Study: To determine that aortic atherosclerosis occurs earlier and more commonly than carotid atherosclerosis in patients with systemic lupus erythematosus (SLE). This finding may help clarify mechanisms of peripheral versus cerebrovascular ischemia in SLE patients.

Methods Used: 35 patients with SLE (32 women, 40 ± 12 years) and 15 healthy volunteers (13 women, 37 ± 12 years) underwent multiplane transesophageal echocardiography to measure intima media thickness (IMT) and plaques of the aortic arch and proximal, mid, and distal descending thoracic aorta. Aortic IMT was measured by M-mode in the short and long axis of each portion of the aorta. All subjects underwent carotid ultrasonography to determine carotid IMT and plaques of the common carotid arteries by standard M-mode method. Abnormal aortic or carotid IMT was defined as >1 mm and plaque as IMT ≥1 mm and >50% thickness of the surrounding wall. Studies were interpreted by experts unaware of subjects’ clinical data.

Summary of Results: 1) The overall mean and maximum aortic IMT was worse in patients than in controls (P < 0.03); 2) the carotid IMT was similar in patients and controls (P > 0.35) (Table 1); 3) in patients with SLE, aortic IMT was worse relative to carotid IMT (P < 0.001) (Table 2). Also, the prevalence of abnormal aortic IMT or plaques was higher in patients (31%) than in controls (7%) (P = 0.04), but carotid atherosclerosis was similar in patients and controls (6% and 7%, respectively).

Conclusions: Premature atherosclerosis affects the aorta earlier and more often than the carotid arteries in patients with SLE. These findings explain why atherosclerosis in patients with SLE is an important cause of visceral and peripheral ischemia, but not of cerebrovascular ischemia that is more commonly associated with thromboembolic disease.

TABLE 1. Aortic and Carotid IMT in Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic mean</td>
<td>0.84 ± 0.22</td>
<td>0.70 ± 0.17</td>
<td>0.02</td>
</tr>
<tr>
<td>Aortic max</td>
<td>0.96 ± 0.29</td>
<td>0.79 ± 0.22</td>
<td>0.03</td>
</tr>
<tr>
<td>Carotid max</td>
<td>0.52 ± 0.08</td>
<td>0.50 ± 0.10</td>
<td>0.53</td>
</tr>
<tr>
<td>Carotid max</td>
<td>0.61 ± 0.11</td>
<td>0.56 ± 0.14</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Aortic versus Carotid IMT in Patients and Controls

TABLE 2. Aortic versus Carotid IMT in Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD (mm)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic IMT - Carotid IMT (mean)</td>
<td>0.32 ± 0.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic IMT - Carotid IMT (max)</td>
<td>0.35 ± 0.30</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

366 A NOVEL DESIGN FOR INJECTABLE REGENERATIVE MYOCARDIUM

M. Desmond1,2, M. Lee2, C. Pan2, B. Wu3,4 1UCLA, Los Angeles, CA; 2UCLA, Los Angeles, CA and 3UCLA, Los Angeles, CA.

Aortic and Carotid IMT in Patients and Controls
objective of Study: So-called engineered heart tissue was fabricated several years ago to have functional characteristics strikingly similar to native myocardium, including rhythmic contractions. A desired high cell density must be balanced with the concomitant death of the tissue construct’s interior cells due to nutrient transport limitations. In this study, we propose a scaffold design that optimizes mass transfer and the ability to be injected into diseased tissue. Cylindrical scaffolds of relatively small diameter carrying cells with regenerative potential can be placed in a carrier solution and injected into diseased tissue.

Methods Used: As oxygen is likely the most transport-limited myocardial nutrient, oxygen diffusion in an alginate/cardiomyocyte system was modeled using finite element analysis. Cylindrical constructs 300 μm and 900 μm in diameter were characterized mathematically. Fiber length was assumed to be very long relative to fiber diameter; therefore, end-effects were ignored. Neonatal rat ventricular myocytes (NRVMs) were used. Immunohistochemical investigation of the cells was undertaken using the cardiac marker MF-20. The cells were embedded in a 1% alginate solution (107 cell/mL). This cell/alginate solution was injected via 25-gauge needles into swirling 0.1M CaCl2 to form cylindrical hydrogels. Calcein AM/Ethidium homodimer (Live/Dead) assay was used to determine viability at various time points and locations.

Summary of Results: Modeling demonstrated more optimal oxygen concentration in the interior of the narrower construct. The diameter of the fabricated cylinders was usually 250-300 μm and showed excellent architecture. Cells stained positively for MF-20. NRVM-embedded alginate constructs were cultured for up to one week and a large number of living cells was observed.

Conclusions: Nutrient transport is sufficient for one week for NRVMs in alginate cylinders 250-300 μm in diameter. These fibers may be suspended in an optimized carrier solution and loaded into a syringe with a relatively small-gauge needle. Cardiovascular progenitor stem cells with proliferative potential carried in this way are a potential injectable method of regenerating myocardium.

367 IMPROVED SURVIVAL WITH VENTRICULAR ASSIST DEVICE VERSUS PREDICTED SURVIVAL WITH MEDICAL MANAGEMENT USING THE SEATTLE HEART FAILURE MODEL

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Purpose of Study: 2005 ACC/AHA guidelines suggest consideration of implantation of a left ventricular assist device (LVAD) as destination therapy in congestive heart failure patients with >50% predicted one year mortality with medical management alone. We sought to test the Seattle Heart Failure Model (SHFM) as a patient selection tool by comparing predicted medical to actual LVAD survival in patients receiving LVADs at the University of Washington Medical Center.

Methods Used: All patients receiving an LVAD between 1997 and 2007 were prospectively recorded. Labs and clinical data were extracted from medical records and used to calculate predicted survival using the SHFM. This was then compared to actual survival with censoring alive for transplant.

Summary of Results: 88 patients met inclusion criteria of a 30 day history of refractory congestive heart failure prior to LVAD placement. Ejection fraction was 17.6 ± 8% (±SD). 80% of patients were dependent on a balloon pump, and 88% required either dobutamine or milrinone for hemodynamic stability. SHFM predicted one month, six month and 1 year survival with medical management to be 54 ± 34%, 20 ± 26%, and 10 ± 19%. Only 7% of patients had a predicted 1 year survival of >50% with medical management. Actual LVAD survival was 85% at 6 months. The estimated hazard ratio for LVAD therapy was 0.09 (P < 0.01) at 6 months. A sub-group analysis of patients with LVADs capable of being managed as outpatients revealed that patients with a SHFM predicted 1-year survival of >5% (n = 20) had much greater probability of being discharged within 60 days of procedure than those with predicted survival < 5% (n = 33) (85% vs. 42%, P < 0.01).

Conclusions: Patients receiving LVADs at the UWMC are a critically ill population whose risk as calculated by the SHFM is significantly above levels predicted by medical management. Unfavorable risk factors for survival include advanced age, high LVAD use, low LVAD ejection fraction, and diastolic dysfunction.

368 ACUTE MYOCARDIAL INFARCTION WITH SUBSEQUENT STENT THROMBOSIS AND CORONARY, VENTRICULAR, AND FEMORAL PSEUDOANEURYSMS IN BEHÇET’S DISEASE

A. Harrison, M. Kern UC Irvine Medical Center, Orange, CA.

Case Report: A 40-year-old healthy Hispanic male without risk factors for coronary artery disease presented with an inferior ST-segment myocardial infarction and underwent emergent percutaneous coronary intervention with a drug eluting stent to his mid right coronary artery (RCA). He returned with a painful right femoral artery pseudoaneurysm (PSA) at the site of the collagen plug vascular closure device used during his cardiac catheterization which required surgical intervention. Later, he was incidentally found to have an inferior wall myocardial PSA by echocardiography. Repeat cardiac cath prior to surgical repair of the myocardial PSA demonstrated a large RCA aneurysm and stent thrombosis. Surgical repair of his ventricular PSA and ligation of the RCA aneurysm was successful. Histopathology of the RCA aneurysm suggested Behcet’s disease. He is doing well on therapy for Behcet’s disease with methotrexate and infliximab over one year later.

Behcet’s disease is a multisystem vasculitis affecting all sizes of arteries and veins. There are no pathognomonic laboratory tests in Behcet’s disease; the diagnosis is made on the basis of the clinical findings. The pathologic findings include arteritis and inflammatory obliterative endarteritis of the vasa vasorum with destruction of the media and fibrosis that predisposes the arterial wall to aneurysm formation.

369 PREDICTING CARDIAC PHENOTYPE BY EXAMINING GENOMIC VARIATIONS IN DIGEORGE SYNDROME

D.N. Schidlow1, S. McGhee2 1 UCLA, Los Angeles, CA and 2 UCLA, Los Angeles, CA.

Purpose of Study: 22q deletion syndrome (22qDS or DiGeorge Syndrome) is a phenotypically heterogeneous genetic syndrome usually attributed to microdeletions of chromosome 22q11.2. Affected individuals have lesions of varying severity in the immune, endocrine, and cardiac systems. Variations in cardiac disease are particularly broad, with some individuals having severe congenital heart defects while others are unaffected. We believe this is due to small genotypic variations among affected individuals. The purpose of this pilot study was to determine if there are consistent genotypic modifiers of the cardiac phenotype and to determine the sample size needed for a genome-wide association study (GWAS) of cardiac disease in 22qDS.

Methods Used: We collected DNA of 10 patients with 22q11.2 deletions previously detected by fluorescence in situ hybridization. By echocardiography, 8 of the 10 patients had cardiac disease (Tetralogy of Fallot or Interrupted Aortic Arch), and 2 had no cardiac disease. We performed microarrays on the collected DNA with Affymetrix 250K NspI SNP mapping arrays looking for single-nucleotide polymorphism (SNP) markers that correlated with the presence of cardiac disease. We analyzed the SNPs’ basic allelic frequencies using Fisher’s exact test to arrive at the most likely candidate genes for the cardiac-affected phenotype.
Summary of Results: We identified several different SNPs and their concordant genes, which may contribute to cardiac phenotype. Notable examples include DNAHS, implicated in ciliary dyskinesia syndromes, and PMP22, which is highly expressed in heart tissue. These SNPs are not located on chromosome 22 and possibly act as gene modifiers, suggesting polygenic influence on phenotype. We were able to determine that for GWAS, approximately 50 to 75 patients would be needed to achieve significance after accounting for multiple comparisons.

Conclusions: A sample size of 50 to 75 patients would be sufficient to demonstrate associations with genes that modify cardiac phenotype in 22qDS. This sample size is considerably less than is generally thought necessary for GWAS and reflects the strong genetic component modifying the disease. Findings from GWAS could have implications not only for 22qDS but for idiopathic congenital heart disease as well.

370 CIRCADIAN HEART RATE RHYTHM IN ASIAN INFANTS

T. Hoppenbrouwers1, F.M. Oliveira2, S. Sandarupa3, M.C. Khoo4, M. Neuman5, J.E. Hodgman1,2, USC, Keck School of Medicine, Los Angeles, CA; 2USC, Los Angeles, CA; 3Hasanuddin University, Makassar, Indonesia and 4Michigan Technological Univ, Houghton, MI.

Purpose of Study: In three months-old Caucasian infants the overnight circadian heart rate rhythm (CHR) is well established. Does the CHR develop later in Asian babies who are at a significantly decreased risk for Sudden Infant Death Syndrome (SIDS)?

Methods Used: Heart rates (HR) of 16 Caucasian babies (median age 7 weeks) and 18 Asian babies (median age 6 weeks) were monitored either in the laboratory or at home; monitoring was repeated twice for 16 and 14 Asian babies (median age 14 wks and 23 wks, respectively). HR during active wakefulness were deleted. Episodes of Quiet sleep (QS) with low interquartile ranges were visually identified and verified. Median HR values based on 3-5 minutes of QS were calculated. A computer algorithm aided in the recognition of a nightly HR minimum if present, verified by visual inspection.

Summary of Results: The characteristic decrease in overnight heart rates, well-established in Caucasian infants at 3 months of age in all sleep states, was only present in a third of Asian infants at that age (Table). Fewer Asian infants exhibited CHR than Caucasian infants of comparable age but this difference was not significant. Overall, the percentage CHR in the Asian infants at every age was less than that of the Caucasian infants at the median age of 7 weeks.

Conclusions: The emergence of the CHR appears delayed in Asian infants. Previously, the same was found in the temperature rhythm. Early appearance of HR and, in particular, cortisol minima, during the age of highest risk for SIDS, could place infants at risk. We speculate that this delay in Asian babies protects them from SIDS. It could be due to genetic factors, but is more likely influenced by prolonged breast feeding or indirectly by bed-sharing that fosters breast feeding.

371 EPISODES OF CYANOSIS/DESATURATION IN NEONATES DURING THE TRANSITIONAL PERIOD ARE ASSOCIATED WITH TRANSIENT RIGHT-TO-LEFT SHUNTING ACROSS THE PATENT FORAMEN OVALE

S. Bhombla1, M. Ebrahimi2, A. Payan2, B. Tam1, P. Wong3, L. Serril1, S. Bhombla1, M. Ebrahimi2, A. Payan2, B. Tam1, P. Wong3, L. Serril1, Children's Hospital LA and Women's and Children's Hospital, LAC+USC Medical Center, Los Angeles, CA and 2Children's Hospital LA and Women's and Children's Hospital, LAC+USC Medical Center, Los Angeles, CA.

Purpose of Study: A number of otherwise well-appearing term and late preterm neonates present with intermittent cyanosis/desaturation episodes (C/DE) occurring mostly with agitation or feeding in the first few postnatal days. These patients often undergo a thorough workup to identify the cause of cyanosis/desaturation. While in the vast majority of cases the episodes resolve without treatment and an identified etiology, the workup and the frequently associated antibiotic administration carry the risk of side effects and the subsequent delayed discharge increases health care costs and parental anxiety. We hypothesized that these infants have a delay in the decrease in pulmonary vascular resistance (PVR) and pulmonary vascular reactivity resulting in periodic right-to-left shunting (R-LS) across the patent foramen ovale (PFO). Therefore, we sought to obtain information about the incidence of R-LS across the PFO in neonates that had echocardiograms performed due to the C/DE.

Methods Used: Retrospective analysis of echocardiographic data obtained over the past 8 years in infants >34 weeks gestation that underwent echocardiography studies as part of the workup for C/DE. Findings of PFO and shunting across the PFO were assessed. Patients with congenital anomalies including heart defects were excluded.

Summary of Results: Echocardiography findings of 32 patients with C/DE and without congenital anomalies were identified. Twenty-eight patients (87.5%) had a PFO during the time of echocardiography and 19 of these patients (59%) had bidirectional flow documented even without agitation and apparent C/DE during the study.

Conclusions: These preliminary findings suggest that among infants who appear clinically well but have a history of intermittent C/DE, a significant proportion have a PFO with R-LS during the echocardiography. We speculate that a delay in the decrease in PVR and pulmonary vascular reactivity predisposes these patients to sudden increases in PVR resulting in intermittent cyanotic episodes during the immediate postnatal period.

372 RAPID PROVISION OF ADVANCED LIFE SUPPORT IMPROVES SURVIVAL FROM VENTRICULAR FIBRILLATION CARDIAC ARREST IN A TIERED-RESPONSE EMERGENCY MEDICAL SERVICES SYSTEM

D.T. Markel1,2, L.S. Gold3, C.E. Fahrenbruch3, M.S. Eisenberg1,2, 1University of Washington School of Medicine, Seattle, WA; 2King County Emergency Medical Services, Seattle, WA; 3University of Washington, Seattle, WA.

Purpose of Study: To determine whether the interval between the arrival of basic life support (BLS) providers and advanced life support (ALS) providers is associated with patient outcome after cardiac arrest.

Methods Used: We conducted a retrospective cohort study of all witnessed, out-of-hospital ventricular fibrillation (VF) cardiac arrests that occurred between January 1, 1991, and December 31, 2007. Eligible patients (n = 17, 781) received full resuscitation efforts from both BLS and ALS providers.

Summary of Results: The BLS-to-ALS arrival interval was a significant predictor of survival to hospital discharge (Table 1, OR 0.96, 95% CI 0.93-0.98). Other significant predictors of survival were whether a bystander administered cardiopulmonary resuscitation (CPR) (OR 1.33, 95% CI 1.07-1.67), and the interval between the 911 call and BLS arrival (OR 0.78, 95% CI 0.73-0.83).

Conclusions: We found that a shorter BLS-to-ALS arrival interval increased the likelihood of survival to hospital discharge from witnessed, out-of-hospital VF cardiac arrest. We conclude that ALS interventions provide additional benefits over BLS interventions alone when utilized in a well-established, two-tiered emergency medical services (EMS) system already optimized for rapid defibrillation. The highest priorities in any EMS system should still be early CPR and early defibrillation, but timely ALS services can supplement these crucial interventions.

373 PROXIMAL ANASTOMOTIC DEVICE PATENCY IN OFF-PUMP CORONARY BYPASS GRAFTING SURGERY

Purpose of Study: In recent years, the proximal anastomotic device (PAD) has been recommended for facilitating the connection of the Saphenous Vein Graft (SVG) to arteries in coronary bypass grafting surgeries (CABG). This study was designed to determine if use of the PAD decreases the graft patency rate of patients with off-pump coronary bypass grafting surgery (OPCAB).

Methods Used: The authors reviewed all patients undergoing OPCAB from the period of 2001 through 2004 in a single health maintenance organization hospital. Angiographic data were obtained on all patients who had cardiac related events within one year after their surgery. SVG closure rate is defined as more than 70% stenosis anywhere along the length of each vessel. SVG closure rate comparisons were made between surgeries done off-pump with the proximal anastomotic device (OPCAB-D) and off-pump without the proximal anastomotic device (OPCAB-O).

Summary of Results: A total of 242 patients had OPCAB during this period. 30 patients had angiographic follow up within one year of the surgery. A total 287 SVGs were performed with anastomotic device (OPCAB-D), of which 27 had clinical evidence of closure within a year. 158 SVGs were performed without the anastomotic device (OPCAB-O), of which 14 closed within a year (P = 0.89, Table). Of those patients who had demonstrated angiographic SVG closure, 13 presented to the hospital with acute coronary syndrome. All 13 patients required revascularization procedures; two were bypass surgery and eleven were catheter-based interventions.

Conclusions: Our findings suggest that off-pump coronary artery bypass surgeries done with a proximal anastomotic device does not carry a higher saphenous vein graft failure rate than those done using traditional hand-sewn techniques without a proximal anastomotic device. In this study, our results showed acceptable short term SVG graft patency with PAD. We recommend PAD remains part of the treatment strategy for OPCAB patients but should be tracked closely for long term patency.

734 SIMPLIFIED PEDIATRIC EKG INTERPRETATION

W.N. Evans, R.J. Acherman, G.A. Mayman, R.C. Rollins Children’s Heart Center Nevada, University of Nevada, School of Medicine, Las Vegas, NV.

Purpose of Study: An EKG provides information on the electrical health of the heart; it is not a good screen for ruling in or ruling out structural cardiac abnormalities. As pediatric cardiology services are not always rapidly available, a simple approach to pediatric EKG interpretation is valuable to nonpediatric cardiology healthcare providers.

Methods Used: We describe a simplified method for pediatric EKG interpretation. The method uses 4 steps and requires only a few memorized rules:

Step 1: Determine rate and rhythm
Step 2: Evaluate PR, QRS, and QTc intervals
Step 3: Determine frontal QRS and P wave axis using only AVF
Step 4: Evaluate for right ventricular hypertrophy (RVH) using V1 and left ventricular hypertrophy (LVH) using V6.

Memorized rules are minimized to: 1) normal PR, QRS, and QTc intervals and 2) three RVH criteria and one LVH criteria.

Summary of Results:

Conclusions: This simplified method for pediatric EKG interpretation allows a wide-range of healthcare providers the ability to read pediatric EKGs. Abnormal EKGs should have confirmatory interpretations by a pediatric cardiologist.

737 BALLOON DILATION MAY RELIEVE SUPERIOR VENA CAVA OBSTRUCTION FOLLOWING CAVOPULMONARY ANASTOMOSIS

A. Rothman, A. Galindo, W.N. Evans, R.J. Acherman, G.A. Mayman, J.C. Collazos, H. Restrepo Children’s Heart Center Nevada, University of Nevada, School of Medicine, Las Vegas, NV.

Purpose of Study: Superior vena cava (SVC) obstruction is an important complication after congenital heart disease surgery. While balloon dilation and stent implantation have been used to relieve SVC obstruction, it is not known if a certain subset of patients may respond to balloon dilation alone. We evaluated our results of percutaneous intervention for SVC obstruction from various causes.

Methods Used: Retrospective review of 24 consecutive patients who underwent percutaneous treatment of SVC obstruction.

Summary of Results: Eight patients had SVC obstruction after cavo pulmonary anastomosis (Group A) and 16 patients had SVC obstruction from other causes (Mustard = 5, Senning = 1, indwelling lines = 4, SVC-RA appendage anastomosis obstruction = 5, heart transplantation = 1) (Group B).

Balloon dilation alone was acutely successful (final gradient <2 mm Hg) in 3 of 8 patients in group A and only 1 of 16 patients in group B (62.5% vs. 6.3%, P = 0.003). The median gradient and SVC diameter in group A improved from 5.0 to 0.0 mm Hg and from 4.0 to 8.5 mm, respectively. In group B, the 15 patients who failed balloon dilation underwent stent implantation; the median gradient and SVC diameter improved from 9.5 to 0.0 mm Hg and from 4.2 to 11.0 mm, respectively. There were no complications. Median follow-up after balloon dilation in group A was 13.5 months (range 2.4 to 42.7 months). Median follow-up after stent placement in group B was 29 months (range 0.5 to 89 months). Two patients required stent re-dilation to keep up with somatic growth.

Conclusions: Our data suggest that patients with SVC obstruction after cavo pulmonary anastomosis may respond to balloon dilation alone, while SVC obstruction from other causes generally requires stent implantation.

376 ADHERENCE TO GUIDELINE BASED SECONDARY PREVENTION THERAPIES IN CORONARY ARTERY DISEASE IN THE AGED


Purpose of Study: Studies have examined the adherence to guidelines in managing coronary artery disease (CAD) in the acute setting and at hospital discharge. However no studies have evaluated adherence to ACC/AHA guidelines in secondary prevention in geriatric patients with CAD. Therefore we examined the adherence to guidelines by VA primary care providers (PCPs) in each section enumerated in the ACC/AHA guidelines.

Methods Used: 115 consecutive patients over the age of 65 years referred to the Southern Arizona VA Health Care System Care Coordination Home Telehealth (CCHT) Heart Failure Management Program with a diagnosis of CAD were selected. Retrospective evaluation of the comprehensive intake evaluation performed by CCHT and chart review performed using a systematic chart abstraction tool were used to evaluate management by PCPs prior to referral.

Summary of Results: Mean age was 77.7 years. 12.2% were current smokers; all had received smoking cessation counseling. The blood pressure management goal was achieved in 57.4%, and the LDL-C level was achieved in 73.9% of patients. Only 20% of patients had a normal BMI, despite 71.3% having received dietary advice from a registered dietitian. HbA1C level was greater than 7% in 46.1% of patients. 25.2% of all patients with no documented contraindication were not on any form of anti-platelet or anti-thrombotic therapy.

Conclusions: Aspirin was not prescribed in 60% of aged patients and 25.2% of patients were not on any anti-platelet or anti-thrombotic therapy. Hypertension and diabetes goals were not met in approximately half of this sample. Weight management was suboptimal in 80% of patients, despite dietary counseling.

In secondary prevention of coronary artery disease in geriatric patients, quality improvement efforts need to be focused on increased use of anti-platelet therapy and improved management of hypertension, diabetes and obesity.

377 T WAVE POLARITY ALTERTANS: A RARE VARIANT OF LONG QT SYNDROME

S. Chen, K. Yabumoto, J. Haywood LAC USC, Los Angeles, CA.

Case Report: Purpose of Study: T wave polarity alternans, a rare ECG phenomenon, has been observed in clinical settings such as acute alcoholism, hypomagnesemia, and long QT syndrome. This electrocardiographic finding of alternating T wave polarity falls under the broad category of “T wave alterations”, defined to include cyclic beat-to-beat variation of the amplitude and morphology of the T wave, but rarely the polarity. Prompt identification
of T wave polarity alternans is essential to assessing immediate and long term progression.  

Methods: A unique case report.

Summary: A 62 year old Filipina female with known diabetes mellitus and hypertension presented to the emergency room with a one day history of subjective fever with rigors. Her mother died of heart attack at age 65, and brother died of an unclear cardiac event at age 30. Social and medication history were noncontributory. E Coli bacteremia was diagnosed and treated with IV antibiotics. Admission ECG showed prolonged QT interval. However, while in emergency room, patient became alert and was observed to have one episode of torsades de pointes, which resolved spontaneously. A month later, patient regained consciousness. Her electrocardiogram showed prolonged corrected QT interval of 663 ms, and alternating polarity of T waves. She was admitted to cardiac care unit for further monitoring. An echocardiogram showed normal left ventricular function. Because of her observed episode of torsade de pointes, questionable syncopal episode, possible family history of sudden cardiac death, and the ECG finding of T wave alternans, the diagnosis of long QT syndrome was made by Schwartz criteria. Patient was offered implantable cardiac defibrillator but refused. Subsequent ECGs continued to show prolonged QT interval. She improved clinically and was discharged home without further arrhythmia. One and half year later, patient presented with symptoms of anjina, and had a non ST elevation myocardial infarction. She was found to have triple vessel coronary artery disease, received coronary artery bypass graft surgery, and did well postoperatively.

Conclusions: This case illustrates a classic example of T wave polarity alternans. This ECG finding plays an significant role in the diagnosis of long QT syndrome, and may be a predictor of life threatening ventricular arrhythmias and sudden cardiac death.

Endocrinology II

Concurrent Session

8:30 AM
Saturday, January 31, 2009

378 TESTOSTERONE SUPPLEMENTATION PREVENTS AGE-RELATED LOSS OF SKELETAL MUSCLE MASS BY INHIBITING JNK AND MYOSTATIN SIGNALING


Purpose of Study: Anabolic intervention in preventing or reversing age-related loss of muscle mass (sarcopenia) is highly desirable. Testosterone (T) supplementation especially when given in supraphysiologic doses, increases muscle mass and strength in older men, similar to those observed in young men. Recently, we have advocated a mouse model for investigating the molecular mechanisms of T action on muscle growth in young mice. In additional studies, we have shown the involvement of oxidative stress and JNK-mediated intrinsic pathway signaling in age-related loss of muscle mass through increased muscle cell apoptosis. In this study, we studied the role of T in preventing aging-associated loss of muscle mass in mice. In the process of doing so, we characterized the specific steps in the upstream signaling pathways that are affected by T treatment.

Methods Used: Groups of 15 older (22-month) mice received a single sc injection of gonadotropin releasing hormone antagonist to suppress endogenous T production and were implanted subdermally under anesthesia with empty (control) or 0.5 or 1.0 cm T-implanted for 2 months. Fifteen 4-month-old mice were used as young controls.

Summary of Results: Compared to young animals, a significant (P < 0.05) decrease in the weight of gastrocnemius muscles (by 11.1%) and in the muscle fiber cross sectional area (CSA) of both fast (23.5%) and slow (28.1%) fiber types was noted in old mice. These age-related changes were fully prevented by higher doses (1-cm) of T treatment. Most importantly, T treatment significantly (P < 0.05) suppressed oxidative stress, as evidenced by a decrease in 8-hydroxy deoxyguanosine levels, and activation of JNK, measured by ELISA kit, associated with aging. Unlike young animals, T-induced muscle growth in old mice was, however, independent of p38 MAPK. T supplementation was also capable of suppressing age-related increase in myostatin levels.

Conclusions: We speculate that T promotes muscle growth in aging, not only by suppressing JNK-mediated activation of muscle cell apoptosis but also by augmenting cellular proliferation by suppressing the growth inhibitory role of myostatin.

379 IGFBP3 ENHANCES GERM CELL APOPTOSIS INDUCED BY TESTICULAR HORMONAL DEPRIVATION

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Purpose of Study: Gene microarray analysis showed that insulin-like growth factor binding protein 3 (IGFBP3) was up-regulated (2.7-fold) in human testes in intra-testicular testosterone deprivation. This study is to determine whether testicular hormonal deprivation induced germ cell apoptosis is mediated through IGFBP3 action in testes.

Methods Used: We characterized testicular phenotype of adult IGFBP3 knockout mice. We treated 5 adult (14-15 wk-old) IGFBP3 knockout and 5 age-matched wildtype mice with Acyline (GnRH-A, 20 mg/kg BW) for 2 weeks to induce germ cell apoptosis. To further investigate the effect of IGFBP3 in spermatogenesis, groups of 4 adult rats received one of the following treatments for 5 days: 1) daily intratesticular injections of saline (controls) or IGFBP3 (50 mcg), 2) a single sc injection of GnRH-A (Acyline, 30 mg/kg BW) on day 1, and 3) GnRH-A injection on day 1 and daily intratesticular injection of IGFBP3.

Summary of Results: There were no differences in testis weight (TW) and the rate of germ cell apoptosis between wildtype (TW: 86.8 ± 13.2 mg) and IGFBP3 knockout (TW: 96.3 ± 2.3 mg) mice. GnRH-A treatment significantly decreased TW of wildtype mice (TW: 80.6 ± 3.7 mg), but not of IGFBP3 knockout (TW: 95 ± 5.2 mg) mice. GnRH-A treatment significantly increased the incidence of germ cell apoptosis (apoptotic germ cells/100 Sertoli cells) in wildtype mice at stages VII-VIII (51.5 ± 11.3) and XI-XII (53.6 ± 5.5) as compared to age-matched IGFBP3 knockout mice (VII-VIII: 9.5 ± 1.2; XI-XII: 26.2 ± 2.8). Intra-testicular administration of IGFBP3 alone in rats significantly increased germ cell apoptosis at stages VII-VIII (8.9 ± 0.6) and XIV (46.5 ± 9.2) as compared to control (VII-VIII: 2.1 ± 0.3; XIV: 12.1 ± 1.2). GnRH-A treatment increased germ cell apoptosis at stages VII-VIII (38.4 ± 4.8) and XIV (21.1 ± 1.0). Addition of IGFBP3 to GnRH-A treatment further increased germ cell apoptosis at stages VII-VIII (82.5 ± 6.3) than either treatment alone.

Conclusions: 1) testicular hormonal deprivation induced germ cell apoptosis is partially mediated through IGFBP3 action in the testes; 2) administration of IGFBP3 further enhances hormone deprivation-induced male germ cell apoptosis. These findings may have implications for male fertility and testicular disease.

380 DIRECT INTERACTIONS BETWEEN INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN-3 AND BAX PROMOTES MALE GERM CELL APOPTOSIS IN RAT

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Purpose of Study: The mitochondria-dependent (intrinsic) pathway, governed by BCL-2 family members, is the key pathway for male germ cell apoptosis across species. Gene microarray analysis showed significant up-regulation of Insulin-like Growth Factor Binding Protein-3 (IGFBP-3) after intra-testicular testosterone deprivation in human testes. This study tries to elucidate potential role of IGFBP-3 in the induction of male germ cell apoptosis.

Methods Used: Groups of 4 adult SD male rats treated with intra-testicular injections with vehicle (Saline) or IGFBP-3 50 ug per testis daily for five days. The effect of IGFBP3 with or without BAX on mitochondrial protein release was measured. ELISA were used to measure IGFBP-3 levels in the lysates. Mitochondrial fractions of testicular lysates were prepared and the interaction between IGFBP-3 and BAX was studied by co-immunoprecipitation (Co-IP). Dot blotting was used to confirm the BAX-IGFBP-3 binding in vitro.
Summary of Results: Germ cell apoptosis, detected by TUNEL assay, increased significantly after IGFBP-3 treatment. Co-IP with BAX antibody, demonstrated binding of IGFBP-3 to mitochondrial fractions after treatment with IGFBP-3 as compared with controls, accompanied by an increase of germ cell apoptosis. ELISA assays after Co-IP confirmed the increased binding of IGFBP-3 and BAX after IGFBP-3 treatment. Dot blotting studies validated the binding of BAX to IGFBP-3 in vitro. IGFBP-3 (40 ng/50 ul) induced release of Cytochrome C and DIABLO from isolated mitochondria in vitro. IGFBP-3, at a 4-fold lower dose, when combined with BAX (5 ng/50 ul), triggered release of these proteins from mitochondria in vitro.

Conclusions: IGFBP-3, via binding to BAX, activates the mitochondria-dependent pathway triggering male germ cell apoptosis. This represents a novel pathway that could have significance for male fertility and testicular disease.

381 ALTERATION OF BLOOD COMPONENTS IN THYROID DISEASE
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Purpose of Study: Case presentation

Methods Used: Case studies, literature review

Summary of Results: There is a poorly known connection between thyroid disease and altered blood components. We report data from two patients that provide insight in this connection. Lab values are: result [normal range]. Case 1 is a 57 year old white female with metastatic papillary thyroid carcinoma with thrombocytosis (platelets = 852 [150-400 K/ul]) and increased HCT (49.5 [36-44%]) during active disease, including after near complete thyroidectomy, but which resolved after radioiodine treatment. There are two reports from 1991 linking medullary and follicular thyroid carcinoma with thrombocytosis. The tumor itself might be adding to the increased platelets via activation of thrombocyte stimulating factor. Case 2 is a 51 y old white female with uncontrolled Graves’ disease; the patient’s HCT was 42.9% (high normal) and is well above her usual level; in addition, her leukocytes were low (lymphocytes = 0.5*10^3 [1.5*10^3]), and her mean platelet volume (MPV) high normal (9.1 [6-10 um^3]. Generally, in mice, hyperthyroidism is associated with increased blood viscosity, which depends on the increased amount of RBC’s. Increased HCT may result from anti-thyroid medications. There is contrasting evidence, however, of a case of primary hyperthyroidism associated with anemia, which might be erythropoietin-resistant. Another case of hyperthyroidism in a cat was strongly linked to increased serum lactate dehydrogenase, which might signify increased hemolysis, and thus, decreased HCT. Hyperthyroidism in cats is also strongly associated with leukopenia, which supports the findings in our patient. In addition, our patient’s macrocytosis (increased MPV) is consistent with macrocytosis seen in other patients with Graves: a New Zealand study indicated that upon return to the euthyroid state, hyperthyroid patients exhibited a 16% decrease in the MPV. Such an increase in MPV with hyperthyroidism might be due to increased thrombopoiesis and increased "young" platelets.

Conclusions: There is a link between thyroid cancer and thrombocytosis and between hyperthyroidism, leukopenia, and macrocytic platelets. The link between hyperthyroidism and increased HCT is questionable. Practitioners should be aware of the link between active thyroid disease and blood components to better counsel patient with comorbid conditions.

382 ANOGENITAL DISTANCE IN CHILDREN WITH GENITOURINARY DISORDERS
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Purpose of Study: Anogenital distance (AGD) is a sexually dimorphic marker used as an indicator of fetal androgenization of newborn mice. A shortened AGD in males reflects decreased androgen exposure in utero. Hypospadias and cryptorchidism are common male birth defects associated with insufficient androgenization (hypospadias and cryptorchidism), patients with other genitourinary (GU) system disorders (hydronephrosis and/or VUR), and patients without GU disorders.

Methods Used: Study participants (n = 50) were recruited from the Seattle Children’s Hospital pediatric urology clinic as well as from the surgical pre-operative area. All subjects were under 32 months of age. AGD was defined as the distance between the cephalad base of the penis and the center of the anus. Participants were measured in the dorsal decubitus position with legs flexed. Measurements were obtained to the nearest millimeter using a dial caliper. Anthropometric and demographic data on weight, height, race, ethnicity, and age was collected. In order to adjust for weight, we calculated an anogenital index (AGI = AGD/weight).

Summary of Results: Mean AGI measurement was 8.06 ± 1.62 mm/kg for the hypospadias group (n = 18), 7.92 ± 1.68 mm/kg for the cryptorchid group (n = 16), and 8.45 ± 2.26 mm/kg for the hydrenephrosis/VUR group (n = 16). In multivariate analyses, weight was the biggest predictor of AGD. Height, race, and age also predicted AGD but were not significant in these models.

Conclusions: We observed little variation among adjusted AGD measurements within different patient groups with GU disorders. This finding may reflect a similar embryological origin of development or be due to measurement error and small sample size. In the future, we hope to increase our sample size of cases and recruit control subjects for case-control analyses comparing AGD measurements.

383 TREATMENT OF MALE INFERTILITY SECONDARY TO MORBID OBESITY
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Case Report: A 29-year-old man presented to a clinic with infertility and hypogonadism in the setting of morbid obesity. On presentation, he had notable gynecomastia and a low testicular volume. The patient’s weight was 154 kg and his height was 168 cm (BMI 54.5 kg/m2). Before referral to the clinic, the patient had been treated with testosterone therapy for 4 months for hypogonadism. This treatment had caused his initially low sperm concentration to fall to undetectable levels.

Initial work-up with reproductive hormone levels, pituitary MRI, and semen analysis revealed hypogonadotropic hypogonadism with suppressed LH and FSH levels in the setting of low free and total testosterone. The estradiol level was normal at 172 pmol/l (reference range 73-275 pmol/l) with a low total testosterone level of 5.3 nmol/l (reference range 7.7-27.3 nmol/l). There was no other evidence of pituitary dysfunction.

A growing body of literature has identified obesity as a cause of infertility in men. The etiology is likely increased peripheral and central conversion of testosterone to estrogen by aromatase enzymes. Estrogen causes negative feedback in the hypothalamus and pituitary, thereby suppressing LH and FSH release, with subsequent suppression of testosterone production in the Leydig cells and decreased spermatogenesis. We chose to treat this patient with anastrozole, an aromatase inhibitor, to block peripheral conversion of testosterone and promote endogenous testosterone production by normalizing LH and FSH levels. Within 3 months of initiating treatment, our patient had near normal sperm concentration, and his wife became pregnant within 6 months of treatment.

This case illustrates the challenges in diagnosing and treating infertility in the setting of obesity. The off-label use of aromatase inhibitors to decrease peripheral conversion of testosterone to estradiol provides a unique method of manipulating the normal regulatory mechanisms of the hypothalamic-pituitary-gonadal axis to promote endogenous normalization of testosterone levels and to enhance spermatogenesis and fertility. This case suggests that aromatase inhibition could be an effective treatment for infertility in the setting of obesity-related hypogonadotropic hypogonadism.

384 GYNECOMASTIA AND PRIMARY HYPOGONADISM DURING TREATMENT WITH MELPHALAN
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Case Report: A 74-year-old man developed gynecomastia four months after beginning a six-month treatment course with melphalan, prednisone and lenalidomide for multiple myeloma. Laboratory evaluation revealed hypergonadotropic (primary) hypogonadism with an elevated FSH of 48

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mIU/ml (normal 0-14) and LH of 29 mIU/ml (normal 0-14) and profoundly low total testosterone of 1.2 ng/ml (normal 1.5-5.5) and free testosterone of 20.2 pg/ml (normal 30-140). The patient had normal pubertal development and had fathered four children. Treatment was started with 5 grams of testosterone gel daily. After seven weeks of treatment the patient noticed a 15 lb. weight gain, decrease in gynecomastia, increase in energy level and improvement in sleep. He also experienced a marked increase in his libido and began dating for the first time since the death of his wife three years prior. Repeat laboratory evaluation showed a total and free testosterone (7.5 ng/ml and 142.7 pg/ml, respectively) slightly above the upper limit of normal, and suppressed FSH and LH.

Most literature on gonadal function and cytotoxic chemotherapy focuses on spermatotoxicity and preservation of fertility in young men. More recent studies have addressed Leydig cell dysfunction but have questioned the clinical significance of mild hypogonadism in young men after treatment with high-dose melphalan as part of bone marrow transplant regimens. This case illustrates the importance of evaluating gonadal function in older men treated with lower dose melphalan. In this case, the melphalan is the most likely cause of the testicular injury, as neither prednisone nor lenalidomide are known to be gonadotoxic. Melphalan can be toxic to Leydig cells when used in lower doses for the treatment of multiple myeloma and lead to hypogonadism, which is likely an underdiagnosed complication of treatment for multiple myeloma.

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BETA-BLOCKER(BB), CALCIUM CHANNEL BLOCKER(CCB), AND STATINS AFFECT EGFR IN PATIENTS WITH TYPE 2 DIABETES

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Purpose of Study: Chronic kidney disease (CKD) is one of the most common diabetic complications. eGFR, calculated by MDRD formula, is widely used in clinic setting to monitor kidney function. It is well known that ACE inhibitor and ARB are renal protective in type 2 diabetes. We attempted to study several other medications commonly used in diabetic patients to determine their potential effects on eGFR

Methods Used: A retrospective chart review was conducted on 1032 patients with type 2 diabetes in our clinic at VACCHS. Clinical data included eGFR, medications, age, sex, and blood pressure. T test and multiple linear regression model were used for statistical analysis.

Summary of Results: The study population was predominantly male(>98%) with mean age of 69.5 years; eGFR of 72.3%; and BP of 127/67 mmHg. The treatment profiles were as follows: 38% on beta-blocker(15%atenolol;22%metoprolol); 64% on statin; 61% on simvastatin; 66% on ACE-I/ARB; 19% on CCB; 40% on sulfonylurea and 30% on insulin. The eGFR was significantly lower in beta-blocker(P 0.001) and CCB(P 0.001)user, but higher among statins users (P0.001), even adjusting for ACE-I/ARB use and age. eGFR was not effected by sulfonylurea or insulin.

Conclusions: It is still a major challenge to delay the onset or progression of CKD in type 2 diabetes. In addition to aggressive BP and glucose control, with ACE-I/ARB and hypoglycemic agents, there are few studies focusing on the effects of other medications on eGFR. Although the exact mechanisms remain unclear, our study results indicated that the statins could protect kidney function, while beta-blocker and CCB may worsen CKD, regardless of patient’s age and use of ACE-I/ARB. Our results suggest that we should consider the potential effects of these medications on eGFR in diabetic patients. Further study among relatively younger individuals with female patients is needed.

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DIABETIC KETOACIDOSIS RESULTING AFTER TREATMENT WITH DIAZoxide IN A PATIENT WITH A HISTORY OF AN INSULINOMA

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Case Report: Insulinoma’s are manifested by fasting hypoglycemia, with discrete episodes of neuroglycopenic symptoms, which may be preceded by sympathoadrenal symptoms. They typically arise from ductular/acinar cells of the pancreas. They are considered rare, with an incidence of 4 per every million people. Diagnosis is based on demonstrating inappropriately high serum insulin levels and hypoglycemia, as can be accomplished with a 72 hour fast. After a diagnosis is made, imaging is used to localize a tumor. Spiral CT scans, endoscopic ultrasounds, octreotide imaging, and PET scans are some of the modalities available. Surgical removal is the treatment of choice. If unable to operate, medical management should be considered. Diazoxide can be used, as it decreases insulin secretion.

An 82 year old female, with a history of an insulinoma, presented to University Hospital for further evaluation and treatment. Diagnosis was based on elevated insulin levels, despite hypoglycemia. Patient was initially admitted to another facility due to persistent hypoglycemia in spite of oral diazoxide use. Somatostatin infusion was instituted, however, due to persistent hypoglycemia and the development of hypotension requiring pressor therapy, she was transferred to University Hospital. Initial labs showed glucose values in the 50s with symptoms of dizziness and lightheadedness. D50 was required to maintain glucose in the normal range. Diazoxide was restarted with an increased dose, however, patient then developed diabetic ketoacidosis. Labs revealed a glucose value of 365, with HC03 value of 14, positive serum ketones, and an elevated anion gap of 20. CT and MRI of the abdomen suggested a lesion in the head of the pancreas. CECT scan was performed, but failed to localize the lesion. Endoscopic ultrasound was to be performed, but patient was deemed not to be a suitable surgical candidate, and this study was therefore not done.

Insulinoma’s are rare tumors, and when they do occur, surgical resection is the preferred treatment. The use of medical therapy can alternatively be used to control hypoglycemia. While rare, we document a case of diabetic ketoacidosis occurring as a result of diazoxide treatment in a patient with a poorly localized insulinoma.

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MECHANICAL VENTILATION OF PRETERM LAMBS FOR 3 DAYS ALTERS mRNA EXPRESSION OF GLUCOCORTICOID PATHWAY AND APOPTOTIC GENES IN THE LIVER OF CHRONICALLY VENTILATED PRETERM LAMBS


Purpose of Study: Animal models of bronchopulmonary dysplasia (BPD) indicate that prolonged mechanical ventilation (MV) induces changes in gene expression in the lung, secondary to altered chromatin structure. Those changes may be due to chronic stress of the preterm neonate, which alters gene expression of glucocorticoid pathway molecules (glucocorticoid receptor, GR; glucocorticoid enzyme, 11β HSD; and apoptosis (p53, Bax, caspase 3). Because BPD is associated with secondary injury to other organs, we tested whether the liver of chronically ventilated preterm lambs is affected. We hypothesized that MV for 3d will lead to altered GR pathway and apoptotic gene expression in the liver of preterm lambs.

Methods Used: Preterm (PT) lambs (~132d gestation; term ~150d), treated with antenatal steroids and postnatal surfactant, were managed by MV or high-frequency nasal ventilation (HFNV; positive outcome control) for 3d. Gestation controls were fetal start (FS; ~132d gestation) and fetal end (FE; ~136d gestation). Liver tissue was analyzed by quantitative real time RT-PCR and normalized for GAPDH mRNA expression.

Summary of Results: The PT MV group had the lowest relative expression of mRNA among the groups (table). The difference between the PT MV versus HFNV groups was significant (*P < 0.05).

Conclusions: MV of preterm lambs for 3d decreases GR pathway and apoptotic gene expression in the liver of preterm lambs. These changes were not evident with HFNV. We speculate that those differences, based on ventilation mode, may contribute to multi-organ dysfunction that is characteristic of BPD (HL62875, HL56401, HD41075, CHRC).
388 FUNCTIONAL OVARIAN CYST PRODUCING SELECTIVE ESTROGEN-INDUCED CHANGES IN A PREMATURELY BORN INFANT

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Case Report: Ovarian cysts of varying sizes develop sporadically in female newborns, especially in those who are premature. The ultrasound availability has increased the frequency of ovarian cyst detection, particularly of those which are asymptomatic and/or non-functioning. Most cysts in neonates and infants are small, produce no symptoms, and are without detectable function. Clinical concern is raised with inappropriate feminization, large cyst size, or possible torsion. We have observed a premature infant with functioning ovarian cysts producing selective, atypical feminizing changes. The patient was born at 23 5/7 weeks of gestation (birth weight 552 grams). Early postnatal course was complicated by lung disease, transiently requiring assisted ventilation. At 3 months she developed vaginal discharge and marked labial enlargement. Laboratory evaluation revealed elevated estradiol (499 pg/ml) and luteinizing hormone (12 mIU/ml). Pelvic ultrasound showed an enlarged uterus (3.1 x 1.9 x 1 cm) with an endometrial stripe of 2.1 mm. Her right ovary was enlarged (2.7 x 2.5 x 2.3 cm) and contained a cyst measuring 1.9 x 1.5 x 1.8 cm in addition to two smaller daughter cysts. The left ovary measured 1.6 x 0.6 x 0.1 cm and had a small follicle present. On physical examination the major evidence of estrogen effect included marked prominence and engorgement of the labia majora and minora and vaginal discharge. There was no physical evidence of breast stimulation. The infant’s physical findings were followed, as were the hormone values, and the cysts were closely monitored with serial ultrasound examinations. There was no need for surgical or medical intervention. This infant’s findings can be explained by the ovarian hyperstimulation syndrome in which a physiological surge of gonadotropins in the postnatal period stimulates ovarian estrogen production. This case is interesting in the absence of breast stimulation and in the marked engorgement of the labia. It also supports the evolving evidence that most neonatal cysts resolve spontaneously and do not require surgical intervention, although close observation is important to identify the rare torsion of large cysts.

389 ACCESS TO AFFORDABLE COMFORTABLE FOOTWEAR FOR DIABETIC PATIENTS IN KUMI, UGANDA

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Purpose of Study: Diabetes has increased exponentially in Uganda from 254 cases in 1972, to over a million in 2006. Rural Kumi is the poorest district in eastern Uganda and many people in Kumi walk barefoot because they cannot afford shoes (a comfortable pair of sandals costs $6-12 US). The increasing prevalence of diabetes combined with a lack of affordable footwear has resulted in an increase in diabetic foot ulcers and foot amputations in Kumi. The goal of this project was to increase community awareness of the need for protective footwear and work with a local craftsman to manufacture locally-produced, affordable footwear for diabetic patients.

Methods Used: A craftsman in Kumi was identified who made sandals from old rubber tires. The tire shoes with a rubber strap sold locally for $2 US a pair, but the craftsman agreed to reduce his price for diabetic patients to $1 a pair. A more comfortable shoe with a leather strap was developed for patients with diabetic neuropathy. The tire shoe craftsman reduced the price of the improved shoes with the leather strap from $3 to $2 a pair. Community involvement was sought at every stage from the District Health Office, the staff and orthopedic surgeon at Kumi Hospital, the District Diabetes Focal Person, and diabetic patients.

A poster emphasizing the importance for diabetic patients to wear shoes and control their blood sugar was developed, translated in to the local language of Ateso, and printed in both English and Ateso.

Summary of Results: Community support for the project was overwhelmingly positive. A total of 48 pairs of shoes were made for diabetic patients over a two week period. Patients were pleased with the shoes and expressed that $2 was an affordable price for a pair of comfortable and durable shoes. A total of 10 educational posters, 5 in English and 5 in Ateso, were put up in the Kumi private hospital, the government hospital, the District Health Office, the Town Health Center, and Mulago Hospital.

Conclusions: This project successfully met its goal of increasing access to affordable comfortable footwear for diabetic patients in Kumi, Uganda. Hopefully, this will decrease morbidity and mortality associated with diabetic foot ulcers and amputations in the community. This project is only one facet of an approach which would ideally involve better treatment of diabetes.

390 METFORMIMODIFIABLE FOE: METABOLIC ACIDOSIS IN A 68-YEAR-OLD WOMAN

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Case Report: 68 year old Latina woman with history of HTN, DM2, and hyperlipidemia presented to the ED with left back and flank pain. The patient described decreased urine output for two weeks and emesis for five days associated with chills. Metformin had been prescribed for months, and dose had been increased at the last routine primary care visit. Renal fxn was normal at that time. Other outpatient medications included HCTZ, ASA, prilosec, furosemide, ezetimibe/simvastatin, MTP, nifedipine, and insulin. On exam, vitals signs were significant for tachycyanx with RR 27. Physical exam was normal. Initial lab data included Na 128, K 6.4, Cr 82, HCO3 18, BUN 61, Cr 9.3, glucose 46, and AG 28. CBC revealed WBC 12,000 with 81.4% neutrophils and hemoglobin 10.3. Lactic acid was 13.1. Arterial blood gas on room air showed pH 7.31, pCO2 20, pO2 90, HCO3 10, and O2 Sat 96. Initial management included volume resuscitation and administration of vancomycin and piperacillin/tazobactam for presumed sepsis. Repeat labs revealed worsening acidosis with HCO3 8 and AG 39. Emergent hemodialysis for correction of metabolic acidosis was ordered with good clinical response. The etiology of acute renal failure was felt secondary to volume depletion in the setting of gastroenteritis and diuretic use. This subsequently caused a mixed acid-base disorder, with contraction alkalosis secondary to GI losses. The patient was discharged after improvement of renal function was noted, and the patient was advised to discontinue metformin use.

Metformin has been established as one of the mainstays of treatment for type 2 diabetes, with both cardiovascular and mortality benefit. However, metformin associated lactic acidosis (MALA) is a serious but rare complication of this commonly prescribed hypoglycemic medication. Reported incidence of lactic acidosis is less than one case per 10,000 patient years. Contraindications to metformin treatment include conditions that predispose to increased lactate production and hence to the potentially fatal complication of lactic acidosis. Case reports have suggested that bicarbonate hemodialysis treatment early in the management of MALA may be beneficial. Volume resuscitation may stabilize the patient, and discontinuation of metformin is essential to prevent recurrence of MALA.

Hematology and Oncology II

Concurrent Session

8:30 AM
Saturday, January 31, 2009

391 ANTIBODY-MEDIATED FOXP3 PROTEIN THERAPY INDUCES APOPTOSIS IN CANCER CELLS IN VITRO AND INHIBITS METASTASIS IN VIVO

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Purpose of Study: In addition to its immune suppressive function in T-regulatory cells, the nuclear transcription factor, FOXP3, has been identified...
as a tumor suppressor. The purpose of this study was to evaluate the clinical efficacy of monoclonal antibody (mAb) 3E10 Fv antibody-mediated FOXP3 protein therapy in cancer.

Methods Used: An Fv-FOXP3 fusion protein produced in Pichia pastoris was tested on breast, ovarian, and colon cancer cells in vitro, and with colon cancer cells in vivo in a mouse model of colon cancer metastasis to liver.

Summary of Results: Treatment with Fv-FOXP3 resulted in dose-dependent cell death of cancer cells in vitro. Apoptosis was established as a mechanism of cell death by demonstrating increased production of the p17 activated fragment of caspase-3 by cancer cells in response to Fv-FOXP3 and inhibition of cell killing by the caspase inhibitor, Z-VAD-FMK. Fv-FOXP3 treatment resulted in clinically significant reduction in tumor burden in a syngeneic model of colon cancer metastasis to liver in Balb/c mice.

Conclusions: These results represent the first demonstration of effective full-length FOXP3 protein therapy and emphasize the clinical potential of mAb 3E10 as an intracellular and intranuclear delivery vehicle of FOXP3 for prevention and treatment of cancer metastasis.

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ASSESSMENT OF ANEMIA IN A POPULATION OF CHILDREN LIVING IN THE INDIAN HIMALAYAS


Purpose of Study: To determine the prevalence and etiology of anemia among school-aged children in the Spiti District, India.

Methods Used: Hemoglobin (Hb) levels were measured for all 377 ethnically Tibetan children (4 to 16 years old) attending a local school. The levels were determined using a beta-hemoglobin photometer and adjusted for age and gender prior to the determination of anemia. Due to the lack of a definitive relationship between altitude and Hb in Tibetan children, the prevalence of anemia was also determined based on altitude-adjusted Hb levels complying with the recommendations of the Centers for Disease Control.1 Peripheral blood smears were obtained for the most severe cases of anemia. Using World Health Organization guidelines, anemia was defined as Hb <140 g/L for age under 5, <145 g/L for ages 5-11, <150 g/L for ages 12-14, <150 g/L for non-pregnant females age 15 and older, and <160 g/L for males age 15 and older. The smears were morphologically analyzed by a hematopathologist in New Delhi and the results interpreted with the assistance of hematopathologists in Vancouver, Canada.

Summary of Results: The prevalence of anemia was very high at 77%. Twenty-two (11%) of the smears showed hypochromic anisocytic red blood cells (RBCs), while the majority (57%) demonstrated normocytic normochromic RBCs.

Conclusions: The hypochromic anisocytic anemia is suggestive of iron deficiency. The observed normocytic normochromic anemia could be explained by: 1) mixed nutritional (iron, B12, folate) deficiencies due to a low-meat diet and a lack of fresh vegetable intake in winter months; 2) early iron deficiency; and/or 3) genetic and physiologic adaptations in oxygen transport.2 If a genetic variance in Hb levels exists in Tibetan children, the prevalence of anemia could be substantially lower than 77%. Further studies are necessary for definitive diagnosis.

REFERENCES:

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IDENTIFICATION & CHARACTERIZATION OF NOVEL SMALL MOLECULES WITH ANTIPROLIFERATIVE EFFECTS IN WERI-RB1 RETINOBLASTOMA CELL LINE


Purpose of Study: Children with retinoblastoma are at risk for blindness and secondary tumor development. Combination chemotherapy with focal therapy is first-line treatment. However, broad-based chemotherapy causes systemic adverse effects. In effort to preserve eyesight and reduce systemic toxicities, improvements should be made in chemotherapy by targeting specific RB molecular characteristics. This project is the first step in identifying molecules that may be more effective and less toxic RB therapeutic regimens in effort to prevent blindness.

Methods Used: Novel compounds from the NCI Developmental Therapeutics Program were screened in human RB Weri cell line to identify compounds that have anti-tumor effects. Based on initial screening results, selected compounds were further characterized with Western blots and quantitative PCR.

Summary of Results: 5 compounds showed strong cytotoxic effects in Weri and their 50% growth inhibitory concentrations were determined. Western showed p53 levels were elevated in Weri cells in response to treatment by the compounds in dose-dependent relationship. QPCR results show that the most compounds have increased quantitative p53 target gene expression of DCR3 normalized to housekeeping gene HPRT.

Conclusions: p53 pathway is inactivated in RB; thus, molecular targeting to restore wild-type p53 activity is an interest for drug development. Out of the initial screening, 5 drugs were of interest: NSC 5159, 143491, 146109, 254681, 639174 all showed strong stimulatory effect on p53 level in dose-dependent manner. QPCR results show that NSC 143491 and 254681 have increased p53 target gene expression level. This study has identified small molecules that can induce p53-responsive transcriptional activity and apoptosis in RB cells that were originally p53-inactive.

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DETERMINING THE INFORMATION NECESSARY FOR PATIENT TREATMENT DECISIONS IN DUCTAL CARCINOMA IN SITU OF THE BREAST

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Purpose of Study: DCIS of the breast is a pre-cancerous condition often diagnosed with screening mammography. Previous studies have demonstrated a lack of understanding among DCIS patients regarding treatment options. Often DCIS patients would like to be involved in treatment decisions, and we hypothesize that they seek more information than they are currently receiving. This study aims to define the information needs of women with DCIS.

Methods Used: Four focus groups involving 23 patients previously treated for DCIS were conducted to develop an exhaustive list of questions that these patients felt were important. This list was then entered into a survey and distributed to a separate group for their judgments on the importance of having each question addressed at the time of diagnosis. Response options were essential, desired, not
important, no opinion and avoid. For each essential/desired question, respondents identified the reason(s) that the question was important; for understanding, for deciding, for planning, not sure, or other. One hundred and four patients were surveyed: 26 were randomly selected from each of four cancer centres.

**Summary of Results:** Focus group information generated a list of 117 questions used in the survey. Fifty-seven surveys were returned (response rate: 55%). On average each respondent rated 66 of the 117 questions essential and 94 questions essential or desired. There was wide variation in the number of questions deemed essential (14-117) and essential or desired (21-117). Seventy-five questions were rated essential by at least 50% of the respondents, and 113 were rated essential or desired by at least 50%. Using an agreement threshold of 67%, 36 of 117 questions were agreed to be essential and 11 questions were agreed to be not essential. The ten questions most important to patients for decision making were judged essential specifically for deciding by at least 46% of respondents.

**Conclusions:** DCIS patients responding to the survey want a variable but overall large number of questions answered. A decision aid addressing a large number of questions would help ensure that each individual patient has access to the specific information that she needs.

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A TETRACYCLINE-INDUCIBLE PLASMID CONSTRUCT FOR CONTROLLING ONCOSTATIN M EXPRESSION IN BREAST CANCER CELL LINES

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**Purpose of Study:** Oncostatin M (OSM) is an interleukin-6 family cytokine up-regulated in neutrophils found in the presence of various cancer cell lines. Previous in vitro studies in human mammary carcinoma cells have suggested that OSM prevents cell proliferation and is a viable candidate as an anticancer agent. Contradictory to this conclusion is in vitro evidence suggesting that this period of growth inhibition is followed by increased tumor cell detachment and invasive capacity suggesting the potential for increased tumor metastasis in vivo. Mouse models utilizing OSM over-expressing cancer cell lines have attempted to characterize this effect in vivo but have met with limited success due to OSM inhibition of initial tumor cell growth. The use of an inducible OSM plasmid system will allow researchers the ability to shut off OSM production in the initial tumor growth phase, then turn it on to observe whether OSM increases the tumor’s metastatic potential in vivo.

**Methods Used:** Human and murine OSM (hOSM/mOSM) cDNAs were cloned into the inducible expression vector of the T-REX™ tetracycline-regulated expression vector system (Invitrogen, Carlsbad, CA) in which OSM transcription is allowed only in the presence of tetracycline. The new constructs were confirmed via gel electrophoresis and transformed in XL1-Blue competent E. coli. Purified plasmids were then transfected into two mouse and two human tumor cell lines using Invitrogen’s lipofectamine transfection reagent, and stably transfected cell colonies were selected using appropriate amounts of blasticidin.

**Summary of Results:** Restriction digests of the final inducible plasmid constructs show that hOSM and mOSM were successfully cloned into the inducible expression vector. Initial results from tumor line transfections show several drug-resistant cell colonies, indicating successful transfections. Work on transfection of the inducible expression plasmid is on-going and will be followed by in vivo orthotopic and spontaneous metastasis studies.

**Conclusions:** Elucidation of the role of OSM in tumor growth and metastasis is important in understanding the progression of breast cancer as well as in devising future pharmacotherapeutics. This experiment will allow more controlled in vivo studies to confirm or disprove the hypothesis that OSM is crucial in cancer metastasis.

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THE EFFECT OF NUMBER OF OLDER BROTHERS ON THE PREVALENCE OF BREAST CANCER

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**Purpose of Study:** It has been proposed that high intrauterine estrogen environment may increase the risk of developing breast cancer (BC) later in life. Studies show that males with a greater number of older brothers (OB) are more likely to have a homosexual orientation, possibly due to altered steroid level exposure in utero. Studies have also shown that BC patients had a larger variation in the 2nd to 4th digit lengths compared to controls, which may be due to differences in sex steroid levels during development. We hypothesized that the more OBs a person has, the greater the risk of developing BC. To test this, we looked at the number of older brothers that BC patients have.

**Methods Used:** Questionnaires were administered to patients with BC (N = 185) as well as controls (N = 363), including patients, staff and visitors in five hospitals and clinics in southern California. Data including birth order, family size, number of older brothers, and pertinent medical history was collected from each subject.

**Summary of Results:** The mean number of OB was not significantly higher between BC patients and controls (P = 0.085). However, a chi-square analysis showed that the relative number of BC cases increased with increasing numbers of OBs compared to the controls (chi-sq. = 2.16; DF = 4, P = 0.0002). This could possibly be attributed to an increasing family size or increasing maternal age in the breast cancer patients with more older brothers. A regression analysis showed relatively more BC cases in later birth order positions (x2 = .56, F = 7.91, DF = 1, 6, P = 0.03).

**Conclusions:** The data suggests a possible relationship between the number of OB and an increased risk of developing BC. Moreover, an increasing birth order may also be associated with an increasing prevalence of BC. A further analysis with controls for subject age, family size and maternal age is needed to assess if the number of older brothers is related to increased risk of developing breast cancer.

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THE INCIDENCE OF VENOUS THROMBOEMBOLISM AND THE IMPACT ON SURVIVAL IN PATIENTS WITH BLADDER CANCER

University of California Davis, Sacramento, CA.

**Purpose of Study:** The purpose of this study was to identify the incidence, risk factors, time course, and impact on survival of VTE in a large population-based study of bladder cancer patients and controls.

**Methods Used:** We used the California Cancer Registry to identify all bladder cancer cases diagnosed in California within a 6 year period. We merged this information with the California Discharge Data Set to determine the incidence of VTE. We then used a Cox proportional hazards model to analyze the effects of certain risk factors for VTE and death after VTE.

**Summary of Results:** Among 24861 patients with bladder cancer, the 2 year incidence of VTE was 1.9%. The highest incidence of VTE occurred in the first 6 months regardless of age, sex, race, tumor stage, or histological subtype. In a multivariate model, significant risk factors for VTE included major surgery, advancing stage, and increasing number of co-morbidities. In a similar model of death, patients with transitional cell carcinoma were significantly less likely to die after VTE than patients with other histological subtypes. African Americans were significantly more likely to die after VTE than other racial groups. The risk of death was increased with increasing stage and medical co-morbidities. VTE was a significant predictor of death within 2 years of cancer diagnosis.

**Conclusions:** Patients who develop bladder cancer have a 1.9% incidence of developing VTE. Metastatic disease was the strongest predictor of both the development of VTE and death after VTE. Interestingly, cancer associated surgery was associated with a higher risk of VTE, as opposed to other studies in solid tumors. When comparing matched groups of bladder cancer patients with and without VTE, VTE was a significant predictor of death in the first 2 years. Further studies in the highest risk bladder cancer patients are needed to possibly improve survival or prevent VTE.
398 INCREASED TREATMENT RELATED MORTALITY IN ADOLESCENTS AND YOUNG ADULTS FOLLOWING BONE MARROW TRANSPLANT

C. Shin1, T. Nguyen2, E. Nemecck1 1Doernbecher Children’s Hospital, Portland, OR and 2Oregon Health and Science University, Portland, OR.

Purpose of Study: Older adolescent and young adult (AYA) patients may have worse outcomes than younger patients after bone marrow transplantation (BMT). A previous retrospective review of patients treated at a single institution reported increased transplant related mortality (TRM) in older AYA patients (15-21 years of age) compared to a younger cohort (10-14.9 years of age). The generalizability of these findings has not been demonstrated. We hypothesized that, in patients treated at our institution, TRM would be higher in the older AYA group compared to younger patients with similar disease characteristics and treatment following BMT.

Methods Used: A retrospective chart review of patients undergoing first allogeneic BMT for malignant disease at Oregon Health and Science University from 1996 to 2007. Patient demographics, oncologic disease status, and transplant characteristics were collected. Outcomes evaluated were survival, disease recurrence, transplant-related mortality, and incidence of graft-versus-host disease. For purposes of analysis, patients were divided into a younger cohort (10-14.9 years of age) and an older AYA cohort (15-21 years of age).

Summary of Results: 70 patients were included in the study with 47 and 23 in the older and younger cohorts respectively. For patients treated in first complete remission (CR1), overall survival, relapse, and TRM did not differ between the two groups. For patients treated in second complete remission (CR2), TRM was increased in the older AYA group (36.8% vs 0%) with a trend towards statistical significance ($P = 0.09$). Relapse rates for patients treated in CR2 were similar at 43% and 38% for older and younger age groups respectively. Mortality was 100% for all patients receiving BMT beyond CR2, however survival time was significantly higher in the older cohort (median 8.4 months vs. 2.6 months, $P = 0.0014$).

Conclusions: Outcome of BMT patients transplanted in CR1 does not differ significantly by age. Treatment related mortality may be higher for older adolescent and young adult patients receiving BMT for malignant disease in CR2. Younger patients have increased mortality within the first 6 months of HSCT. The true impact of age on BMT outcome remains to be verified in a multi-institutional setting.

399 ATYPICAL TERATOID/RHABDOID TUMOR RECURRENT DISEASE IN THE CHEST: A CASE REPORT AND REVIEW OF THE LITERATURE

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Case Report: PURPOSE OF STUDY: To report a case of a patient with thoracic metastasis of an Atypical Teratoid/Rhabdoid Tumor (ATRT) and to examine the literature for support of a recommendation to increase long-term surveillance of ATRT survivors.

METHODS USED: Case report and review of the literature.

SUMMARY OF RESULTS: A 2 year old boy presented with new onset headaches and acute ataxia. Imaging showed a right frontal lobe tumor which was confirmed to be an ATRT after biopsy. He was treated according to COG 99701 brain tumor protocol with radiation. He did well for two years, undergoing quarterly MRI of the brain without evidence of recurrence or post-treatment. At 4 years of age, he was noted to have left flank and abdominal pain. Imaging showed a tumor originating in the left chest and displacing his mediastinum and spleen. Biopsy of the mass supported a metastasis of his original brain ATRT. Chemotherapy was begun; however, he succumbed to his disease 30 months after his initial diagnosis.

CONCLUSIONS: This case reports one of three known metastatic ATRTs to the thoracic cavity. The literature, and COG brain tumor protocols, recommends serial quarterly brain MRIs for surveillance of ATRT survivors but does not recommend for surveillance outside the CNS. As ATRT treatment improves and patients are surviving longer after initial diagnosis, metastases outside the CNS are becoming increasingly common. The literature also reveals sporadic intra-abdominal metastases of ATRTs along VP shunt pathways. Therefore, we recommend routine imaging of the chest and abdomen in all ATRT survivors for early identification of extraneural metastases. Further long-term follow-up studies are needed for ATRT survivors.

400 2D:4D RATIOS IN RELATION TO BREAST CANCER SUSCEPTIBILITY AMONG DIFFERENT ETHNIC GROUPS

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Purpose of Study: Studies have shown that the ratios of the 2nd (Index) and 4th (Ring) digit may be an indicator of early steroid hormone exposure. It is unclear if female breast cancer (BC) patients experienced varying hormone conditions early in life in relation to controls. Levels of androgens and estrogens during development have been implicated as key sources of variance in 2D:4D ratios. Females are reported to have higher ratios than males.

Methods Used: A total of 84 diagnosed BC subjects and 142 control subjects were measured. Digit length was measured from the tip of the second and the fourth distal phalanges on the ventral side of the hand to the most proximal crease of the digit. Measurements were taken in triplicate and were recorded to 0.01 mm of accuracy. Diagnosed illness and ethnicity were obtained from a questionnaire. Laterality has been shown as a variable in 2D:4D so we sorted based on full lateralization (larger 2D and 4D on same side). Subjects in which both digits were not fully lateralized were excluded. Ethnic differences in digit ratios have been reported so we separated our data into three self-reported ethnic groups.

Summary of Results: White BC patients had a higher 2D:4D ratio than controls whereas Blacks had a significantly lower ratio than controls. Using a Repeated Measures ANOVA with 3 factors we found that laterality was not a significant source of variance but that the factor of disease (BC versus No BC) was significant. The data for the disease factor was as follows: Whites (F
401 RELATIVE ULNA LENGTH IN PRE VS. POST MENOPAUSAL BREAST CANCER PATIENTS

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Purpose of Study: At low levels, estrogen initiates and maintains bone growth during adolescence, as large levels have opposing effects that terminate growth. Studies indicate estrogen levels and breast cancer (BC) prevalence are directly correlated, implicating birth control pills (increased estrogen) as a significant cause of pre-menopausal (pre-m) BC. In previous studies, patients with lower U:S ratios have been observed compared to post-menopausal patients. We hypothesize that pre-m BC patients will have lower U:S ratios compared to the control and post-m BC patients and controls.

Methods Used: To test this hypothesis, anthropometric measures of ulna length were examined in 40 pre-m and 105 post-m BC patients and 88 controls. The ulna was measured by three successive repetitions using an osteometric board and identification of the inferior styloid process. To verify ulnar length, a subtraction method was utilized that subtracts hand measurements from lower arm measurements. The three repetitions of the left ulna were averaged and used to calculate U:S ratio by dividing ulna length by height.

Summary of Results: Patients were divided into a pre-m (≤45 years old at diagnosis) BC group and a pre-m control group (age matched). In a 2-way ANOVA, ethnicity and presence of disease were analyzed. U:S ratio’s varied among ethnicity (F(2,127) = 6.35; P = 0.0024) and between BC patients and controls (F(2,127) = 4.06; P = 0.0459) with U:S ratios being lower in pre-m BC patients than in controls, and higher in African Americans than in other ethnic groups. The pre-m values also differed from the post-m values (F(1,139) = 6.68; P = 0.0098) which supports the hypothesis that pre-m BC patients have lower U:S ratios possibly due to increased estrogen.

Conclusions: Pre-m BC patients have been shown to have decreased U:S ratio compared to the control and post-m BC groups, which adds additional support to a link between estrogen and pre-m BC. Patients who get BC prior to menopause may have elevated estrogen exposure during early development, as suggested by lower U:S ratio’s.

402 EFFECT OF ALFIMEPRASE VERSUS DELTA-PLASMIN ON HEMOSTASIS USING THE RABBIT EAR BLEEDING MODEL

K.D. Navab, T.M. Gruber, V.J. Marder UCLA, Los Angeles, CA.

Purpose of Study: Plasminogen activators (PA) such as t-PA, streptokinase, urokinase and reteplase are currently approved for use as thrombolytic agents for treating acute thrombotic disorders. While effective, use of PA carries an increased risk of bleeding complications. A new class of “direct-acting” thrombolytics offer the potential for effective therapy that avoids bleeding complications. This study will determine whether a snake venom recombinant (alfimeprase) exhibits hemostatic safety in an experimental model of fibrinolytic hemorrhage, using a mutant derivative of plasmin (‘delta’ plasmin) that is known to be safely tolerated as control agent. Hemostasis will be measured by primary bleeding time after ear puncture in the rabbit, and coagulation status will be determined by assay of alpha-2 antiplasmin, clotting factor VIII and fibrinogen levels before, during and after exposure to each agent.

Methods Used: Five groups (5 animals each) of New Zealand white rabbits (2.1-4.0 kg) were used for this investigation. Inflames were coded and administered blindly over 60 minutes, after baseline bleeding times and blood sampling for coagulation assays. Treatment groups included alfimeprase at the anticipated human therapeutic dose and at 2-fold and 4-fold higher concentrations (0.3, 0.6 and 1.2 mg/kg body weight), delta-plasmin at 4-fold therapeutic dose (4 mg/kg) and saline control. Primary bleeding times and plasma levels of alpha-2 antiplasmin, clotting factor VIII and fibrinogen were assessed during and after infusion.

Summary of Results: As expected, saline infusion had no effect on bleeding time or coagulation factor levels, and “Delta” plasmin induced a partial decrease in alpha-2 antiplasmin, factor VIII and fibrinogen, but no prolongation of primary bleeding time. Contrary to anticipation, alfimeprase had no significant effect on coagulation factors or the primary bleeding time. Conclusions: In this animal model of bleeding, alfimeprase did not decrease plasma coagulation factor levels and did not cause prolongation of bleeding time. The reason for this unexpected result is as yet unexplained, but may reflect higher levels of fibrinolytic inhibitors of alfimeprase in the animal model (rabbit) than exist in humans.

403 ANTITUMOR ACTIVITY OF B-RAF INHIBITOR (PLX4032) AGAINST A PANEL OF HUMAN MELANOMA CELL LINES

M.L. Montecillo,1,2 J. Sonderegger2, A. Ribas1 Charles R Drew University of Medicine and Science, Los Angeles, CA and 1David Geffen School of Medicine UCLA, Los Angeles, CA.

Purpose of Study: Melanoma cell lines with constitutive mitogen activated kinase pathway (MAPK) activation due to harboring the activating missense mutation B-raf V600E are likely to be uniquely sensitive to treatment with the specific B-raf V600E inhibitor PLX4032, and the blocking of this kinase may have antitumor effects that could result in cell cycle arrest and cell death.

Methods Used: Cytotoxicity was determined by using the CellTiter 96® AQueous One Solution Cell Proliferation Assay (Promega). The effects of PLX4032 on cell cycle at 20h post-treatment were determined by flow cytometry.

Summary of Results: Cell viability assay established that PLX4032 treatment at 120h is sufficient for homozygous B-raf V600E mutants (M262, M229, and Skmel-28) to achieve IC50 but not heterozygous B-raf V600E mutants (M308, M321, and M233), B-raf wild type/N-ras mutant (M202), or the B-ras/N-ras wild type (M257). Cell cycle analysis demonstrated that 20h treatment with PLX4032 is adequate to induce cell cycle arrest for all homozygous B-raf V600E mutants but not heterozygous B-raf V600E mutants. PLX4032 on cell cycle at 20h post-treatment were analyzed by flow cytometry.

Conclusions: The collective data strongly suggest that PLX4032 is only cytotoxic against homozygous B-raf V600E mutants but not heterozygous B-raf V600E mutants. PLX4032 is also cytostatic against homozygous B-raf V600E mutants but further studies are warranted to determine whether it is cytostatic against all heterozygous B-raf V600E mutants.

Immunology and Rheumatology II
Concurrent Session
8:30 AM
Saturday, January 31, 2009

404 AUTOIMMUNE EAR DISEASE

S.S. Ansari, R. Monger University of Wyoming, Cheyenne, WY.

Case Report: A 30 year old otherwise healthy man presented to his physician with complaints of dizziness, tinnitus, and mild hearing loss. He had no symptoms of systemic illness such as fever, rash, or fatigue, and his physical examination was unremarkable. He was initially treated with decongestants and antibiotics but did not improve.

The patient’s symptoms persisted, and over the next several years he was evaluated by multiple specialists. Despite an extensive medical evaluation no etiology of his symptoms was discovered.

Four years after the onset of his symptoms the patient was tested for autoimmune disease, and it was discovered that his anti-68kD antibody was positive. A diagnosis of autoimmune ear disease was made and the patient was started on immunosuppressive medications which resulted in complete resolution of his symptoms.
405 TOLL-LIKE RECEPTOR FUNCTION OF NEWBORN POLYMORPHONUCLEAR LEUKOCYTES

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Purpose of Study: Newborn infants are highly susceptible to bacterial infection and syndromes of dysregulated inflammation. Neonatal polymorphonuclear leukocytes (PMNs) display bacterial killing deficits associated with PMN dysfunction. The toll-like receptors (TLRs), which are expressed on PMNs, are membrane proteins which recognize microbe-derived molecules and activate the innate immune system. TLR signaling in neonatal PMNs is incompletely understood. Whether altered TLR function contributes to neonatal PMN bacterial killing deficits and syndromes of dysregulated inflammation is unknown. We hypothesized that in response to various TLR agonists neonatal PMN cytokine production would be decreased as compared to adult PMNs.

Methods Used: We isolated PMNs via positive immunoselection for CD15 expression from the umbilical cord blood of healthy term infants and peripheral blood of healthy adults. PMNs were stimulated with the agonists for TLR 1-9 and incubated for 480 minutes. Supernatants were then collected and frozen at -20°C. Initial analysis via ELISA for interleukin 8 (IL-8) was performed. We will perform analysis for 11 additional cytokines via luminex multiplex immunoassay.

Summary of Results: Here we report the results of the initial IL-8 cytokine assay. For all TLR agonists studied, we found increased IL-8 expression in PMNs isolated from term newborn infants as compared to those isolated from adults. Furthermore, we noted particularly robust IL-8 expression following stimulation of TLRs 2, 6 and 9 in PMNs isolated from both term neonates and adults.

Conclusions: PMNs isolated from term newborns produced more IL-8 than those isolated from healthy adults. Increased IL-8 production, a pro-inflammatory cytokine secreted to recruit PMNs to areas of tissue damage or infection via chemotaxis, suggests it is not impaired IL-8 production following TLR stimulation which contributes to the bacterial killing deficits of neonatal PMNs. It may however contribute to the predisposition of newborn infants to syndromes of dysregulated inflammation. We speculate there are likely other differences in cytokine synthesis following TLR stimulation between neonatal and adult PMNs which will be seen with Luminex cytokine analysis that may explain the neonate’s increased susceptibility to infection.

406 FUSION PROTEIN RNASEA INVESTIGATED AS A POSSIBLE METHOD OF REDUCING AUTO RNA ANTIBODY TITERS IN TOLL LIKE RECEPTOR 7 TRANSGENIC MICE

B. Rush University of Washington, Seattle, WA.

Purpose of Study: Ribonuclease A (RnaseA) was investigated as a possible treatment for Systemic Lupus Erythematosus in Toll Like Receptor 7 transgenic mice (TLR7.1). Increased autoantibodies to RNA are associated with increased progression of lupus-like disease in TLR7.1 mice. TLR7.1 mice that over-express TLR7 by a factor of 12-15 times and develop severe autoimmune disease were used in these experiments. Degradation of RNA could be a possible method of reducing antibodies to RNA and thus help ameliorate systemic inflammation that is associated with SLE.

Methods Used: A fusion protein that ligated a heavy chain mIgG to murine RnaseA was created and amplified using a COS monkey kidney hybridoma cell line. The rationale for using a fusion protein as opposed to isolated RnaseA is that it lies in the extended half life of the fusion protein as well as the ability for quantitative determination of the level of fusion protein in treated mouse serum. A single radial diffusion assay (SRED) technique was used to determine relative serum ribonuclease activity between control and treated mice. Three mice were injected with 100 μL of saline containing 100 μg of RnaseA fusion protein and one mouse was injected with 100 μL of saline only. Mice were bled pre-injection, one day after injection, and every week for 3 weeks. Serum samples were assessed for RnaseA activity using the SRED method. One mouse was re-injected with 100 μg of fusion protein at 2 weeks to test for possible immunogenic reactions against the fusion protein.

Summary of Results: Serum samples were assessed for RnaseA activity using the SRED method. One mouse was re-injected with 100 μg of fusion protein at 2 weeks to test for possible immunogenic reactions against the fusion protein.

Conclusions: Encouraged by the success of this mini-experiment, a larger scale treatment plan with fusion protein RnaseA will be undertaken and a larger population of treated animals can be tested for effects on disease progression.

407 GNATOPHYMA AND OTOPHYMA: CASE REPORT AND REVIEW

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Case Report: Pharyngitis are slowly progressive, disfiguring disorders of the face and ears that represent the end stage of rosacea. The most common phyma is rhinophyma, yet similar swellings may occur on the chin (gnatophyma), forehead (metophyma), one or both ears (otophyma), and eyelids (blepharophyma). Unlike rhinophyma, otophyma is rarely seen. We report two rare phymas, a case of gnatophyma and a case of otophyma. A 56-year-old African American male presented with bilateral cauliflower-like earlobe growths for the past 17 years. A skin biopsy was performed for each patient which demonstrated cystic follicular dilatation with keratin plugging, dermal scarring, psoriasiform epidermal hyperplasia and chronic inflammation of some of the follicles. This case report describes a relatively rare gnatophyma and otophyma. Surgical management is well-accepted as the best mode of therapy to treat rhinophyma and is becoming a first-line treatment for all phymas.

408 HETEROGENEITY OF HUMAN CD8 CLONAL EXPANSIONS AND A NEW MARKER DEFINING ONE SUBSET

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Purpose of Study: Humans and mice both contain T cells bearing diverse T cell receptors expressed in relatively constant numbers. As individuals age, certain CD8+ T cells expand in number, giving rise to large clones within which only one TCR is expressed. In humans, such expansions have also been associated with autoimmune disease. Studies in our lab have shown that one subset shows properties expected of autoreactive T cells. Evidence that such expansions are functionally heterogeneous in man, and that one subset shows properties expected of autoreactive T cells.

Methods Used: We have identified CD8+ clones in healthy individuals and established their surface biomarkers. Blood was drawn from healthy individuals, and peripheral blood leukocytes were prepared and stained with anti-CD8, as well as antibodies against 15 commonly used human Vbs. Analysis was by flow cytometry, and for identified expansions, antibodies were used against several other surface molecules, including KLRG1, whose known ligand is E-cadherin. Cells were also stimulated in vitro with anti-CD3 and anti-CD28, and proliferation was measured using CFSE.

Summary of Results: We have identified a subset of human CD8+ expansions that exhibit diminished proliferation upon stimulation as compared with controls and non-clonal CD8+ cells in the same subject. This phenotype is also defined by increased expression of KLRG1 and loss of IL7Ra on the cell surface, characteristic of suppressed autoreactivity.

Conclusions: KLRG1 defines a memory subset of CD8+ expansions that have poor proliferation potential and other characteristics of suppressed
autoreactivity. Further study of this subset in healthy individuals and patients with autoimmune disease may provide important clues to the nature of T cell autoreactivity in the pathogenesis of human autoimmune disease.

Purpose of Study: Rheumatologists, orthopedists traditionally use palpation

Methods Used: This is an IRB-approved protocol registered at clinical-trials.com. Initially, this study used RPD alone in palpation-guided intrarticular

Summary of Results: We harvested primary cells from B6 mice after

Conclusions: We uncover a previously unrecognized role for IFN-I in CD4+ T cell-mediated immunity and show that IL12 is dispensable for Th1

We find that IFN-I is necessary for robust primary and secondary expansion of CD4+ T cells in this model. However, CD4+ T cells deficient for IFN-I signaling have a proliferative capacity upon secondary expansion similar to wild-type CD4+ T cells. Thus the memory deficit in IFN-I deficient animals may be due to a poor primary expansion. Elicited CD4+ T cells have a Th1, IFNγ-secreting phenotype. This phenotype seems to be independent of signaling by the canonical Th1 cytokine, IL12, and, in contrast to CD8+ T cells, has a variable dependence on CD70.

Purpose of Study: A common three single-nucleotide polymorphism (SNP) haplotype in the complement receptor 2 (CR2/CD21) gene is associated with systemic lupus erythematosus (SLE). SNP2 and SNP3 of the haplotype are located in exon 10, directly 5’ of the alternatively spliced exon 11 that is preferentially expressed in follicular dendritic cells (FDC). Alleles at these SNPs may influence splicing, alter relative amounts of CR2 long and short isoforms, and contribute to lupus susceptibility.

Methods Used: To determine the effect of SNP2, SNP3, and two SNPs in exon 11 on splicing, CR2 genomic DNA from introns 9 to 12 containing the minor allele for all four SNPs was cloned into an exon-trapping vector (pL53lin). A second plasmid containing all major alleles was generated by site-directed mutagenesis. Both plasmids were transiently transfected into Raji (B cell) and HK (FDC) lines. Relative amounts of vector-derived mRNA including or excluding exon 11 were determined by quantitative RT-PCR. The relative amount of each isoform in primary B cells from healthy human subjects was also assessed.

Summary of Results: In Raji cells transfected with the major allele construct, levels of transcripts excluding exon 11 were 8.8-fold higher than those including it, whereas they were 13-fold higher in cells with minor alleles. Similarly, in HK cells, transcript levels excluding exon 11 were 4-fold and 12-fold higher with major and minor alleles respectively. In primary B cells from subjects with major alleles at all four SNPs (n = 3), short isoform mRNA levels were 1.3-fold higher than long, while in subjects with all minor alleles (n = 2), they were 3-fold higher.

Conclusions: In conclusion, the major alleles of four SNPs in exon 10 and 11 of the CR2 gene decrease the splicing efficiency of exon 11 in vitro and ex vivo. Identification of the specific SNPs involved and characterization of their effects on protein expression and function will broaden our understanding of the role of CR2 in the pathogenesis of lupus.

Purpose of Study: Activated human polymorphonuclear leukocytes (PMNs) effect extracellular bacterial killing by secreting lattices of DNA and anti-microbial proteins termed neutrophil extracellular traps (NET). PMNs isolated from neonates fail to form NETs and exhibit extracellular bacterial killing defects. NET formation by stimulated PMNs isolated from...
healthy adults requires endogenous reactive oxygen species generation. Whether NET formation is dependent on expression of hypoxia inducible factor 1 alpha (HIF1α), the regulated subunit of the hypoxia responsive transcription factor HIF1, is unknown. We hypothesized that pretreatment with 2-methoxyestradiol (2ME2), an inhibitor of HIF1α nuclear translocation, would inhibit NET formation in LPS-stimulated adult PMNs.

Methods Used: We therefore stimulated human PMNs isolated from healthy adults with LPS [100 ng/ml] with/without 2ME2 [2 μM] pretreatment for 60 minutes. Other PMNs were pretreated with the microtubule disruptive agents taxol [10 μM] and vinblastine [10 μM]. We assessed NET formation of live PMNs stained for extracellular and nuclear DNA via confocal microscopy. We also assessed HIF1α protein expression and nuclear translocation via immunocytochemistry in PMNs isolated from both healthy adults and newborn infants.

Summary of Results: We found that 2ME2 inhibited NET formation in LPS-stimulated PMNs while taxol and vinblastine pretreatment did not, suggesting inhibition of HIF1α nuclear translocation and not microtubule disruption as the 2ME2 mechanism of action. We next found that LPS induced nuclear translocation in adult PMNs, an action inhibited by 2ME2 but not by taxol or vinblastine. Finally, we demonstrated minimal HIF1α protein translocation to the nucleus of PMNs isolated from neonatal PMNs following LPS stimulation.

Conclusions: We conclude that 2ME2 inhibits NET formation in PMNs isolated from healthy adults, most probably via inhibition of HIF1α nuclear translocation preventing its incorporation into the HIF1 transcription factor. We speculate that absent HIF1α nuclear translocation in stimulated PMNs isolated from newborn infants may contribute to impaired NET formation and extracellular bacterial killing in this cell type.

Neonatology - Developmental Biology

Concurrent Session
8:30 AM
Saturday, January 31, 2009

413 ALTERED GROWTH FACTOR PRODUCTION IN FETUSES OF DIABETIC RATS

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Purpose of Study: Growth hormone (GH) is a major growth-promoting and metabolic regulatory hormone that acts through its cell surface receptor (GHR). GH binding protein (GHBP) is a soluble form of GHR that correlates with hepatic GHR abundance in vitro. GHBP is low in fetal life resulting in unbalanced GH/GHR signaling and may not be critical for fetal growth. However, IGF-I and -II are the major growth-promoting factors in the fetus, and may be impaired in diabetic pregnancies. We examined the hypothesis that hepatic GH/GHR signaling and insulin-like growth factor (IGF)-II levels are altered in fetuses of diabetic rats.

Methods Used: Three groups of pregnant rats were studied: 1) Non-diabetic control (CTL), 2) Diabetic, non-treated (DNT), and 3) Diabetic insulin-treated (DIT). For groups 2 and 3, diabetes was induced in non-pregnant rats using streptozocin (65 mg/kg IV). Once diabetes was confirmed by blood glucose levels, treatment with 2ME2, an inhibitor of HIF1α, was administered. The experimental groups included: male (M) or female (F), hypoxia (H) or control (C), Epo (E) or saline (V), right-side ischemia (R) or left-side control (L). GR mRNA was measured by real-time RT-PCR.

Summary of Results: We conclude that 2ME2 inhibits NET formation in PMNs isolated from healthy adults, most probably via inhibition of HIF1α nuclear translocation preventing its incorporation into the HIF1 transcription factor. We speculate that absent HIF1α nuclear translocation in stimulated PMNs isolated from newborn infants may contribute to impaired NET formation and extracellular bacterial killing in this cell type.
specific. Identification of the best endogenous control genes for tissue type and experimental design is important for accurate quantification of gene expression.

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Summary of Results: IUGR significantly decreased total cell count in both P0 males and females compared to controls. IUGR significantly decreased CD4<sup>+</sup>CD8<sup>+</sup> cells in P0 males compared to control males. IUGR significantly increased CD4<sup>+</sup>, T-helper cells, and significantly decreased CD8<sup>+</sup>, cytotoxic T cells in P0 males and females when compared to controls. At P7 IUGR did not significantly affect total cell count in IUGR males but did significantly decrease cell count in P7 females compared to controls. The CD4<sup>+</sup>CD8<sup>+</sup> naive undifferentiated T-lymphocytes were also significantly increased in IUGR females at P7. There was no significant difference in CD4<sup>+</sup> or CD8<sup>+</sup> cells in males or females when compared to controls at P7.

Conclusions: IUGR decreased total cell count in P0 male and female rats with a gender specific alteration in CD4<sup>+</sup>CD8<sup>+</sup> lymphocytes suggesting increased cell turnover and resulting in a phenotype with a higher percentage of T-helper cells than cytotoxic cells when compared to controls. By P7 the males have returned to control levels in all categories, however the females continue to have decreased total cell number when compared to controls as well as a decrease in the CD4<sup>+</sup>CD8<sup>+</sup> cells. This suggests the IUGR females have a more difficult time recovering for the IUGR insult.

418 DEVELOPMENTAL EXPRESSION AND FUNCTION OF COLLAGEN TYPE XI IN ZEBRAFISH

B.L. McMahan, J. Adams, University of Washington, Seattle, WA and Boise State University, Boise, ID.

Purpose of Study: Collagen Type XI (Col XI) plays an important role in the embryonic development of many species. Human mutations in Col XI result in Marshall and Stickler Type 2 syndromes which are characterized by congenital craniofacial abnormalities, eye defects, hearing loss and joint pathologies. Developing a zebrafish model for the study of Col XI will offer advantages over similar studies in other vertebrate species.

Methods Used: PCR was used to confirm the presence of Col XI transcripts in zebrafish at several stages of embryonic development as well as alternative splicing. PCR products were run on an agarose gel and representative PCR products were excised for subsequent purification and sequencing. One isoform identified, V1aV2, was ligated into a vector and cloned using standard cloning techniques. Purified V1aV2 plasmid was then used as a template for riboprobe synthesis.

Wild type zebrafish embryos were collected and fixed at four developmental time points. Embryos were then subject to standard in-situ hybridization procedures using the V1aV2 riboprobe as a marker of transcription, allowing for characterization of the spatial and temporal expression patterns of Col XI. Col XI knockdown experiments were performed by microinjection of an anti-sense morpholino. Morphant embryos were then stained with alcian blue to detect abnormalities in craniofacial cartilage structures.

Summary of Results: PCR experiments showed alternative splicing of Col XI. Three separate isoforms were characterized by sequence analysis. In-situ hybridization experiments showed expression in the notochord, otic vesicle and several craniofacial structures at different developmental time points. Morpholino micro-injection and alcian blue staining revealed marked craniofacial abnormalities in the morphant embryos.

Conclusions: This study clearly confirms the viability of zebrafish as a model organism for the study of Col XI and provides evidence for a functional role of Col XI in craniofacial bone development. Further studies will focus on determining isoform specific expression patterns in the tissues already described and elucidating the functions of the several Col XI isoforms in craniofacial and ear development.

417 IUGR ALTERS T-LYMPHOCYTE PHENOTYPE IN NEWBORN AND JUVENILE RATS

Y. Contreras, M.A. Hale, X. Fu, E. Enioutina, C.W. Calloway, R.H. McKnight, R.A. Lane University of Utah, Salt Lake City, UT.

Purpose of Study: IUGR infants have qualitative and quantitative abnormalities in lymphocyte function resulting in increased susceptibility to infection. Low birth weight infants show persistent immunological impairment throughout childhood, associated with higher risk of illness and death. Previous studies in our lab have shown an overall decrease in cellularity and a depopulation of early naive undifferentiated lymphocytes We also demonstrated that IUGR affects multiple organ systems in a gender specific manner. However, not much is known about the full extent of the immune dysfunction seen in SGA infants. We hypothesized that IUGR would decrease the cellularity and immature populations of T-Lymphocytes in the P0 and P7 IUGR male rat thymus to a greater extent than the female when compared to controls.

Methods Used: Bilateral uterine artery ligation was used to produce IUGR rats. Thymus tissue was harvested at P0 and P7 (n= 24). Monoclonal antibodies and flow cytometry were used to compare lymphocyte phenotype at P0 and P7.

Summary of Results: IUGR significantly decreased total cell count in both P0 males and females compared to controls. IUGR significantly decreased CD4<sup>+</sup>CD8<sup>+</sup> cells in P0 males compared to control males. IUGR significantly increased CD4<sup>+</sup>, T-helper cells, and significantly decreased CD8<sup>+</sup>, cytotoxic T cells in P0 males and females when compared to controls. At P7 IUGR did not significantly affect total cell count in IUGR males but did significantly decrease cell count in P7 females compared to controls. The CD4<sup>+</sup>CD8<sup>+</sup> naïve undifferentiated T-lymphocytes were also significantly increased in IUGR females at P7. There was no significant difference in CD4<sup>+</sup> or CD8<sup>+</sup> cells in males or females when compared to controls at P7.

Conclusions: IUGR decreased total cell count in P0 male and female rats with a gender specific alteration in CD4<sup>+</sup>CD8<sup>+</sup> lymphocytes suggesting increased cell turnover and resulting in a phenotype with a higher percentage of T-helper cells than cytotoxic cells when compared to controls. By P7 the males have returned to control levels in all categories, however the females continue to have decreased total cell number when compared to controls as well as a decrease in the CD4<sup>+</sup>CD8<sup>+</sup> cells. This suggests the IUGR females have a more difficult time recovering for the IUGR insult.
insulin resistance and type 2 diabetes. We hypothesize that IUGR will increase adipose TNFα, TNFR1, and NFκB mRNA levels in a gender and adipose depot specific manner.

**Methods Used:** IUGR (induced through utero-placental insufficiency) rat adipose (subcutaneous and retroperitoneal) was compared to control tissue. mRNA levels of TNFα, TNFR1, and NFκB were measured at day 21 using real-time RT-PCR in male and female rat adipose tissue.

**Summary of Results:** Results are expressed as IUGR as percent of control = SEM. IUGR increased TNFα mRNA levels in subcutaneous (204% ± 27%) adipose tissue of males with a trend increasing in female subcutaneous (145% ± 24% p = 0.1) and male retroperitoneal (175% ± 29% p = 0.07) adipose tissues. IUGR significantly increased mRNA levels of NFκB (281% ± 15%*) and TNFR1 (195% ± 12%*) in male retroperitoneal adipose tissue. No significant differences were observed in female retroperitoneal or subcutaneous adipose depot specific manner.

**Conclusions:** We conclude that IUGR results in an increase in male rat adipose tissue TNFα and NFκB in an adipose depot specific manner at day 21, before the onset of obesity or other metabolic complications. The specifity of the increase in retroperitoneal adipose tissue is relevant given visceral fat increases risk for insulin resistance. We speculate that this increase might be associated with increased insulin resistance later in life.

**420 MATERNAL ZINC DEFICIENCY INCREASES HEPATIC IGF-1 mRNA VARIANT EXPRESSION IN JUVENILE RATS**

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1University of Utah, Salt Lake City, UT and 2UC Davis, Sacramento, CA.

**Purpose of Study:** Dietary zinc deficiency is a worldwide perinatal problem that causes IUGR, predisposes towards postnatal metabolic diseases, and alters IGF-1 levels in affected progeny. Serum IGF-1 levels are controlled by hepatic IGF-1 gene expression. IGF-1 gene expression is characterized by multiple mRNA species, which affect IGF-1 translational efficiency and post-translational modifications. Though perinatal malnutrition affects hepatic IGF-1 expression, little is known about isolated perinatal zinc deficiency affects hepatic IGF-1 mRNA in postnatal progeny. Because other models of IUGR decrease postnatal IGF-1 expression, we hypothesize that maternal zinc deficiency also decreases hepatic IGF-1 expression.

**Methods Used:** A zinc deficiency diet of 7 ppm zinc was fed to dams 3 days to 15 hours before the onset of pregnancy (p0.05) and maternal zinc deficiency also decreases hepatic IGF-1 expression.

**Summary of Results:** Results expressed as % of control

**Conclusions:** Maternal zinc deficiency decreases hepatic IGF-1 mRNA at day 21. A diet of 25 ppm zinc reduces the risk for insulin resistance later in life.

**421 BIOACTIVITY OF TRANSFORMING GROWTH FACTOR-β IN POWDER INFANT FORMULA**

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Powder Infant Johnson & Co., Evansville, IN.

**Purpose of Study:** TGFβ is a multipotent cytokine involved in immune regulation, cell-growth, matrix-synthesis, and apoptosis. TGFβ is synthesized as a large peptide with a propeptide (Latency Associated Peptide) that is proteolytically cleaved but is tightly bound to the active portion. TGFβ is secreted as a Large Latent Complex where the Latency Binding Proteins are covalently attached to the latent complex. The extracellular quantification of TGFβ bioactivity is primarily regulated by its conversion from the latent to the active form.

The aim of the study is to demonstrate bioactivity of various milk matrices using the Cellomics® bioassay.

**Methods Used:** TGFβ signal through cell surface receptors via serine-threonine kinase activity to intracellular signaling components known as Smads. Smad complexes formed in the cytoplasm accumulate in the nucleus leading to interaction with target genes and assembly of the transcriptional apparatus.

The Smad2 Redistribution® Assay utilizes MDA-MB-468 cell line. It measures TGFβ induced Smad2 translocation by monitoring the translocation of a GFP-Smad2 fusion protein from the cytoplasm to the nucleus.

**Summary of Results:** The range of EC50 for Enfamil® LIPIL® powder (n = 6) is 0.06-0.89 DF units (0.07-4.38 DF units for human milk, n = 18). The maximum activity (Y-axis) for Enfamil® LIPIL® is 57-115% relative to that of rTGFβ2 (18-110% for human milk).

**Conclusions:** The presence of TGFβ in Enfamil® LIPIL® powder infant formula (Stage 1, 0-6 months) can be demonstrated by cell culture bioassays and is qualitatively similar to that observed for human milk.

**422 MATRIX METALLOPROTEINASE mRNA AND PROTEIN CONCENTRATIONS IN THE DEVELOPING HUMAN EYE**

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1University of New Mexico, Albuquerque, NM and 2Des Moines University, Des Moines, IA.

**Purpose of Study:** Retinopathy of prematurity (ROP) is an important cause of blindness in infants born in developed countries. ROP is a biphasic disease that alters angiogenesis in developing retinal tissue. Angiogenesis is a complex process that has been linked to many signaling factors including matrix metalloproteinases (MMP). MMPs degrade the tight junctions found between endothelial cells, resulting in increased vascular permeability. In an effort to determine if MMPs play a role in the developing eye, we measured MMP-2 and MMP-9 mRNA concentrations and MMP-9 protein concentrations in the mid-gestation human eye.

**Methods Used:** Fetal retinal and vitreous samples were obtained from 10 to 24 weeks gestation. The contents of the globe was extracted, the lens removed, and the retina and vitreous collected from fetal eyes. The retina was isolated and RNA extracted for quantitative MMP-2 and MMP-9 mRNA determination by PRISM PCR. Total RNA was measured spectrophotometrically, verified by gel electrophoresis, and reverse transcribed using 10 ng/µL total RNA. Vitreous samples were stored at -20 degrees C until analyzed for MMP protein by ELISA. Data were analyzed using unpaired t-tests and ANOVA.

**Summary of Results:** In fetal retina, both MMP-2 and MMP-9 mRNA expression increased with increasing gestational age. MMP-2 expression increased 3-fold from 10 weeks gestation to 24 weeks gestation (R = 0.603; P < 0.004). MMP-9 expression increased 10-fold over the same period (R = 0.814; P < 0.001). Because of this significant increase, MMP-9 protein concentrations were measured in vitreous. Unlike mRNA concentrations, protein concentrations remained unchanged over the gestational ages tested, averaging 6.6 ± 4.2 pg/µL at the earliest gestations tested to 7.1 ± 2.1 pg/µL at the latest gestations tested.

**Conclusions:** MMP-2 and MMP-9 mRNA concentrations increase significantly with increasing gestation. MMP-9 protein concentrations remain unchanged. Further study is required to measure tissue MMP-2 and MMP-9 protein concentrations.
423
CHARACTERIZING CAENORHABDITIS ELEGANS OOCYTE MRNA USING RNA SEQUENCING

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Purpose of Study: The mother and father of many species make an unequal contribution to offspring. One unique contribution of the mother is the mRNA present in the oocyte that the developing embryo relies upon to coordinate development and produce proteins. Understanding exactly which mRNAs are present in the oocyte before fertilization can hold important clues about the subsequent development of an organism and the mechanisms of pluripotency, both vital aspects of stem cell therapy.

Characterizing the mRNA content of the oocyte was previously difficult as microarray studies only provided relative expression levels, and Serial Analysis of Gene Expression (SAGE) was cost prohibitive. New RNA sequencing technologies have drastically reduced the price of sequencing making such a counting based approach more feasible and allowing for gene splicing information that was previously unavailable. The goal of this project was to characterize the mRNA in the oocyte of Caenorhabditis elegans (C. elegans).

Methods Used: Oocytes were acquired using a mutant form of C. elegans (fer1) that produces defective sperm. This strain accumulates unfertilized eggs which were extracted from the worms using a bleach/filter protocol published by the Alberts group. Total RNA was extracted from purified oocytes using a TRIZOL (Invitrogen) protocol and RNA expression was measured using the Illumina digital gene expression system.

Summary of Results: Analysis of sequence results revealed the expression of many genes in the oocyte, including those involved in eggshell development and protein synthesis. However, degradation of transcripts appears to be a concern due to an overrepresentation of 3’ end reads (a method of determining the quality of RNA).

Conclusions: This experiment validated the utility of using RNA sequencing as a method of characterizing mRNA content inside of C. elegans oocytes. Future experiments will use wild type C. elegans oocytes to help reduce RNA degradation.

424
CONCENTRATION OF TRANSFORMING GROWTH FACTOR BETA IN HUMAN MILK FROM US AND MEXICAN MOTHERS

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1Mead Johnson Nutritionals, Evansville, IN and 2Cincinnati Children’s Hospital Medical Center, Cincinnati, OH

Purpose of Study: Transforming growth factor beta (TGF-β) in human milk appears to play an important role in maintaining appropriate immune function in infants. In the present study, we assessed its morphology and activity in human milk.

Methods Used: Oocytes were acquired using a mutant form of C. elegans that produces defective sperm. This strain accumulates unfertilized eggs which were extracted from the worms using a bleach/filter protocol published by the Alberts group. Total RNA was extracted from purified oocytes using a TRIZOL (Invitrogen) protocol and RNA expression was measured using the Illumina digital gene expression system.

Summary of Results: Analysis of sequence results revealed the expression of many genes in the oocyte, including those involved in eggshell development and protein synthesis. The analysis shows that the distributions of human milk TGF-β concentrations among these mothers were positively skewed, and high variability was observed within and between mothers, which was not explained by their clinical status, seasonality, lactation period or sampled region.

Conclusions: A geometric-mean and its variance were calculated for each of thirteen collection times and the three locations, from which a grand geometric-mean of 2,700 pg/ml and 95% confidence intervals (550 - 13,000 pg/ml) were obtained. These results suggest that if an infant consumes 750 ml of milk daily his/her total consumption of TGF-β would be 0.4 - 9.8 μg/day.

Neonatal – Pulmonary II
Concurrent Session
8:30 AM
Saturday, January 31, 2009

425
A SUBSET OF EPITHELIAL CELLS IDENTIFIED BY CCSP-PROMOTER ACTIVITY PARTICIPATES IN ALVEOLAR FORMATION

V.A. Londhe1, T.M. Maisonet1, K. Rodgers1, C. Li2, A. Li2, P. Minoo2
1UCLA, Los Angeles, CA and 2USC, Los Angeles, CA

Purpose of Study: To determine whether a subset of epithelial cells with CCSP-promoter activity participates in alveogenesis. We hypothesize that deletion of a unique stem/progenitor cell population identified by CCSP-promoter activity during lung development impairs normal alveogenesis. Recent studies have described a subpopulation of cells with CCSP-promoter activity that are necessary for regeneration of airway epithelium following injury. This transgenic mouse model ablates all lung cells with CCSP-promoter activity and results in deletion of alveolar type II cells secondary to inflammation and injury of the epithelium.

Methods Used: CCtk transgenic mice (Reynolds et al., AJP-Lung 2000) were used to conditionally ablate all cells with CCSP-promoter activity in lung epithelium. Heterozygous Ctk female mice were mated with WT control males and newborn pups were injected with 25 μl ganciclovir (GCV, 50 mg/ml) or saline i.p. on day 1 and day 4 after birth before sacrifice on day 8. Exposure to GCV ablates cells expressing thymidine kinase (tk) transgene. The animals were genotyped and lungs were harvested following inflation with fixative at 25 cm H20 constant pressure for histological analysis and mRNA collection. Similar comparative experiments were conducted using naphthalene injection (200 mg/kg) i.p. on day 1 followed by lung harvest on day 8.

Summary of Results: CCtk-treated transgenic CCtk mice showed marked alveolar simplification with thin septae and reduced secondary crest formation as compared to GCV-treated WT controls. Saline-treated and naphthalene-treated CCtk and WT mice maintained normal lung alveolar structure. Immunochemistry and quantitative PCR analysis confirmed significant reduction in CC10 expression in addition to markers of alveolar epithelial cells (Nkx2.1, SP-C, and SP-B). Interestingly, changes in lung phenotype were not accompanied by obvious lung injury or inflammation.

Conclusions: Depletion of a cell type with CCSP-promoter activity interferes with alveogenesis. This cell type may play a tissue-specific stem/progenitor cell role in postnatal lung development. This study provides new insights into the role of resident lung stem/progenitor cells in alveogenesis as well as distal lung pathologies such as bronchopulmonary dysplasia.

426
MATERNAL DHA CONSUMPTION DURING GESTATION ABALATES IUGR INDUCED CHANGES IN LUNG PPARγ MRNA EXPRESSION AND LUNG MORPHOLOGY IN RAT OFFSPRING

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Purpose of Study: Intrauterine growth restriction (IUGR) predisposes individuals towards bronchopulmonary dysplasia (BPD), which is characterized by thickened mesenchyme. Appropriate epithelial-mesenchymal interactions and lung development involve the transcriptional regulator PPARγ. PPARγ expression is responsive to the essential omega-3 fatty acid, DHA. IUGR in the rat decreases PPARγ mRNA variant and protein expression in the lung and thickens pulmonary mesenchyme. However, the effect of DHA on the IUGR induced alterations in lung PPARγ expression and morphology is unknown. We hypothesize that maternal DHA supplementation during gestation will prevent the IUGR induced decrease in PPARγ mRNA variants and that this will be accompanied by improved lung morphology.

Methods Used: Pregnant rats were fed a diet that contained 1% DHA from E13 to term. Lungs from IUGR (induced through utero-placental insufficiency) offspring harvested at birth were compared to lungs of control offspring. PPARγ1, γ1b and γ2 mRNA transcript levels were measured using real-time RT-PCR at birth (d0). Distal airspace thickness was quantified in IUGR and control lungs by morphometric analysis using H&E stained sections.

Summary of Results: All results refer to offspring of DHA supplemented dams. Results are expressed as % of control ± SEM. IUGR did not
significantly alter levels of PPARγ1a, γ1b or -2 mRNA in male rats at birth (γ1a = 95.5 ± 7%, γ1b-90.3 ± 12%, γ2 -82.9 ± 15%). In female offspring only the PPARγ1a variant mRNA was significantly reduced (82.2 ± 5%, P = 0.05), while the γ1b and γ2 mRNA levels remained unchanged. Morphometric analysis of male and female lung tissue showed no significant difference in distal airspace thickness (μm²) body weight between IUGR and control lungs (IUGR-1.65 ± 0.09, control-1.47 ± 0.1, P = 0.1).

Conclusions: We conclude that maternal DHA supplementation ablates our previous observed decrease in lung PPARγ mRNA expression and accompanying mesenchymal thickening. We speculate that maternal DHA supplementation increases PPARγ signaling and thereby decreases mesenchymal thickness in the IUGR lung.

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P53 AFFECTS VASCULAR ENDOTHELIAL GROWTH FACTOR MRNA EXPRESSION IN DEVELOPING MOUSE LUNG

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Purpose of Study: Intrauterine growth restriction (IUGR) predisposes both humans and rats to bronchopulmonary dysplasia (BPD) which is characterized by mesenchymal thickening of distal airways. Mesenchymal thickening may result from dysregulation of multiple p53-sensitive processes including angiogenesis. We have shown that IUGR decreases mRNA of Vascular Endothelial Growth Factor (VEGF), a mediator of angiogenesis required for normal alveolar formation, and increases p53 mRNA and in the developing rat lung. Evidence suggests that p53 inhibits mRNA expression of VEGF. Interestingly, using p53 transgenic mice, we have demonstrated that p53 deficiency is protective against oxygen-induced mesenchymal thickening in the developing mouse lung. The role of p53 on VEGF mRNA expression in oxygen-induced mesenchymal thickening remains controversial.

Objective: We hypothesized that p53 deficiency increases VEGF mRNA expression in developing lungs of oxygen-exposed mice.

Methods Used: To test this hypothesis, p53+/- mice were time mated. Dams and their pups were exposed to 60% O2 from day 3 to day 6, during initiation of alveolar formation. On D21, pups were killed and lungs isolated and flash frozen in liquid N2. Real-time RT PCR was performed to assess VEGF mRNA levels. (n = 7-8 pups +/-, +/+ controls, oxygen exposure did not significantly alter VEGF mRNA expression.

Summary of Results: In response to 60% oxygen exposure, p53 deficient mice (+/-) do not have significant changes in VEGF mRNA compared with oxygen exposed p53 +/+ and +/+ mice. Compared with room air genotype-matched (+/+, +/-) controls, oxygen exposure did not significantly alter VEGF mRNA expression.

Conclusions: While p53 deficiency is protective against oxygen-induced mesenchymal thickening of distal airways, it does not increase VEGF mRNA expression. Mesenchymal thickening, a morphometric characteristic of BPD, does not result from many different processes including cellular proliferation, apoptosis and angiogenesis. We speculate that altered expression patterns of other p53-sensitive genes, such as the cell cycle inhibitor p21, may confer protection to oxygen-induced mesenchymal thickening in the p53 deficient state.

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ANTENATAL ADMINISTRATION OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR (PPAR) γ AGONIST ROSIGLITAZONE (RGZ) PREVENTS HYPEROXIA-INDUCED LUNG INJURY POSTNATALLY

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Purpose of Study: Nuclear transcription factor PPARγ plays a critical role in normal lung development and injury/repair. Our laboratory has recently shown that a potent PPARγ agonist RGZ administration postnatally can prevent hyperoxia-induced neonatal lung injury, suggesting the potential therapeutic usefulness of PPARγ agonists in preventing and/or treating neonatal lung injury. However, it is not known whether PPARγ agonist administration antenatally can prevent neonatal lung injury postnatally. We hypothesized that antenatal administration of PPARγ agonist RGZ will prevent hyperoxia-induced neonatal lung injury postnatally. This study examines the effect of antenatal administration of RGZ on hyperoxia-induced lung injury postnatally.

Methods Used: Pregnant Sprague-Dawley rat dams were administered either diluent or RGZ (3 mg/kg), at embryonic day 21 (term ~ 22). After spontaneous delivery at term, pups were placed in either 21% O2 or 95% O2 before sacrificing them after 24 hours. The lungs were examined for morphometry and specific markers of lung injury and repair, in particular, the markers of TGF β, Wnt, and Parathyroid Hormone-related Protein (PTHrP)PPARγ signaling.

Summary of Results: 24 h exposure to hyperoxia alone resulted in decreased alveolar saculation, which was blocked by RGZ administration (184 ± 17 vs. 165 ± 21 vs. 203 ± 33 saccules/mm² [mean ± SD]); 21% O2 vs. 95% O2 vs. 95% O2+RGZ, P < 0.05). Hyperoxia-induced decrease in septal wall thickness (4.4 ± 0.6 vs. 3.9 ± 1.1 vs. 5.1 ± 1.1 μm; 21% O2 vs. 95% O2 vs. 95% O2+RGZ, P < 0.05) was also blocked by antenatal RGZ administration. Similarly, hyperoxia-induced increase in TGFβ and Wnt signaling (p-Smad3 and LEF-1) and decrease in PTHrPPARγ signaling were also blocked by antenatal RGZ administration.

Conclusions: Antenatal administration of RGZ virtually blocked 24 h hyperoxia-induced lung morphometric and molecular changes postnatally, suggesting a novel antenatal intervention to protect against hyperoxia-induced neonatal lung injury. (Grant Support: NIH-HL 75405, HL55268, HD051857, TRDRP-14RT-0013, 1517-0250, 17R-0170).
Conclusions: In spontaneously-breathing piglets with HCl-induced ALI, treatment with KL4 resulted in better gas exchange, better physiologic stability, and prolonged survival. Funding: Children’s Hospital Foundation, Discovery Labs.

430 PROTECTION OF HYPEROXIA-INDUCED NEONATAL LUNG INJURY BY PARENTRALLY ADMINISTERED BONE MARROW-DERIVED MESCENCYMAL STEM CELLS

P. Guo, E. Cruz, K. Chap, S. Mittal, J. Torday, V. Rehan LA Biomed, Torrance, CA

Purpose of Study: Under appropriate conditions, bone marrow derived mesenchymal stem cells (BMMSCs) can differentiate into a wide variety of tissues, and have recently been shown to be important for lung injury/repair. We have previously shown that the lipogenic phenotype of the alveolar interstitium is critical for lung homeostasis and injury/repair. This study examines whether driving BMMSCs to a lipogenic phenotype, will augment the protection provided by BMMSCs against hyperoxia-induced neonatal lung injury.

Methods Used: BMMSCs were isolated and cultured from Sprague Dawley rats using standard methods. After confirming the stem cell phenotype of passage 3 BMMSCs, the cells were labeled with 0.02% DAPI for 24 h. 7 day rats using standard methods. After confirming the stem cell phenotype of Torrance, CA

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Conclusions: 9 VLBW infants completed the study. Weight was 667 ± 106 gm and gestational age was 24 3/7 weeks ± 12 days. All patients had received exogenous surfactant prior to study initiation. Average of 12,738 breaths evaluated for each patient (range 9950 - 13973). When the patients were in PSV+VG versus SIMV+VG modes, there were no significant differences in heart rate (P = 0.18), total respiratory rate (P = 0.32), end-tidal CO2 (P = 0.52), or FIO2 (P = 0.76). Similarly, there were no significant differences in mechanical variables, including average tidal volume (P = 0.29), mean airway pressure (P = 1.0), and peak inspiratory pressure (P = 0.49).

Conclusions: PSV+VG and SIMV+VG appear to be equally effective in the early management of ELBW infants with RDS. Although these ventilation modes are routinely used in many NICUs, no other studies to date have compared their use in the initial management of the ventilated ELBW infant. Funding: Children’s Hospital Foundation, Discovery Labs.

432 SMAD3 FACILITATES NUCLEAR TRANSPORT OF β-CATENIN IN LUNG EPITHELIAL CELLS

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Purpose of Study: The Wnt/β-Catenin/TCF/LEF signaling pathway is an important mediator of cell growth and differentiation during embryogenesis and beyond. Wnt activation inhibits β-catenin phosphorylation and degradation, leading to accumulation of unphosphorylated β-catenin and transport to the nucleus where it induces transcription of Wnt target genes. TGF-β regulates epithelial cell proliferation and differentiation and evidence of cross-talk between the Wnt and the TGF-β pathway has been reported. We sought to study the relationship between TGF-β and Wnt pathways in the lung.

Methods Used: In order to characterize Wnt activity, we measured STF-luciferase expression and β-catenin levels in MLE-15 cells and in Smad3(-/-) type II cells treated with and without Wnt3a. In addition we compared X-gal staining in the lungs of wild type TOPGAL mice with the lungs of Smad3(-/-) TOPGAL mice.

Summary of Results: STF-luciferase reporter activation is blunted in Smad3(-/-) cells treated with Wnt3a compared to MLE-15. The cytoplasmic β-catenin in Smad3(-/-) cells treated with Wnt3a is increased compared to MLE-15 cells. X-gal staining in the lungs of Smad3(-/-) TOPGAL mice is decreased when compared to wild type TOPGAL mice. Conclusions: Smad3 may be necessary for the nuclear transport of β-catenin which may explain the decreased Wnt activity and the increased levels of cytoplasmic β-catenin observed in Wnt3a treated Smad3(-/-) lung epithelial cells.

433 MATERNAL-FETAL LEAD POISONING FROM AN OLD SLUG: 10-YEAR FOLLOW-UP

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Case Report: A 31 year old cashier was shot at age 16. The bullet lodged in vertebra L4. When she became pregnant 15 years later, her blood lead level (BPb) was 31 mcg/dL (toxic ~25 mcg/dL). She described recurrent headache, back pain and difficulty opening containers. She required Caesarean section (BPb) was 31 mcg/dL (toxic ~25 mcg/dL). She described recurrent headache, back pain and difficulty opening containers. She required Caesarean section at term due to pre-eclampsia and fetal distress. Two months post-partum, BPb had risen to 75 and 85. Her infant weighed 2825 grams with Apgar scores of 7 and 9 at 1 and 5 minutes. Bronchoscopy showed tracheobronchomalacia, the left main bronchus being compressed by a large patent ductus arteriosus, Cardiac catheterization showed a dysplastic aortic valve, early bifurcation of the pulmonary artery and a large patent foramen ovale. Magnetic resonance of the brain at 3 months showed a hypoplastic septum pellucidum, thinning of the corpus callosum and dilated lateral ventricles. Bilateral sensorineural hearing loss exceeded 55 decibels. In Toxicology Clinic at 19 weeks, she had a blood lead level of 37 mcg/dL, falling to 20 mcg/dL after 4 cycles of dimercaptosuccinic acid, and stabilizing at 4 mcg/dL from 30 to 87 months of age. Her oxygen requirement resolved at 12 months, but she developed mild intermittent asthma at 14 months of age. Left lower lobe pneumonias occurred at 2.5, 7.5, 9 and 9.5 years of age. Body weight rose from the 5th centile at 12 months to the 20th centile at 3 years, and 95th centile at age 6 and beyond. Height increased from the 35th centile at 3 years to the 40th at 5.5 years, and 75th centile at age 9. Menarche occurred at age 10. She has
done well in school with no behavioral problems or special needs. Thus, brain imaging and audiometry have not been repeated.

Because of her poor performance at chelation but fell to 54 after surgical removal of 1 gm of lead, and to 40 mcg/dL without further treatment. However, she has required medication for hypertension and depression.

Despite severe birth defects, which appear related to congenital lead poisoning, the child has developed normally and is functioning well. The role of early chelation in her clinical improvement is debatable. Her mother’s spine surgery stabilized what might have been structural and functional deteriorations from toxic effects of lead on bone.

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PREVENTION OF IN UTERO NICOTINE-INDUCED BONE MARROW MESENCHYMAL STEM CELL (BMSC) MYOFIBROBLAST DIFFERENTIATION BY AUGMENTING LIPOFIBROBLAST PHENOTYPE

P. Guo, E. Cruz, K. Chap, S. Mittal, J. Torday, V. Rehan

Purpose of Study: Alveolar lipofibroblasts (LIFs) are critical for lung homeostasis and injury/repair. Our laboratory has recently shown that in utero nicotine exposure drives the differentiation of LIFs to a myofibroblasts (MYFs). Under appropriate conditions, BMSCs can differentiate into a wide variety of tissues and have recently been shown to be important for lung repair. However, whether BMSCs can be preferentially driven to a lipofibroblastic phenotype is not known. We hypothesized that in utero nicotine exposure blocks offspring BMSC lipogenic differentiation and drives these cells towards a MYF phenotype. Further, peroxisome proliferator-activated receptor (PPAR)γ agonists can prevent in utero nicotine-induced MYF differentiation of BMSCs and drive these cells to a lipofibroblastic phenotype.

Methods Used: Sprague Dawley dams were given 1 mg/kg nicotine from the 3rd day of pregnancy until term (day 22). After spontaneous delivery, pups were given either 1 or 3 mg/kg RGZ, or equal volume of saline (control) from postnatal day 1 to 3 weeks. 3 week old pups were sacrificed and BMSCs were isolated and characterized for their morphologic, molecular, and functional characteristics by Oil Red O staining, Western blotting, real time PCR, triolein uptake, and 1,2-3H-glucose labeling.

Summary of Results: BMSCs isolated from control animals were >95% CD45(-), CD73(+), and CD90(+), confirming their mesenchymal, but non-endothelial origin. In utero nicotine exposure resulted in decreased Oil Red O staining, triolein uptake, oxidative/non-oxidative ribose synthesis, PPARγ expression by BMSCs, but markedly increased α-SMA expression; all features, suggestive of in utero nicotine-induced lipo-to-MYF transdifferentiation (F < 0.05 for all, nicotine vs control). More importantly, concomitant treatment with the PPARγ agonist RGZ virtually blocked all of these nicotine-induced morphologic, molecular, and functional changes.

Conclusions: BMSCs can be directionally induced to differentiate into the lipofibroblastic phenotype, and PPARγ agonist can effectively block in utero nicotine-induced lipo-to-MYF transdifferentiation, suggesting a possible molecular preventive and/or therapeutic approach to prevent in utero nicotine-induced lung injury. (Grant Support: NIH-HL 75405, HL55268, TRDRP-14RT-0013).

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A NOVEL MECHANISM FOR BLEOMYCIN-INDUCED PULMONARY FIBROSIS: SELECTIVE APOPTOSIS OF BONE MARROW MESENCHYMAL STEM CELL-DERIVED LIPOFIBROBLASTS

E. Cruz, K. Chap, P. Guo, J. Torday, V. Rehan

Purpose of Study: Bone Marrow-Derived Mesenchymal Stem Cells (BMSCs) have recently been suggested to play an important role in pulmonary fibrosis, both as a contributor to fibrosis-associated myofibroblasts (MYFs) and as an important mediator in injury/repair. However, selective contributions of naive BMSCs and lineage specific BMSCs to these processes are not known. We hypothesized that naive BMSCs and lineage-specific BMSCs will have selective and different roles in the pathogenesis of pulmonary fibrosis. The purpose of this study was to examine MYF differentiation following bleomycin treatment of naive and lipofibroblast-directed BMSCs.

Methods Used: Following standard methods, BMSCs were obtained from female Sprague Dawley rats. Two passage cells were confirmed to be BMSCs by characteristic stem cell markers via flow cytometry and immunohistochemistry. The cells were treated with bleomycin (0.2, 2, and 20 mcg/ml) in the absence or presence of lipofibroblast induction medium (α-MEM+10% FBS + 1 μM dexamethasone + 0.5 mM 3-isobutyl-1-methylxanthine) and harvested 72 h later for Western blotting, RT-PCR, immunofluorescence, and apoptosis assays.

Summary of Results: Isolated BMSCs were >95% CD45(-), CD73(+), and CD90(+), confirming their mesenchymal, but non-endothelial origin. Lipofibroblast induction resulted in small spindly BMSCs transforming into large round adipocyte-like cells, with lipid droplets (ORO+) in >50% of cells, accompanied by a significant increase in PPARγ and significant decrease in α-SMA mRNA and protein expression. TUNEL assay showed that bleomycin treatment resulted in marked apoptosis in only lipofibroblast differentiation, but not naive BMSCs, in a dose-independent manner. BeLC/Bag, pAKT, and nuclear translocation of β-catenin further confirmed apoptosis and Wnt signaling activation in only lipofibroblast differentiation, but not naive BMSCs.

Conclusions: Bleomycin causes selective apoptosis and transdifferentiation of lipofibroblast-directed BMSCs to MYFs, whereas naive BMSCs are resistant to these changes, providing novel insights into pathogenesis and potential targets for pulmonary fibrosis. (Grant Support: NIH-HL 75405, HL55268, HD051857, TRDRP-14RT-0013, 1517-0250, 17R-0170).

Neuroscience II
Concurrent Session
8:30 AM
Saturday, January 31, 2009

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THE BRAIN’S RESPONSE TO TUMORS IN LANGUAGE AREAS: FMRI OF PRESURGICAL PATIENTS

A. Alexander-Bloch, S. Bookheimer

Purpose of Study: To investigate the effect of brain tumors in language areas on the functional MRI signal of ipsilateral and contralateral language centers.

Methods Used: Forty-three consecutive surgical patients were subdivided into 17 with tumors in Broca’s Area (BA), the opercular and triangular sections of the left hemisphere inferior frontal gyrus; 12 in Wernicke’s Area (WA), the posterior part of the superior temporal gyrus and the supramarginal gyrus; and 14 controls tumors in neither area. Scanning with language tasks included two comprehension with naming tasks (one auditory and one with printed cues) and an object naming with verb generation task, using a 3T Siemens Allegra with an EPI sequence (matrix 64 × 64 × 28, voxel 3.13 × 3.13 × 3.99 mm, TR 2500 ms, TE 25 s). Motion correction, linear model parameter estimation, and registration used the FSL software library. BA and WA were defined in a standard anatomical space, transformed into subject space, and manually repositioned if mass effects interfered with the normalization algorithms. Activation in the region of interest was measured as mean percent signal change and volume of activated brain over a percent change threshold.

Summary of Results: The difference in activation between BA and contralateral BA decreased in patients with BA tumors relative to the control tumors, in all the tasks. This difference was driven by decreases in ipsilateral BA, and was proportional to the proximity of the tumor to BA. Contralateral BA decreased in activation with ipsilateral BA, even though the tumors did not impinge directly on the contralateral area. WA showed increased activation proportional to tumors’ proximity to BA, especially for the auditory naming task, which was the best activator of WA. For tumors in WA themselves, as a contrast statistic reached significance.

Conclusions: The decrease in fMRI signal in BA points to vascular irregularities or an interruption of neural activity, which must be distinguished from decreases due to the brute presence of the tumor in the region of interest. The effects of BA tumors on the activation of ipsilateral WA and contralateral BA points to the functional interconnectedness of these areas. The lack of clear results for WA tumors reflects the more diffuse organization of processing in posterior receptive language regions.
437 EFFECT OF GLATIRAMER ACETATE ON EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS

V. Reece¹, M. Kala², F. Shi² ¹University of Arizona College of Medicine, Tucson, AZ and ²Barrow Neurological Institute, Phoenix, AZ

Purpose of Study: This study’s purpose is development of Enzyme Linked Immunoabsorbant Assay (ELISA) for mice induced with experimental autoimmune encephalomyelitis (EAE). Multiple sclerosis (MS) is classified as an immune-mediated demyelinating disease of the central nervous system (CNS). Morbidity and mortality associated with MS is primarily due to axon destruction in a Th1 (proinflammatory) response. EAE is induced in mice after injection with MOG 35-55 peptide. The mice develop symptoms close if not very similar to MS in patients. Glatiramer acetate (GA), a synthetic copolymer, is used for the treatment of relapsing remitting multiple sclerosis.

Methods Used: To examine GA’s pre-treatment effect on EAE mice, we injected 5 C57BL/6 mice with GA (100 ug) for 7 consecutive days followed by induction of EAE with MOG peptide. Sera of GA treated and untreated mice were assayed for IgG1, IgG2a and IgG2b by using ELISA.

Summary of Results: GA treated mice showed increased levels of IgG1 in comparison to untreated EAE mice (Fig. 1a,b). IgG2b and IgG2a levels in the GA mice were lower than that for the untreated mice. The untreated mice had the highest levels of IgG2b.

Conclusions: Data indicate that mice treated with GA had an increased Th2 response and a decreased Th1 response, which is consistent with previous studies showing that GA promotes development of anti-inflammatory type II monocytes. The protocol and set up used for the ELISA can be considered proper.

438 MITOXANTRONE RESCUE

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Purpose of Study: To determine whether Mitoxantrone can be used effectively to treat acute demyelinating attacks of optic neuritis and transverse myelitis.

Methods Used: Retrospective chart review of all previously treated patients (18) at the UBC Multiple Sclerosis Clinic. Patients presenting with acute attacks of optic neuritis and/or transverse myelitis were given standard first line therapies such as prednisone and/or plasmapheresis. Patients failing these therapies were subsequently tried on mitoxantrone. These patients were reviewed for their outcomes based on accepted clinical measures at defined time intervals.

Summary of Results: 85% of treated patients showed a moderate to marked improvement of their symptoms within 1 year on the mitoxantrone therapy used (that is, they had an objective and significant gain in their function relative to pre treatment).

Conclusions: Mitoxantrone is a chemotherapeutic agent that shows promise in treating acute attacks of optic neuritis and or transverse myelitis in patients who have previously failed other therapies.

439 A NOVEL MURINE MODEL OF PRIMARY DEMYELINATING NEUROPATHY

A. Hazel¹, M.E. Bathen², W. Palipsi³, L.S. Rummler¹, E. Strandberg¹, T. Mozaffar², R. Gupta¹ ¹University of California, Irvine, Irvine, CA and ²University of California, Irvine, Irvine, CA

Purpose of Study: Chronic nerve compression (CNC) injuries such as carpal tunnel syndrome affect millions yet many questions remain concerning the pathogenesis of these disorders. In order to further our understanding of common compressive neuropathies, we created a novel murine model of a primary demyelinating neuropathy. This will allow us to study specific genes and gene products related to the myelination and axonal regeneration process.

Methods Used: Five-week, male C57BL/6 mice were anesthetized with ketamine/xylazine. Sciatic nerves were exposed dorsally through a gluteal-splitting approach. The right sciatic nerve was mobilized and returned to its host bed to serve as a surgical control. Weekly electrophysiological recordings were performed in vivo. Sciatic nerves were harvested at 2 and 6 weeks after surgery, embedded in Spurr Resin, and cut in 1-µm sections. With light microscopy, g-ratios (ratio of axon to total fiber diameter) of all axons were calculated from nerve cross sections. The student’s unpaired t-test was used for statistical analysis.

Summary of Results: The average conduction velocity (CV) in normal nerves was 54.71mV/ms [standard deviation (SD) 1.65]. The average CV value was 33.24mV/ms (SD 11.94) two weeks post-CNC injury, which declined to 16.06mV/ms (SD 2.58) six weeks post-CNC injury. The observed decrease in NCV was accompanied with minimal changes in amplitude. Average normal g-ratio was 0.623 (SD 0.096). CNC axons displayed a gradual increase in g-ratio, signifying a decrease in myelination. Average g-ratio 2 weeks post-CNC was 0.719 (SD 0.078), and the average g-ratio 6 weeks post-CNC was 0.792 (SD 0.058).

Conclusions: In humans, chronic nerve compression is characterized by a decrease in nerve conduction velocity with minimal loss of amplitude over time. In the present study, we have developed a novel murine model that recreates these findings. With this new model, it will be possible to advance our current understanding of Schwann cell response to injury and the process of demyelination after compressive neuropathies.

440 THE SEARCH FOR TGF-BETA IN APYLSIA

S. Lundy¹, M. Habibª, J. Byrne² ¹University of Washington, Shoreline, WA and ²University of Texas Medical Branch at Houston, Houston, TX

Purpose of Study: Consisting of more than 30 unique proteins, the Transforming Growth Factor-β (TGF-β) superfamily is involved in a multitude of critical metabolic pathways in the cell, including development, wound healing, angiogenesis, and oncogenesis. The archetypal member of this family is Transforming Growth Factor-β (TGF-β) sensu stricto, a cytokine
441 DNA MICROARRAY ANALYSIS OF MELANOPSIN-CONTAINING RETINAL GANGLION CELLS

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Purpose of Study: The circadian pacemaker in the mammalian suprachiasmatic nucleus is synchronized with the solar cycle by direct synaptic input from a small subset of retinal ganglion cells (RGCs). These RGCs contain the novel photopigment, melanopsin, and are intrinsically photosensitive. Due to the scarcity of these cells (~2000/retina), it has proven difficult to elucidate the melanopsin-based phototransduction cascade. The recent production of a mouse strain expressing GFP in the melanopsin-containing (m)RGCs has enabled us to use florescence-activated cell sorting (FACS) to generate highly-enriched cell populations for differential gene expression profiling.

Methods Used: Transgenic mice were constructed that express GFP in the mRGCs. Retinas from transgenic and control mice were dissociated by treatment with papain, yielding a suspension of single cells. FACS analysis was performed on 1000 GFP-positive cells. Control RGCs were specifically labeled with the Thy-1 marker and purified by FACS. Total RNA was isolated from both cell populations, converted to cDNA, and amplified in a linear fashion. This cDNA was applied to an Illumina mouse-6 v1.1 array, containing probes for 94,000 genes and expressed sequence tags. Hybridization results were analyzed using "Genesifter" (VizXLab).

Summary of Results: As expected, the melanopsin transcript (Opn4) was enriched in mRGCs by 31-fold over whole retina, and 17-fold over the total RGC population. The transcript encoding the pituitary adenyl cyclase activating peptide (PACAP), another marker for the mRGCs, was also enriched by 38-fold over whole retina and 14-fold over the RGCs. In contrast, the relative abundance of standard photoreceptor markers was reduced by 10- to 20-fold in the mRGCs. Furthermore, TRPC7, previously reported to be enriched in mRGCs, was enriched 9-fold over total retina, and Gq14 (G protein isoform) was enriched 11-fold over total retina (10-fold over RGCs).

Conclusions: Elucidation of the melanopsin-based signaling pathway is crucial to the understanding of circadian photentrainment. Our study has identified several candidates as potential components of the phototransduction cascade; future functional characterization studies will be required to confirm their role.

442 NEURAL STEM CELL RESPONSE AND NESTIN DNA METHYLATION STATUS IN NEWBORN RAT BRAINS AFTER INTRAUTERINE GROWTH RESTRICTION

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Purpose of Study: Intrauterine growth restriction (IUGR) causes long-term neurodevelopmental delays, with males particularly vulnerable to injury. In addition, animal studies of IUGR show significant decreases of mature neurons. Since neurons are descendants of neural stem cells (NSCs) and NSC response after IUGR is not understood, we investigated the effects of IUGR on NSCs by determining the expression of nestin, an intermediate filament predominantly expressed in NSCs. We hypothesized that IUGR decreases nestin expression with DNA hypermethylation as a potential epigenetic mechanism of downregulation.

Methods Used: IUGR offspring was produced through uteroplacental insufficiency (UPI) by bilateral uterine artery ligation in pregnant Sprague-Dawley rats at E19 (term = 21.5 days). Nestin mRNA expression at term was determined by quantitative real-time RT-PCR (n = 10/group). Nestin protein expression was assessed by immunofluorescent histochemistry of the subventricular zone of lateral ventricle (LV) and dentate gyrus (DG) of the hippocampus (n = 6/group). DNA methylation of the promoter of nestin was determined by bisulfite sequencing of whole brain genomic DNA (n = 6/group).

Summary of Results: IUGR females significantly upregulated nestin mRNA expression (P < 0.01) with no difference in nestin immunofluorescence compared to sham females. In contrast, IUGR males despite showing no difference in nestin mRNA, demonstrated a ~45% decrease in nestin immunofluorescence in LV compared to sham males (P < 0.01). Lastly, IUGR and sham offspring showed similar DNA methylation patterns of the nestin promoter immediately upstream of the transcription start site.

Conclusions: To our knowledge, this study is the first to examine NSCs’ response after IUGR. UPI elicits a differential gender-specific response where females increase but males decrease nestin expression. The congruent DNA methylation pattern of this promoter region between sham and IUGR provides evidence that epigenetic regulation is not confined to the promoter. Regions outside of the promoter may also modulate gene expression. We speculate that intron 2, which harbors an enhancer element critical to the generation of central nervous system progenitor cells, may be important in the epigenetic regulation of nestin expression.
Conclusions: Correlation of neural firing in L2/3 neurons of barrel cortex decreases abruptly after postnatal day 12. Correlation of firing is related to distance between cells, and this relationship decreases with postnatal age. Neuronal decorrelation persists under anesthesia states that resemble natural sleep. Sparse firing of neurons after P12 may allow more efficient coding of information by the cortex.

444 PRESENCE OF NETRIN-1 RECEPTORS IN POSTNATAL RAT COCHLEA AGED 21 DAYS OR OLDER

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Purpose of Study: During synaptogenesis a number of growth factors and peptides control the guidance of auditory neuronal axons to their target cells. Netrin 1 peptide plays an important role in guiding axonal growth from Spiral ganglion cells (SGNs) in the embryonic and early post-natal age to their target cells. In this study, we hypothesized that the presence of netrin 1 peptide receptors in postnatal rats spiral ganglion cells at the age of 21 days or older would support the role of netrin 1 peptide at these ages as well.

Methods Used: Postnatal Wistar rats were used as the experimental subjects for this study. Spiral Ganglion cells were taken from rats at the postnatal age 21 to 25 days. Spinal cord cells from postnatal rats age 21 to 25 days were used as positive controls. Rats were dissected and spiral ganglion cells were isolated and cultured according to protocol. Immunohistochemistry was performed according to protocol. HRP-conjugated secondary antibodies were used. Properly stained cells were then seen using fluorescent microscopy.

Summary of Results: No netrin-1 peptide receptors were detected in spiral ganglion cells in postnatal rats age 21 to 25 days. Netrin-1 peptide receptors were detected in spinal cord samples from postnatal rats age 21 to 25 days. Some cell cultures from postnatal rats age 21, 22 days showed staining for netrin -1 receptors but this was not statistically significant. Results were consistent in multiple cycles of cell culture and Immunohistochemistry studies.

Conclusions: This study showed that postnatal rats age 21 and older have very little to no expression of netrin-1 receptors. Although netrin-1 may be involved in guiding axonal growth in the embryonic and early postnatal life, it is unlikely that it plays a role in axonal growth at more advanced ages when synaptic connections are already established.

Pulmonary and Critical Care II
Concurrent Session
8:30 AM Saturday, January 31, 2009

445 A COMPLICATED CASE OF SECONDARY SPONTANEOUS PNEUMOTHORAX: EARLY RECURRENT PREVENTION IS KEY

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Case Report: A 63 year-old man with severe COPD presents with acute shortness of breath. Chest radiograph reveals large pneumothorax. A chest tube is placed, and repeat radiograph demonstrates re-expansion of the lung. On day 3, the chest tube is connected to a water seal, after which he develops diffuse chest subcutaneous emphysema. His 16F tube is then replaced with a 24F tube, which subsequently kinks, and the pneumothorax redevelops. On day 8, the patient again develops pneumothorax that resolves after the chest tube is flushed. The next day the tube is again replaced. On day 12, a pleurodesis is performed after insertion of yet another chest tube. Secondary Spontaneous Pneumothorax(SSP) is a well known and deadly complication of COPD, with recurrence rates without a preventative intervention reaching 43%. This case illustrates the need to follow the American College of Chest Physicians(ACCP) consensus statement on the management of SSP. After SSP the ACCP recommends early pleurodesis or bullectomy to prevent recurrence. Early SSP recurrence prevention can reduce unnecessary procedures and shorten hospital stays.

446 OCTREOTIDE FOR PLEURAL EFFUSIONS IN INFANTS AND CHILDREN FOLLOWING CONGENITAL HEART SURGERY

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Purpose of Study: Pleural effusions and chylothorax occurring after pediatric cardiothoracic surgery lead to complications including respiratory distress, fluid loss, and immunodeficiency. Octreotide has been used for the treatment of chylothorax with varying success. This study analyzes octreotide use and decreased chest tube output in children who develop persistent pleural effusions after heart surgery.

Methods Used: We retrospectively reviewed all patients who received octreotide for pleural effusions >5 ml/kg/day for more than five days after pediatric congenital heart surgery from 2000-2006. Demographics, surgical characteristics, chest tube output, dosing and adverse effects of octreotide, and outcome such as thoracic duct ligation and mortality were collected. Two groups were then separated: responders (R) with decrease in chest tube output by day three, and nonresponders (NR). Two-tailed t-tests of independent samples were used to determine statistical significance.

Summary of Results: 29 patients who received octreotide after surgery were included. Mean age at time of surgery was 65.7 weeks (range: 1 day-7 years). Mean dose of octreotide infusion was 1.8 mcg/kg/hour (range: 0.2-8 mcg/kg/hour). Baseline chest tube output was 47.3 ± 8.2 ml/kg/day which by day 2 decreased to 36.3 ± 8.1 (P < 0.5). The NR group (12 patients) had day 1 and 2 values of 62.1 ± 16 and 58.9 ± 15.4 respectively, while the R group (17 patients) decreased from 36.8 ± 9.4 to 21.7 ± 8 (P < 0.05). On day 14 the NR group was 45.3 ± 16.2. A significant difference was noted from day 2 and beyond. No adverse events were associated with octreotide use.

Conclusions: Octreotide can be safely used for treatment of postoperative pleural effusion in infants and children following congenital heart surgery. Although a decrease in chest tube output was seen in the total population, a decrease in chest tube output by day 3 was predictive of a significant positive response. With the absence of a control group, it is unknown if a similar decrease would have occurred in this subgroup without octreotide. A prospective, randomized trial would be necessary to accurately define responses.

447 BALLOON DILATION OF COARCTATION OF THE AORTA IN NEONATES WEIGHING <2,500 GRAMS

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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 results of balloon angioplasty (BA) in a group of newborns with discrete CoA and weight <2,500 grams. Coarctation of the aorta (CoA) in premature infants with very low birth weight is a therapeutic challenge. Compared with normal sized neonates, surgery is associated with increased risk and a higher restenosis rate.

Summary of Results: The mean age at BA was 14 days (range: 9-20 days); the mean weight was 1,900 grams. (range: 790 to 2,500 grams). The average minimum diameter increased from 1.5 to 3.3 mm and the average gradient decreased from 37.7 to 10.8 mm Hg. There were no procedural complications. Mean follow-up was 30 months after BA (range: 7 to 48 months). Three of 6 patients did not require further intervention; they had a mean follow-up of 39 months (range: 31 to 48 months) after BA. The other 3 patients required a second BA within 2 to 3 months and 2 patients required surgical correction of the CoA to 3 months later. One patient required repeat BA 2 months after surgery.

Conclusions: Selected neonates weighing ≤2,500 grams with discrete CoA respond well to BA. Others appear to develop restenosis rapidly, even after surgical repair. The risk factors for restenosis in this group of patients remain to be elucidated.

448 SIMVASTATIN ATTENUATES ALLERGIC AIRWAY INFLAMMATION AND BRONCHIAL HYPERREACTIVITY
A.A. Zeki1,2, N.J. Kenyon1,2
1University of California, Davis Medical Center, Sacramento, CA and 2Center for Comparative Respiratory Biology & Medicine (CCRBM), Davis, CA

Purpose of Study: Statin use has been linked to improved lung health in asthma and COPD. The statin drugs have pleotropic immunomodulatory effects beyond cholesterol-lowering. We hypothesize that statins inhibit allergic airway inflammation and reduce bronchial hyperreactivity (BHR).

Methods Used: BALB/c mice were sensitized to ovalbumin (OVA) over 4 weeks, then exposed to 1% OVA aerosol over 2 weeks. Mice were treated with simvastatin (Sim) 40 mg/kg and mevalonate (MA) 20 mg/kg. Sim or Sim+MA were injected intraperitoneally before each OVA exposure. Lung physiology measurements were made using a plethysmograph for restrained animals. Bronchoalveolar lavage fluid (BALF) cytokines were measured using multiplex assays.

Summary of Results: Simvastatin reduced BALF total cell counts by 60% in the OVA-exposed mice (P = 0.0073). This inhibition of leukocyte influx was reversed in the Sim+MA group (P = 0.0026) to OVA control levels. BALF differential cell counts including eosinophils (P < 0.05), lymphocytes (P < 0.05), and macrophages (P < 0.05) showed a similar pattern (reduced inflammation with Sim and reversal of this effect with Sim+MA). OVA-exposed BALF IL-4 (P = 0.030) and IL-13 (P = 0.035) were significantly reduced after Sim treatment. In the OVA groups at baseline, lung compliance was significantly higher in the Sim group (P < 0.05), but there was no significant difference in airway resistance. Following mevalonate balloon inflation in OVA-exposed mice, lung compliance was significantly higher in the Sim-treated group (P = 0.0001), and BHR was significantly inhibited by Sim treatment (P = 0.0001).

Conclusions: Simvastatin attenuates allergic airway inflammation, inhibits key Th2 chemokines, and improves lung physiology. These data demonstrate for the first time the beneficial effects of simvastatin on lung compliance and BHR in the OVA mouse model. Reversal of the protective Sim effect seen in the Sim+MA group implicates the MA pathway in modulating asthmatic inflammation. These inhibitory effects of simvastatin may be beneficial for the treatment of asthma.

(Supported by the following grants: NIH HL07013, NCRR UL1 RR024146, HL-076415, and VA Medical Center).
Methods Used: Freshly isolated sputa obtained from CF patients (n = 20; 19-67 yrs) and exhibiting a wide range of MPO levels were incubated with varying concentrations of ascorbic acid, GSH, NAC, GSNO, trolox and mannitol and their 50% inhibitory concentrations (IC50) of MPO activity were determined. Correlations of sputum MPO activity with pulmonary function were also carried out.

Summary of Results: Not unexpectedly, the higher the level of sputum MPO, the higher the required antioxidant IC50 for MPO inhibition. Unexpectedly, MPO activities in sputa were found to be inversely correlated with measurements of lung function.

Conclusions: Sputum MPO activities represent an important determinant for efficacious “antioxidant” therapy dosing in CF. Presumably, this would also hold for the case of antiprotease therapies. MPO levels appear to present an important biomarker of the increased inflammatory processes occurring in advancing CF lung disease.

452 PROSPECTIVE, RANDOMIZED DOUBLED BLOOD STUDY TO TEST VITAMIN A TREATMENT IN PATIENTS WITH SEPSIS
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Purpose of Study: To test the benefits of Vitamin A treatment in patients with sepsis on length of stay in ICU, days on mechanical ventilation, days on vasopressors, and 28-day mortality.

Methods Used: Prospective, randomized and double-blind trial. Sixty three patients with sepsis were randomized to receive either 50,000 IU of Vitamin A intramuscular or placebo over 7-days. Data analysis was by ANOVA with two tailed test and P < 0.05 as significant.

Summary of Results: The mean age of the patients was 51±2 (mean±SEM) and 54% were female. Serum Vitamin A concentration was below normal in 54% of the patients tested (n = 35). Table 1 describes the two groups with regard to baseline APACHE III score, baseline WBC, and percent of patients with bacteremia. Vitamin A was given to 32 patients and placebo was given to 31 patients. The average number of days of the ICU prior to entry into the study was similar for both groups (5.8±2.8 vs 4.0±1.1 days; placebo vs Vitamin A, respectively). Days on the ventilator prior to entry into the study were also similar (3.8±1.9 vs 3.2±1.0, placebo vs Vitamin A, respectively).

Conclusions: The number of days in the ICU was slightly, but not significantly (P = 0.17), reduced in Vitamin A treated patients. The average number of days on vasopressors, the number of days on the ventilator and the 28-day mortality rate were also not significantly different between the treatment groups. Vitamin A treatment in septic adult patients failed to significantly reduce the number of days in the ICU, days on the ventilator, days on vasopressor therapy or 28-day mortality. Seven days of high dose Vitamin A treatment has no benefit in adults with sepsis.

<table>
<thead>
<tr>
<th>Groups</th>
<th>APACHE III</th>
<th>Bacteremia</th>
<th>Days in ICU</th>
<th>Days on Vasopressors</th>
<th>Days on Ventilator</th>
<th>28-Day Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>45±4</td>
<td>19.3±2.8</td>
<td>7.6±1.1</td>
<td>1.5±0.6</td>
<td>4.5±1.0</td>
<td>34±9%</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>44±5</td>
<td>14.7±1.5</td>
<td>5.6±1.0</td>
<td>1.7±0.8</td>
<td>5.0±1.0</td>
<td>42±9%</td>
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</tbody>
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453 LIPOPOLYSACCHARIDE-INDUCED LUNG INJURY IS INDEPENDENT OF ALVEOLAR EPITHELIAL CASPASE ACTIVATION IN MECHANICALLY VENTILATED MICE
B. U’Ren1,2, S. Gil3, A. Farnand3, G. Matute-Bello2,3,1 University of Washington School of Medicine, Seattle, WA; Veterans Affairs Puget Sound Health Care System, Seattle, WA and 3UW Medicine Research, Seattle, WA

Purpose of Study: Acute lung injury (ALI) and its more severe form, the acute respiratory distress syndrome (ARDS), are characterized by neutrophilic alveolitis and destruction of the alveolar epithelium, often in the setting of a local or systemic inflammatory process. The mechanism of ALI/ARDS has not been fully elucidated; however, previous work shows that lipopolysaccharide (LPS)-induced lung injury is decreased in mechanically ventilated mice lacking the Fas receptor, suggesting involvement of the Fas/Fasl system. One of the canonical signaling pathways of Fas involves proteolytic activation of a series of cysteine proteases known as caspases. The goal of this study was to determine whether caspase-dependent apoptosis is required for the development of LPS-induced lung injury.

Methods Used: We used double transgenic mice that express the baculoviral pan-caspase inhibitor p35 in alveolar epithelial cells in the presence of doxycycline (CSSP-p35/eta/o-p35). Mice treated with or without doxycycline received intratracheal instillations of E. coli LPS, 0.015 ng/g i.t. Immediately afterwards, the mice were exposed to mechanical ventilation for 4 hours at TV = 10 cc/kg, PEEP = 3 and FiO2 = 0.21, with RR adjusted to keep the ETCO2 at 40. Measurements of lung injury included total PMN counts in bronchoalveolar lavage fluid (BALF), lung homogenate myeloperoxidase (MPO) and lung caspase-3 activity.

Summary of Results: The total PMN count was 1.8 ± 0.9 × 106 cells in the doxy-treated mice, and 1.5 ± 0.5 × 106 cells in the control (non-doxo treated) mice (p = NS). Lung MPO and caspase-3 activities were similar in both groups of mice.

Conclusions: Our study suggests that caspase activation in the alveolar epithelium does not play a role in the inflammatory response of ventilated mice to LPS.

Surgery II
Concurrent Session
8:30 AM
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454 EFFECTIVENESS OF THE PAIN PUMP FOR POSTOPERATIVE PAIN MANAGEMENT IN CHILDREN WITH CEREBRAL PALSY
S. Recktenwall-Work1, K. Muthusamy1, R.M. Friesen1, J. Zuk1,2, J. Gralla1, N.H. Miller1,2, J.L. Galinkin1,2, F.M. Chung1,2 The Children’s Hospital, Aurora, CO and 2University of Colorado Denver School of Medicine, Aurora, CO

Purpose of Study: Children with cerebral palsy (CP) frequently undergo orthopedic surgical intervention to correct skeletal deformities and address soft tissue contractures. These children often also have associated communication impairments that make pain assessment challenging for caregivers and health care providers. Effective postoperative pain management is vital for comprehensive surgical care in this vulnerable patient population where children may suffer from unrecognized pain and under medication. This prospective, randomized study evaluated a local anesthetic continuous infusion device (pain pump) for the management of postoperative pain in children with CP following lower extremity orthopedic procedures.

Methods Used: Children with a diagnosis of CP undergoing ambulatory lower extremity orthopedic procedures were included in this study. Following IRB approval and consent, subjects were randomized into an experimental group receiving a pain pump with oral analgesics, or a control group receiving oral analgesics only. For four days, subjects’ parents recorded pain intensity using a modified visual analog scale (VAS), and the amount of oral analgesics administered. The mean daily differences between the two groups were analyzed using a t-test.

Summary of Results: Fifty-four subjects were enrolled, with complete pain diaries returned for 37 subjects. The mean daily pain intensity, as measured by parent report VAS score, was significantly higher in the control group than the postoperative day 2. The mean amount of oral analgesics administered on each day was higher for subjects in the control group, although these results did not reach statistical significance.

Conclusions: Incorporation of the pain pump in postoperative pain management for children with CP was shown to be an effective method to significantly reduce pain intensity following orthopedic surgical procedures. Children with CP demand unique pain management considerations due to a
complex presentation of spasticity, cognitive impairments and communica-
tion limitations. The addition of the pain pump to currently accepted anaphylactic practices has the opportunity to substantially improve postoperative care in this challenging patient population.

455 REFERENCE ACCURACY AND ITS ASSOCIATION WITH IMPACT FACTOR IN THE GENERAL SURGERY LITERATURE

J. Awrey, K. Inaba, G. Barmparas, G. Recinos, P. Teixeira, B. Schmuerger, L. Chan, D. Demetrias University of Southern California, Los Angeles, CA

Purpose of Study: Several studies have demonstrated that the references utilized in scientific articles often contain both citational and quotational errors. While some of these errors are insignificant, major errors bring the scientific validity of the research into question. These errors may also create difficulty in accessing the cited background data and perpetuate misleading information. The objective of this study was to examine reference accuracy in the general surgery literature, and to examine whether reference accuracy correlates to journal impact factor.

Methods Used: Five general surgery journals were chosen with varying impact factors. From the year 2007, one issue was randomly chosen from each journal, and from each issue, 73 citations were randomly chosen for review. Two independent, blinded investigators evaluated the chosen references for each journal using an algorithm that assessed both citational and quotational accuracy. The impact factor of each journal was compared to the percentage of errors detected within the journal.

Summary of Results: The total number of errors per journal ranged from 13.1-24.7%, with a total of 21.1% of all citations reviewed containing some type of error. The most common error type detected was incorrect citation of the primary source supporting a statement, which ranged from 8.5-15.5% depending on the journal, and accounting for 57.5% of the total errors found. Citational errors, which included incorrect author names, pagination, dates, issue and volume numbers, ranged from 0.0-1.4% and accounted for 5.7% of the total errors detected. Qualitative errors, which occurred when the author misquoted another author’s written assertions or conclusions, ranged from 2.0-8.2% and accounted for 27.6% of the total errors detected. Quantitative errors, which occurred when the author misquoted numerical data, ranged from 0.0-5.5% and accounted for 9.2% of the total errors detected. No association between impact factor and error rate was seen.

Conclusions: Errors of all major types were found in the journals reviewed. However, citing a non-primary source was the most common error detected in all journals. Impact factor had no clear association with the rate of error.

456 THE SIZE OF BOVINE JUGULAR VENOUS CONDUITS IN RIGHT VENTRICULAR RECONSTRUCTION DOES NOT AFFECT OUTCOME OR LONGEVITY

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Purpose of Study: Reconstruction of the right ventricular outflow tract (RVOT) remains a challenge, especially in pediatric patients. Common surgical management involves the introduction of an artificial graft between the right ventricle (RV) and the pulmonary artery (PA) but long term outcomes are significantly limited by the valved conduit - porcine xenografts lack durability, homografts lack availability in small sizes and calcify, and Contegra bovine jugular vein (BJV) xenografts suffer from distal stenosis. This study evaluates the use of the Contegra BJV conduit in RVOT reconstruction in pediatric patients.

Methods Used: Between March 2001 and June 2007, 44 Contegra conduits were implanted as a RV to PA conduit in 40 pediatric patients (4 were replaced). There were 14 females and 26 males. Mean age at implantation was 4.0 ± 5.2 years (range, 5 days to 24.2 years); mean body weight at implantation was 13.8 ± 10.0 kg (range, 2.74 to 47.5 kg). 23 conduits were inserted as a primary repair and 21 conduits were inserted to replace a prior conduit (n = 17) or a prior monocusp patch (n = 4).

Summary of Results: There were 3 mortalities (1 early death and 2 late deaths). The early death occurred 8 days post-operatively in a patient who developed low output syndrome immediately following implantation. Later deaths occurred 7 months and 11 months post-operatively from cardiac arrests. At 48 months, overall freedom from reintervention rate was 85.0% (n = 6) and survival was 92.5% (n = 37). For patients less than one year of age at implant (n = 11), freedom to substantially improve postoperative care in this challenging patient population.

457 NOVEL IN VITRO MODEL FOR THE STUDY OF EPITHELIAL CELL INJURY DUE TO URETERAL STENTS

C. Elwood1,4, D. Lange1, S. Seeney2, B. Chew3, K. Summers4,3, J. Denstedt1,2, P. Cadieux2,3,4 1University of British Columbia, Vancouver, BC, Canada; 2University of Western Ontario, London, ON, Canada; 3University of Western Ontario, London, ON, Canada and 4Lawson Health Research Institute, London, ON, Canada

Purpose of Study: The placement of ureteral stents following a large number of procedures has become common practice in urology however they are associated with high amounts of morbidity. Patients with stents have far more urinary tract symptoms (flank pain, voiding frequency, urgency, dysuria and hematuria) compared to non-stented patients. It is unclear if these symptoms are associated with infection or mechanical trauma due to an indwelling device. In this study we sought to develop an in vitro method to evaluate inflammation in response to mechanical injury due to abrasion of bladder and kidney epithelial cell monolayers. For this we tested the anti-inflammatory properties of Tiviclosan in the context of the bladder and kidney.

Methods Used: Mechanical injury was tested using a 2 cm piece of either the Percuflex or Triumph® (impregnated with the antibiotic tiviclosan) stent in A498 kidney cells or T24 bladder cell monolayers. Following a 1 hr incubation the plate was rotated clockwise until two rotations of the stent pieces was achieved, this was repeated. Cytokine profiles were measured from supernatants after a 1 hr recovery.

Summary of Results: After mechanical injury, bladder cells showed increased levels of IL-8 and basic-FGF. Kidney cells produced IL-8 from 1750 to 1199 pg/ml which was similar to controls (P < 0.05). The production of wound healing cytokines such as basic-FGF was increased in both kidney and bladder cells when comparing Percuflex and Triumph stents from 161 to 684 and 42 to 148 pg/ml respectively (P < 0.05).

Conclusions: Our results demonstrate a simple method for measuring the impact of mechanical injury on inflammation in vitro. This study shows that some of the urinary tract symptoms associated with stent placement are not necessarily due to infection, but rather from the mechanical trauma to uroepithelium. We also show that the inflammatory and growth factors secreted in response to injury are modifiable and that future novel stents should attempt to increase wound healing and reduce inflammation.

458 A BIOMIMETIC SENSATE SCAFFOLD MEASURES LOADING IN A KNEE JOINT

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Purpose of Study: More than twenty million Americans suffer from osteoarthritis. The development of a technique capable of resurfacing damaged cartilage would be a valuable means of restoring function and comfort to these patients. Strain gauged scaffolds will provide support for engineered cartilage and prevent cartilage overloading during rehabilitation.

Methods Used: Images of the medial femoral condyle from a human cadaver were obtained with a high resolution µCT scanner. The images were then inverted, magnified and cropped in order to produce an inverse trabecular structure with a porosity that encourages bone ingrowth. A containment cylinder was added to the inverse trabecular image in order to strengthen the scaffold, allow for strain gauge attachment, and to hold tissue-engineered cartilage. The entire structure was then manufactured with polybutylene terephthalate using a rapid prototyping machine. The strain...
gauges were attached to a micro-miniature telemetry unit. The ‘sensate’ scaffolds were then calibrated in confined compression before being implanted into a cadaver knee and tested with a servohydraulic machine prior to and following cementing of the scaffold in place.

Summary of Results: It was found that the narrow space of the trabecular cores was 55 ± 5% and was similar to the space occupied by the polymer in the manufactured scaffold. Testing prior to cementing of the scaffold revealed a relatively poor correlation between the applied load vs. the measured value (R² = 0.65). This correlation coefficient showed substantial improvement after the scaffold was cemented in place and re-tested (R² = 0.87). These findings indicate that in vivo load monitoring should become more accurate as bone ingrowth anchors the scaffold.

Conclusions: An improved correlation between the applied vs. measured loads was noted following cementing of the scaffold in place which mimics in vivo bone ingrowth. Additionally, it was seen in vivo canine studies that load monitoring increased with bone ingrowth indicating that sensate scaffolds could be used to measure healing. The results of this study suggest that human sensate scaffolds can be used to monitor joint loading in a clinical setting.

We hypothesized that in-line reconstruction of prosthetic graft infection using cryopreserved arterial allografts would be associated with a lower recurrent infection rate, limb loss, and mortality than other reconstruction alternatives previously used at our institution.

Methods Used: We reviewed all adult patients who underwent surgical management of infected prosthetic aortic, iliac, or femoral bypass grafts with cryopreserved arterial allograft at our medical center since it became commercially available.

Summary of Results: Cryo-preserved arterial allografts were used in 9 patients with infected prosthetic grafts in the aorta, iliac, and lower extremity arteries (aortic/central n = 5, distal n = 4). The majority of patients were male (n = 6, 66%), median age was 69 yrs, and median follow-up was 12.1 months. Intraoperative cultures were positive for S. aureus and P. aeruginosa 44%, while 56% had clinical evidence of infection but were culture negative. There have been no recurrent infections or limb loss after in-line repair and no deaths in the follow-up period. There were 3 complications (33%), including pseudoneuromysems formation (n = 1), colonic perforation (n = 1), and lower extremity limb ischemia (n = 1), which required further treatment.

Conclusions: The use of cryo-preserved arterial allografts for in-line repair of infected prosthetic grafts in lower extremity arteries has been associated with no recurrent infection rate, limb loss, or mortality. These encouraging results have resulted in a shift at our institution to the preferential use of cryopreserved arterial allograft with in-line arterial reconstruction for infected prosthetic grafts.

We have engineered a plasmid that expresses the hIDO gene and luciferase under the ROSA26 promoter in transgenic mice. We developed a data abstraction sheet to systematically capture review results. We reviewed all adult patients who underwent surgical management of infected prosthetic aortic, iliac, or femoral bypass grafts with cryopreserved arterial allograft at our medical center since it became commercially available.

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Purpose of Study: Traumatic dislocation of the thumb metacarpal phalangeal joint (MCP) joi nt causes a spectrum of injuries to the ulnar collateral ligament complex (UCLC). Evaluation of the extent of injury to the UCLC of the thumb MCP joint is difficult to determine. Radiologic testing is expensive and may delay treatment. Smith has alluded that the extent of dorsal-volar instability at the thumb MCP joint may provide insight into structures that have been compromised due to injury. This biomechanical cadaveric study demonstrates dorsal-volar instability at the thumb MCP joint following sequential sectioning of the structures that provide ulnar stability at the thumb MCP joint.

Methods Used: Fifteen fresh frozen cadaver hands (8M, 7F, ages 38-59) were used. All thumb MCP joints were diseased free. A specially designed jig was used to secure the specimens in place and to uniformly measure the thumb MCP joint anterior-posterior translation. Load was applied dorsally and volarly and displacement measured. A fixed force of 10N was applied to the proximal phalanx. The moment arm was kept constant throughout the experiment at 1 cm, measured distal to the thumb MCP joint. The displacement was consistently measured at 2 cm distal to the joint. There were three groups tested: thumb MCP joint ulnar structures intact prior to sectioning (intact group), thumb MCP joint with ulnar collateral ligament sectioned (MC group), and thumb MCP joint with ulnar collateral ligament and accessory collateral ligament sectioned (MC+ group). Load was applied to the intact group, MC group and MC+ group. Sequence of loading was randomized.

Summary of Results: The mean and standard deviation were 7.13 ± 4.62 mm for the intact, 12.6 ± 4.96 mm for the MC, and 19.86 ± 5.00 mm for the MC+ groups. Differences between the groups were statistically significant (p < 0.005) using 2-tailed paired student t-test. This analysis showed that the measured displacements in the MC and MC+ groups, respectively, 1.69 times and 2.78 times higher than those of the intact group (P < 0.001).

Conclusions: This biomechanical cadaveric study demonstrates a statistically significant difference in dorsal-volar translation of the thumb MCP joint with increasing disruption of the UCLC. The dorsal-volar translation test may help determine the extent of thumb MCP UCLC injury and help guide appropriate treatment.

463 IN VIVO CONFOCAL ENDOMICROSCOPY OF BLADDER TUMORS
S. Jones1,2, G.A. Sonn1, K. Jensen2, J.C. Liao1
1Stanford University, Palo Alto, CA and 2Stanford University, Palo Alto, CA

Purpose of Study: The standard method to diagnose bladder cancer requires cystoscopy and transurethral resection of bladder tumor (TURBT). Shortcomings of these procedures include invasiveness, operator skill and poor sensitivity for flat lesions. Fiberoptic (fibered) confocal endomicroscopy is a minimally-invasive technology that may provide real-time differentiation between benign and malignant bladder lesions. In this study, we evaluated normal and abnormal appearing human bladder mucosa using in vivo fibered confocal microscopy.

Methods Used: Following IRB approval, patients scheduled for TURBT were recruited. The Cellvizio fibered confocal microscope (Mauna Kea Technologies, Paris, France), capable of acquiring images up to 60 μm in depth at 12 hertz, was used. During the TURBT, normal and abnormal appearing bladder mucosa was first confirmed with standard white light cystoscopy. After administration of intravesical and/or intravenous fluorescein, images were obtained with the confocal microscope. Next, the tumors were resected and sent for pathological analysis. The confocal images were compared with the pathology results and further analyzed for cellular morphology, architecture, and vascularity.

Summary of Results: Analysis of the confocal endomicroscopy data from the first 10 patients in this ongoing study reveals several interesting findings. Differences in size between normal and tumor cells were apparent. As also seen in H&E analysis, tumor cells are larger than normal cells. Normal and tumor cells show different cellular architecture. High-grade cells are poorly organized and pleomorphic compared to normal. Lastly, the lamina propria’s microvasculature, with red blood cells flowing in the lumen, is clearly visible with both intravesical and intravenous fluorescein administration.

Conclusions: Initial results show that confocal endomicroscopy provides in vivo, real-time histologic imaging of bladder mucosa with sufficient resolution to discern cellular morphology, architecture and vascularity of bladder mucosa. With more development and improved image analysis, this technology could potentially be used with other office-based techniques to examine bladder mucosa pathology and obviate operative diagnostic biopsy.

464 FAMILIAL IDIOPATHIC SCOLIOSIS IN MALES: LOCALIZATION TO CHROMOSOME 22Q
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1University of Colorado Denver School of Medicine, Aurora, CO; 2Johns Hopkins Medical Institution, Baltimore, MD; 3National Human Genome Research Institute, Baltimore, MD and 4The Children’s Hospital, Aurora, CO

Purpose of Study: Familial idiopathic scoliosis (FIS) is a structural, fixed lateral curve of the spine of ≥10 degrees that occurs in otherwise normal individuals and demonstrates heterogeneous etiology. One strategy for identifying causative genes in heterogeneous disorders is to isolate subgroups of affected individuals. Studies throughout the literature show differences in scoliosis between males and females. Male spines are clinically found to be more rigid, have a higher prevalence of thoracic curves, and have curve progression that often persists into late adolescence, beyond that of females. Thus, the goal of this study is to examine genetic etiology in males with a scoliotic curvature of ≥30 degrees.

Methods Used: Blood samples were obtained and genomic DNA was extracted from a large study sample of families with two or more individuals affected with FIS (202 families: 1198 individuals). All individuals underwent genomic screening using a modified Weber 9 marker set. Subsequent model-independent linkage analysis on clinical subgroups was accomplished using SIBPAL. A subgroup of males diagnosed with ≥30 idiopathic spinal curvature in adolescence was identified. Results from this subgroup of 241 individuals from 31 families are reported.

Summary of Results: Analyses revealed significant results (2 adjacent markers P < 0.005) in regions of chromosomes 2 and 22. The area on chromosome 2 spans 48 Mb; the area on chromosome 22 spans 13 Mb. Very significant p-values of 4.25 × 10^-9 and 4 × 10^-4 were found for markers on chromosome 22q.

Conclusions: Isolation of this subgroup of patients reveals an area of interest on chromosome 22. Of particular interest is the deletion at 22q11.2 associated with velocardo-facial syndrome, which is implicated in musculoskeletal disorders including scoliosis. Several other candidate genes in this area have been cited for their influence on phenotypic appearance of bone abnormalities and/or scoliosis. Future goals include the finer mapping of this area of chromosome 22q through intragenic SNP analyses.

465 RADIOGRAPHIC OUTCOMES OF THE DLIF/XLIF TECHNIQUE IN COMPARISON TO OTHER FUSION TECHNIQUES FOR THE TREATMENT OF DEGENERATIVE LUMBAR SCOLIOSIS
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UC San Diego School of Medicine, La Jolla, CA

Purpose of Study: The direct lateral approach to the lumbar spine (DLIF/XLIF) is a relatively new minimally invasive method for performing anterior fusion. Similar to traditional open interbody fusion, this technique can correct scoliotic deformity by restoring disc height and alignment of the disc space. A comparison of scoliosis correction using this less invasive procedure and other fusion techniques has not been reported on to date. This study assesses the effectiveness of the XLIF/DLIF procedure in correcting lumbar degenerative scoliosis and compares outcomes with posterolateral fusion (PLF), anterior lumbar interbody fusion (ALIF) and transforminal lumbar interbody fusion (TLIF).

Methods Used: X-ray images were collected for 73 patients treated with the XLIF/DLIF, PLF, ALIF and TLIF for degenerative lumbar scoliosis. In order to review scoliosis correction, various measurements were taken on pre-op and post-op AP and lateral X-rays of the lumbar spine. These include lumbar scoliosis using the Cobb angle, focal scoliosis, global lordosis, focal lordosis and disc height.

Summary of Results: Patients received fusion at an average of 2.9 levels. Global Cobb Angle correction was 8.5° ± 4.6° (n = 39 patients) for DLIF/XLIF; 2.5° ± 3.1° (n = 18 patients) for PLF; 2.5° ± 3.1° (n = 8 patients) for ALIF; and 3.0° ± 3.0° (n = 8 patients) for TLIF. Focal Cobb Angle correction was 4.1° ± 2.7° (n = 117 levels) for DLIF/XLIF; 0.9° ± 2.9° (n = 47 levels) for...
Purpose of Study: A variety of strategies have been proposed over the years for the regeneration of urothelial tissues. Donor tissues such as free skin and mucosa grafts have been proven to be successful but require prolonged surgical and hospitalization time. Thus, there has been a search for an “off-the-shelf material” which would eliminate the need for additional surgical procedures. Electrospinning is a recently developed technology which allows for the production of fibrous polymeric nanofiber scaffolds offering a high surface area for cell attachment, a controlled porous architecture, and a 3D microenvironment for cell-cell contact. The purpose of this study was to objectively compare the tensile strength of electrospun PCL and compare it to small intestinal submucousa (SIS) and human urinary tract tissue to determine the durability of PCL scaffolds.

Methods Used: A solution of 15% PCL was electrospun to form ~1.5-2.0 mm thick mats. Single-strand SIS (SIS1) and 4-ply SIS (SIS4) were obtained from Cook Biotech. Full thickness human urothelial tissue was harvested from the membranous urethra and anterior bladder wall of 2 human cadavers. Thickness readings were taken with a digital caliper. A 3-0 monocal suture was passed 3 mm from the edge of the tissue and was pulled with increasing force until failure and maximum force was measured using a force transducer. Twenty measurements were taken per material. As an initial test of surgical manipulability, a 2 cm × 2 cm 15% PCL patch was sutured to the dome of a porcine bladder ex vivo using a da Vinci® robot.

Summary of Results: PCL had significantly greater tensile strength than SIS1 (0.891 ± 0.415 lbf vs 0.500 ± 0.086 lbf, P < 0.01) and was similar to the tensile strength of human ureter (0.694 ± 0.288 lbf) and urethra (0.914 ± 0.418 lbf). Augmentation of the porcine bladder with the 15% PCL patch was uneventful, and the patch behaved predictably without tearing, folding, or self-adhesion.

Conclusions: 15% electrospun PCL has the mechanical properties necessary to withstand the stresses of suturing and an in vivo environment of urethra. Further study of this material in vivo is planned.

468 CLINICAL AND HEMODYNAMIC ASSESSMENT OF THE HANCOCK II BIOPROSTHESIS IN THE ELDERLY

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Purpose of Study: The goals of valve replacement surgery are to reduce symptoms, improve activity, and restore the highest level of independent function. The success of achieving these goals can be evaluated using physiologic and psychological proven outcome measures. This prospective study aims to evaluate symptoms, hemodynamic performance, physical functioning, and quality of life (QOL) of elderly patients six months post aortic valve replacement (AVR).

Methods Used: From November 2004 to August 2007, 33 patients underwent AVR with a porcine Hancock II bioprosthesis at a single institution. There were 24 males (73%) and 9 females; average age of our cohort was 75.3 ± 5.3 years (63-85). Transthoracic echocardiography and bicycle cardiopulmonary exercise testing (CPET) were performed postoperatively at 6 months. The RAND 36-item Health Survey (SF-36) was administered both pre and post-operatively to evaluate quality of life.

Summary of Results: NYHA Functional Class pre-operatively included 1 patient in FC I (3%), 5 (15%) in FC II, and 27 (82%) in FC III. Post-operatively, 27 patients (82%) were in FC I and 6 (18%) in FC II. CPET was performed on all patients at six months. Patients were able to achieve an average of 73% of their predicted maximal workload (watts) and 80% of their maximal VO2 consumption (ml/min/kg) based on reference levels standardized for age, gender, and body surface area (BSA). Aortic prosthesis mean pressure gradients at rest and peak exercise were 11.7 ± 5.0 mmHg and 21.1 ± 10.0 mmHg, respectively. Patients showed statistically significant improvements (P ≤ 0.01) in QOL six months post-operatively in six of nine health parameters: physical functioning, role limitations due to health, energy-fatigue, social functioning, general health and health change.

Conclusions: Our prospective study demonstrates that replacing the aortic valve in a Hancock II bioprosthesis in the elderly yields low mean pressure gradients during both rest and at peak exercise, above average exercise capacity for the elderly at six months post-operatively, and significant improvements in our patients’ overall QOL. Although elderly patients undergo cardiothoracic surgery with reasonable risk, they can show extraordinary improvements in their symptoms, hemodynamic and exercise function, and overall quality of life.
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SURGERY FOR SCOLIOSIS IN DUCHENNE MUSCULAR DYSTROPHY: A COMPARISON OF TWO SURGICAL TECHNIQUES

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Purpose of Study: To review each case of spinal fusion for scoliosis in Duchenne muscular dystrophy that occurred at Shriner’s Hospital in Northern California (Sacramento, CA) between the years of 1997 and 2007. The degree of scoliosis correction is used as a primary outcome. Descriptive statistics of the patients undergoing surgery is also reported.

Methods Used: The study is a retrospective chart review. The degree of scoliosis (Cobb angle) was measured from radiographic films. The cases were divided into two groups based on the type of instrumentation used. Group 1 had hybrid segmental fixation with pedicle screws, hooks, and sublaminar wires. Group 2 had Luque sublaminar wire fixation with unit rods. The Welch’s t-test was used for statistical comparison. Survival data was generated from the social security death index.

Summary of Results: 19 cases were reviewed. The mean age at surgery was 11.7 (±2.6) years. Pre-operatively, the mean percent predicted forced vital capacity was 70% (±27%), mean maximal inspiratory pressure of -58 cm H20 (± 22 cm H20), and mean left ventricular fractional shortening of 32% (± 10%). Survivopship data showed 100% survival at one year, 93.8% at five years, and 60% at ten years after surgery. The data from both surgical groups is presented in the table below.

Conclusions: Use of Luque sublaminar wire fixation alone (Group 2) yields less correction than the use of hybrid pedicle screws and hooks (Group 1).

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=4)</th>
<th>Group 2 (n=15)</th>
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<tbody>
<tr>
<td>Degree of scoliosis (Cobb angle)</td>
<td></td>
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<tr>
<td>Pre-surgery</td>
<td>53 ± 33</td>
<td>52 ± 24</td>
</tr>
<tr>
<td>Post-surgery</td>
<td>11 ± 12</td>
<td>9 ± 12</td>
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* p < 0.01 ** p < 0.005

470 MUSCLE ARCHITECTURE AND BIOMECHANICS OF THE FLEXOR POLlicis BREVIS SUPERFICIAL AND DEEP HEAD

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Purpose of Study: Flexor Pollicis Brevis (FPB) is used in various surgeries. This muscle has a superficial head (FPBS) and a deep head (FPSD), but their function is driven primarily by the force producing capacity of the muscle. Clinically, these data suggest that the superficial head of FPB dominates function, but functional redundancy may allow one head to be transferred to cause cases where thumb opposition or abduction is lost to injury.

Methods Used: The study design was a mixed design incorporating retrospective review of subject charts and a prospective telephone follow up of subjects. Potential subjects were identified using an electronic database of patients diagnosed at our institution between 1997 and 2003. Subjects were at least 5 years following their most recent gait analysis.

Summary of Results: On follow up with 52 subjects, we found that in 26 (50%) toe walking had resolved while in the other 26 (50%), toe walking persisted to varying degrees. Furthermore, we found that toe walking had resolved in a greater percentage of Type 1 and Type 2 idiopathic toe walkers, while greater persistence was found in type 3 and unclassified idiopathic toe walkers. Lastly, we found that toe walking had resolved in a higher percentage of untreated (55%) subjects compared to treated (46.9%) subjects.

Conclusions: We found that toe walking was quite prevalent (50%) on long term follow of idiopathic toe walkers. Treatment did not appear to significantly alter the outcomes, however we have established the usefulness of classifying idiopathic toe walkers as an aid for determining prognosis for a given patient.

472 INITIATION OF A PEDIATRIC ROBOTIC SURGERY PROGRAM AND CASE-CONTROL ANALYSIS OF ROBOTIC URETERAL REIMPLANTATION

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Purpose of Study: Robotic-assisted laparoscopic (RAL) surgery has been readily adopted in the adult literature, yet its application has lagged in pediatric surgery. To date, only one institution has reported their experiences with initiating a pediatric RAL program. We evaluated the initiation of our pediatric robotics program and performed a case-control analysis to compare this technology to traditional open surgery.

Methods Used: We retrospectively reviewed the first 50 patients that underwent RAL surgery since the acquisition of the Da Vinci surgical robot in 2006 and describe demographic, perioperative, intraoperative, postoperative, and follow-up data. A case-control analysis was performed for patients that underwent ureteral reimplantation, matching each case to 2 historic open controls frequency matched for age, gender, reflux grade, ASA score, and unilateral vs. bilateral disease.

Summary of Results: Overall, 50 RAL procedures were performed over 18 months by the Urologic (84% of total cases) and General Surgeons (16%) with 25 males (56%) and 18 females (44%). The average BMI was 19.45 ± 4.38 and 8 patients (16%) were less than 10 kg. Fourteen different procedures were performed. Intraoperatively, 3 RAL cases were converted to traditional laparoscopy and 2 cases were converted to open. There were 5 mechanical failures. Ureteral reimplantation cases performed robotically had 53% longer total OR times (361 ± 120 minutes vs. 236 ± 58 minutes, P < 0.0001) due primarily to longer procedure times. Longer total OR time was most dramatic for RAL bilateral reimplants. Length of stay, complications, and surgical success were similar between groups. Estimated blood loss was statistically, though not clinically significantly lower in the RAL group (mean 14 mL vs. 60 mL).

Conclusions: Robotic surgery is safe and effective in pediatric patients. Nevertheless, proper instruction and training precedes technological proficiency. We caution that the learning curve can be substantial, especially when multiple surgeons are attempting proficiency.
473 THE LONG TERM FOLLOW UP OF SUPRACONDYLAR FRACTURES OF THE HUMERUS: THE FUNCTIONAL OUTCOME GREATER THAN 10 YEARS AFTER INJURY
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Purpose of Study: Supracondylar fractures of the humerus are one of the most common injuries seen in children, with a peak incidence between the ages of 5-8 years. The potential for neurovascular injury and residual deformities make supracondylar humeral fractures a serious injury. Much information exists in regards to the short term outcomes of the various treatment methods of these fractures; however, few up to date studies exist regarding the long-term outcomes of these patients. The progression of treatment and the increased functional requirements as the pediatric patient ages warrants the need for current study. Thus, the purpose of this study is to assess the long-term functional outcome of those who suffered a supracondylar humeral fracture.

Methods Used: Prospective cohort study. All children admitted to BCCH between 1993 and 1997 with a diagnosed supracondylar fracture were approached via mailed packages to participate in this study. Study packages included items to assess self-reported long-term functional outcomes and included one of these subjects: the Disabilities of Arm Shoulder, and Hand Questionnaire (DASH) to measure symptoms and functional status specific to the upper extremity and either the Short Form 26 (SF36 version 2) or Activities Scale for Kids - performance version (ASKp), depending on age, to assess the general activity and wellness of the patient as a whole.

Summary of Results: The mean ASKp score was 98.6 ± 2. A score less than 95 on the ASKp is indicative of a functioning disability. The mean DASH score was 3.0 ± 3.8. An optional component of the DASH questionnaire assessed sports/music (four items) and work activities (four items) and results for these components were 3.1 ± 9.1, and 1.1 ± 4.1, respectively. Lastly, the mean SF36v2 scores for physical function were 97.5 ± 5.

Conclusions: The results of translating the DASH, SF36v2, and ASKp scores showed high levels of functional outcome indicating minimal disability amongst the participants. The vast majority of subjects went on to full recovery, while very few experienced any residual long-term functional deficit. By incorporating patient’s perception and clinician assessment this study provided a sensitive assessment of patients at long term follow-up.

474 THE LONG TERM FOLLOW UP OF SUPRACONDYLAR FRACTURES OF THE HUMERUS: THE CLINICAL AND RADIOGRAPHIC OUTCOMES GREATER THAN 10 YEARS
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Purpose of Study: Supracondylar fracture of the humerus is the most common pediatric upper extremity fracture and accounts for an estimated two-thirds of all pediatric patients hospitalized for arm fractures. In nearly all cases, this injury results from a fall onto an outstretched hand with the elbow in full extension. There is a relative abundance of literature describing short-term outcomes for these fractures treated with contemporary methods, in part because the most severe complications develop in the short term and because of the relative logistical ease of conducting short-term follow-up. There is, however, a lack of current literature describing long-term outcomes of supracondylar fracture. In pediatric populations, long-term functional requirements may be more demanding than those explored in immediate follow-up, and functional impairment may not become fully apparent until years later. Therefore, research into long-term outcomes of supracondylar fractures treated with contemporary methods is needed.

Methods Used: The present study assessed long-term radiographic and clinical outcomes (assessed using the Flynn’s elbow score) of 18 patients treated for supracondylar fracture at British Columbia Children’s Hospital between 1994-1997 with final follow-up in 2008.

Summary of Results: Radiographic outcomes were determined comparing changes in the humeral-ulnar angle and the humeral shaft-condylar angle between injured and uninjured arms. Of 18 patients, five showed differences of greater than six degrees in humeral-ulnar angle comparing injured and uninjured arms at final follow up. Clinical outcomes were assessed using Flynn’s elbow score, which considers functional and cosmetic factors in assigning patients a single global outcome score of excellent, good, fair or poor. 13 of 18 patients had excellent outcomes, two good and three poor.

Conclusions: Continuing research into long-term outcomes of supracondylar fracture in children is needed to better describe the radiographic and clinical outcomes of contemporary treatment methods.

475 SUCCESS AND COMPLICATIONS OF 729 PERCUTANEOUS NEPHROLITHOTOMIES FROM A SINGLE CENTRE
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Purpose of Study: Percutaneous nephrolithotomy (PCNL) is a minimally invasive procedure that involves dilation of a tract into the kidney through which instruments can be inserted to fragment and remove kidney stones. PCNL is used to treat large kidney stones (>2 cm). We analyzed the success of PCNL and describe complications at our institution. Success was defined as a patient with no residual stones following PCNL. Predictors of residual fragments and major complications in patients undergoing PCNL were identified.

Methods Used: Records from 2000-2008 were analyzed retrospectively. Patient demographics, stone data, lab, admission records and radiology results were analyzed for predictors of complications and success.

Summary of Results: Records for 729 patients were available for analysis. The stone free rate (defined as no calcifications on CT scan after PCNL) was 35%. Amongst patients who were not stone free, 30% had stones smaller than 4 mm (which are considered clinically insignificant and often pass spontaneously); therefore, 55% of all patients were stone free or had clinically insignificant fragments. Minor complications occurred in 15% including infection (7%), emergency room visits (7%), pleural effusions (9%), pneumonia (2%), pneumothorax not requiring chest tube (0.5%), or perforation of renal pelvis (3%). Major complications occurred in 8% of cases including blood transfusion (6.5%) and angioembolization (0.9%). Patients with a larger stone burden were more likely to have residual fragments or develop a major complication. Procedures with lower pole puncture sites were less likely to develop major complications.

Conclusions: At our institution, 55% of patients were rendered stone free or were left with clinically insignificant fragments (<4 mm). Our absolute stone free rate (35%) is lower than most published series (60-95%). These other series, however, utilized less sensitive methods of stone detection such as plain abdominal radiographs, whereas we used stringent CT follow-up which is exquisitely sensitive for detecting even the smallest calcifications in the kidney. PCNL is a safe and effective modality for the treatment of large kidney stones.

476 PROLIFERATIVE EFFECTS OF MULTIPLE GROWTH FACTORS ON MOUSE BONE MARROW MESENCHYMAL STEM CELLS: IMPLICATIONS FOR ENGINEERING ANTERIOR CRUCIATE LIGAMENT GRAFTS
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Purpose of Study: The ACL is one of the most common ligament injuries of the knee and has a very low healing capacity. Thus, current treatment requires surgical reconstruction with an autograft or allograft. Although ACL reconstruction procedures are efficacious, there are disadvantages with both current graft options. Autografts can result in donor site pain, decreased range of motion, and weakness. Allografts carry the possibility of disease transmission and host immune responses which can compromise the graft. These shortcomings all contribute to the need for tissue-engineered ligaments. Work with bone marrow mesenchymal stem cells (BMSCs) has shown that they have the potential to differentiate into a fibroblast-like lineage. The aim of this study was to determine the effect of various growth factors on mouse BMSC proliferation.

Methods Used: Mouse BMSCs were plated at about 25% confluence and allowed to recover overnight at 37 degrees Celsius and 5% CO2 in a growth media consisting of DMEM, 10% FBS, and 1% each of pen-strep, pyruvate,
and non-essential amino acids. Cells were then assigned either basic fibroblast growth factor (bFGF), transforming growth factor beta-1 (TGF-β1), insulin-like growth factor (IGF), or epidermal growth factor (EGF). These were triplicated at concentrations of 10, 25, and 50 ng/ml, except for TGF-β1 which was used at 2, 5, and 10 ng/ml. Cell viability and proliferation were measured at 1, 2, 3, 5, and 7 days using an MTT assay.

Summary of Results: Cells exposed to IGF, EGF, and TGF-β1 showed no change in the proliferation rate compared to control. Cells exposed to bFGF had a decrease in their rate of proliferation once the cells became confluent. Further investigation with microscopy showed a unique conformational change in the bFGF group.

Conclusions: The decrease in proliferation seen with bFGF (without evidence of increased cell death) may indicate that the cells are focusing on differentiating and producing more extracellular matrix (i.e. collagen). The morphological changes seen under the microscope seem to support this but further studies are needed to confirm increased production of collagen.

477 A COMPREHENSIVE ASSESSMENT OF OUTCOMES AFTER LAPAROSCOPIC ANTIREFLUX SURGERY

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Purpose of Study: The reported success of laparoscopic antireflux surgery (LARS) is dependent on outcome variables used. We sought to assess these outcomes in a large cohort of patients using a comprehensive analysis of such variables.

Methods Used: Four hundred patients (208 females; median age 52y/o) who underwent LARS at the University of Washington from 1993 to 2008 were given a comprehensive questionnaire to assess various aspects of their outcomes from LARS.

Summary of Results: The median follow-up was 92 (6-175) months.

Symptom control: These symptoms are currently improved/resolved (presented as a % of patients): Heartburn (N = 376) 86/54%, regurgitation (N = 365) 91/76%, and chest pain (N = 265) 79/62%.

Primary presenting symptom control: The following primary presenting symptoms improved/resolved (presented as % of patients): heartburn (N = 186) 90/60%, regurgitation (N = 150) 90/69%.

Success of operation: Currently, 279 (70%) patients rate their operation as a complete success and 111 (22%) as partially successful. Those with incomplete or no success cited recurrent reflux (N = 70), a side-effect (N = 37), or both (N = 14) as the reason.

Medication use: 79% of all patients are on less medication after LARS, with 59% being completely off medications for GERD. Among the 164 patients taking medication, these were the three most common reasons (presented as % of patients): heartburn (N = 100) 60%, regurgitation (N = 13) 8%, Barrett’s esophagus (N = 13) 8%. Of the same group, 97.5% (N = 156) believe the medication is helpful in controlling GERD.

Reoperations: Fifteen (3.7%) patients required reoperations, 9 for recurrent reflux and 6 for side-effects.

Durability: 83% of patients have successful control of GERD 2 years after the operation, and 74% of patients have successful control of GERD after 10 years.

Side-effects: The following side-effects developed or worsened: dysphagia in 72 (18%) patients; bloating in 96 (24%) patients; diarrhea in 61 (15%) patients.

Conclusions: LARS is a good treatment option for GERD, and a comprehensive understanding of its outcomes will help patients and physicians better understand its role.

478 A NEW TISSUE-POLYMER HYBRID DRUG DELIVERY SYSTEM FOR ARTIFICIAL CORNEAS

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Purpose of Study: We developed and evaluated a new hybrid tissue-polymer drug delivery system using lyophilized cornea and synthetic hydrogel. The feasibility of this system as a carrier and a drug delivery system for an artificial cornea (Boston Keratoprosthesis) was evaluated in vitro while non-modified cornea tissue was used as a control.

Methods Used: Corneal tissue from the eye bank was first lyophilized. The tissue-polymer hybrid was synthesized by reconstituting the lyophilized cornea in a norfloxacin-loaded hydrogel solution followed by polymerization using external heat of 65°C and Azoo-Isobutyroindritile (AIBN) as a free radical initiator. Four different tissue-hydrogel compositions of varying hydrophobicity were synthesized and evaluated over one month for the swelling and the drug release profile. Quantitative analysis of drug concentration was achieved using UV-Vis Spectrophotometry. The hybrid system was further characterized using optical and electron microscopy. Unmodified corneal tissue was used as a control. The mechanical strength and suture characteristics of the hybrid system and unmodified cornea were evaluated as a carrier for Boston K-pro using an artificial anterior chamber.

Summary of Results: Both the hybrid-system and the control show excellent mechanical properties as carriers for the Boston K-pro. They withstood similar challenges of intrachamber pressures (50-70 mmHg) for wound stability. In vitro drug release analysis demonstrates a longer and more controlled drug release profile for the hybrid system as compared to the control. The most hydrophobic hybrid construct shows a release that is above the Minimum Inhibitory Concentration 90 (MIC90) of Staphylococcus epidemidis for the first two days.

Conclusions: The new hybrid tissue-polymer system shows sufficient mechanical stability to serve as a carrier for the Boston K-pro. The sustained release of the antibiotic demonstrates the feasibility of achieving desirable antibiotic concentrations to control potential severe infection during the immediate post operative period. The development of a tissue-hybrid system has the potential to simplify storage and distribution of donor tissue as a carrier for artificial corneas. This can offer a new option of treatment of severe corneal blindness in developing countries where donor tissue is otherwise not readily available.

479 MODIFIED LAPAROSCOPIC TOTALLY EXTRAPERITONEAL INGUINAL HERNIA REPAIR REDUCES OPERATIVE AND RECOVERY TIMES RELATIVE TO OPEN MESH REPAIR

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Purpose of Study: Current methods of inguinal hernia repair include open procedures, which involve an incision directly over the hernia and most commonly repair the defect with a synthetic mesh, and more recently developed laparoscopic techniques which approach the hernia from behind the abdominal wall and implant a mesh in the preperitoneal space. The purpose of this study was to compare the efficacy of the more commonly performed open mesh repair and a modified laparoscopic totally extraperitoneal (TEP) procedure using a pre-formed mesh.

Methods Used: All open and TEP primary inguinal hernia repairs performed at the Veterans Affairs Puget Sound Health Care System in Seattle, Washington between May 2005 and May 2007 were reviewed. Eighty-eight patients (58 open, 30 TEP) completed a retrospective follow-up survey. Operative times, adjusted to account for the difference between bilateral and unilateral repairs, pain assessments, duration of hospital stay, and time until return to work were compared between treatment groups using Student’s T-tests. Qualitative assessments of post-operative functional limitations were compared using Chi-square tests. A P-value of less than 0.05 was considered significant.

Summary of Results: Average duration of hospital stay was reduced in the TEP group (value %95 CI, 0.4 days ± 0.3 days) relative to the open group (0.8 days ± 0.4 days) (P < 0.05). Average time until return to employment was also reduced in the TEP group (5.4 days ± 2.7 days) compared to the open group (13.3 days ± 7.5 days) (P < 0.05). Corrected operative times were lower in the TEP group (57 min. ± 6 min.) relative to the open group (83 min. ± 24 min.) (P < 0.05). No significant differences in post-operative pain assessment (0 to 10) or degree of functional limitation (Extremely limited, Moderately limited, Slightly limited, Normal) were shown between groups at day one, two weeks, or one year.

Conclusions: The modified laparoscopic TEP method appears to result in reduced operative times, reduced hospital stays and faster return to work relative to the more commonly employed open repair. The modified TEP technique can be considered as a viable alternative to open surgery in primary inguinal hernia repair.

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DOES THE MODE OF POST-OPERATIVE OPIOID INFUSION AFFECT PATIENT OUTCOME AFTER SURGICAL CORRECTION OF ADOLESCENT IDIOPATHIC SCOLIOSIS?

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Purpose of Study: Severe pain following surgical correction of idiopathic scoliosis is managed using intravenous opioids delivered via continuous opioid infusion (COI) or Patient Controlled Analgesia (PCA). The purpose of this study was to determine which mode of opioid delivery produces effective pain relief and the fastest recovery with the fewest side-effects.

Methods Used: Retrospective chart review of 63 patients who underwent posterior correction of adolescent idiopathic scoliosis (AIS) from 2000 to 2007. The primary outcome was morphine consumption. Secondary outcomes included length of hospital stay, time to foley catheter removal, time to mobilization and side-effect profile.

Summary of Results: 31 subjects received COI (25F; 6M) and 32 received PCA (29F; 3M). The COI group received an average of 2.1 ± 1.0 mg/kg post-operative morphine versus 3.0 ± 1.2 mg/kg in the PCA group. There was no significant difference between the COI and PCA groups in terms of length of stay, time to foley catheter removal, or time to mobilization. The side effect profile of the two groups was nearly identical for days of nausea, days of vomiting, number of emetic episodes, days of pruritis, treatment of pruritus and respiratory distress. Pain scores for COI infusions were not adequately documented in the charts. Pain scores for patients on PCA are documented but are not able to be compared.

Conclusions: A notable difference in morphine utilisation was found between the groups: from a clinical perspective the PCA group received significantly more morphine versus the COI group. However, there were no differences between patients that received COI or PCA in secondary outcomes. The main weakness of this study was in the retrospective methodology. This project will be used to power a prospective randomised controlled study to examine mode of opioid infusion, pain management, pain scores, patient satisfaction and side effect profiles in this group of patients.

OUTFLOW TRACT OBSTRUCTION IN PEDIATRIC PATIENTS

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THE KONNO PROCEDURE FOR LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION IN PEDIATRIC PATIENTS

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Purpose of Study: To determine the demographic information of team physicians providing care for the NCAA Division I college football athlete and to identify treatment patterns in the management of common injuries in Division I college football players.

Methods Used: Head orthopaedic team physicians for all 119 NCAA Division I college football teams were asked to fill out a survey regarding demographics and preferred treatment of a variety of common and uncommon injuries encountered in the college football player.

Summary of Results: Ninety-three percent of surveys were completed. In ACL reconstruction, patellar tendon was the preferred graft choice (67%). Return to play after ACL reconstruction was allowed by 6 months or sooner by 71% of the physicians. For anterior shoulder instability, arthroscopic stabilization is preferred (69%). Acromioclavicular joint injuries occurring during a game are injected with a local anesthetic by 68% of the physicians to allow immediate return to play and 87% will inject a known AC joint injury prior to a game. Type III AC joint injuries are treated non-operatively by 58% of the physicians. Knee braces are used in 89% of teams to prevent MCL injuries. Complete PCL injuries are fixed primarily with an allograft (69%) and with an arthroscopic single bundle approach (50%). Screw fixation is the primary treatment option for fifth metatarsal fractures (94%) with a return to play by nine weeks allowed by 92% of the physicians. At least 75% of the team physicians have treated one or more tibia fractures in the past five years and 96% favor intramedullary nailing. Intramuscular ketorolac is utilized by 62% of physicians prior to a game in treating the pain from a nagging injury. The average use of ketorolac varies, but 15% will utilize it on average five times or more per game.

Conclusions: There is a wide variety of treatment patterns in the care of the college football athlete. While some injury management has significant agreement, there are aspects in which it is widely disparate. Knowing these patterns will assist in the management of these injuries and in designing future studies that may help improve the management and prevention of injuries in collegiate football players.

CURRENT PRACTICES AND VARIATION IN THE TREATMENT OF INJURIES IN NCAA DIVISION I COLLEGE FOOTBALL PLAYERS

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Purpose of Study: Current complications rates of intramedullary nailing of tibia shaft fractures in diabetic patients

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Purpose of Study: Intramedullary nailing is the standard treatment for the majority of tibial shaft fractures. Numerous studies have demonstrated high union rates with relatively low complication rates following tibial nailing. Increased rates and severity of complications of treatment of ankle fractures in diabetics have been well documented. However, only one small study has documented the results for diabetic patients with tibial shaft fractures, concluding that the rates of complications were the same. We hypothesized that both incidence and severity of complications are higher in tibial nail patients with diabetes.

Methods Used: A retrospective analysis was conducted at a single level one trauma center over an eight year period. We identified 60 patients. Medical records were reviewed to obtain patient demographic data and comorbidities...
as well as to confirm the fracture type, location and management. Outcomes data including healing and complications was gathered from the hospital records of 164 patients (10 male, 54 female) with diabetes who sustained tibia shaft fractures were treated with reamed intramedullary nails and had adequate follow up data to be included. 28 patients sustained closed fractures and 17 patients had open fractures. 37 patients received intramedullary nailing as the primary procedure and 8 received intramedullary nail as a secondary (staged) procedure. Of the 15 patients excluded, 3 patients had an acute below knee amputation for a mangled extremity, 5 patients had previous osteosynthesis due to concomitant ipsilateral intrarticular pilon or plateau fractures, 6 patients were treated with a long leg cast and one was managed with an external fixator.

Summary of Results: Complications occurring in the first 12 months after injury were recorded. The primary complications were infection, nonunion, neurological monitoring is recommended. A four-rod implant in spinal correction surgery, congenital kyphoscoliosis confers a greater risk for neurological deficit post-operatively. Alongside intra-operative monitoring modalities such as SSEPs, and the wake-up test, vigilant post-operative neurological monitoring is recommended. A four-rod implant in spinal correction allows for smaller incision and easier adjustment should a need for readjustment arise.

Conclusions: Diabetic patients with tibia shaft fracture treated with intramedullary nail had greater risk for complications than historical complication rates for non-diabetic patients.

484 DELAYED POST-OPERATIVE NEUROLOGIC COMPLICATION IN A PATIENT WITH CONGENITAL KYPHOSIS: RELIEVED AFTER A NOVEL REVISION TECHNIQUE MADE POSSIBLE BY A FOUR-ROD CONSTRUCT

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Purpose of Study: We report a case of delayed neurologic deterioration and lower extremity neurologic monitoring is recommended. A four-rod implant technique and subsequent resolution after implant readjustment.

Methods Used: Neurologic deterioration following spinal fusion and instrumentation is a catastrophic risk with relatively low incidence. A four-rod construct can allow for greater and safer accessibility should a need for readjustment arise.

Conclusions: Despite low prevalence of neurologically complications in spinal corrective surgery, congenital kyphoscoliosis confers a greater risk for neurological deficit post-operatively. Alongside intra-operative monitoring modalities such as SSEPs, and the wake-up test, vigilant post-operative neurological monitoring is recommended. A four-rod implant in spinal correction allows for smaller incision and easier adjustment should a need for readjustment arise.

Conclusions: A Bayesian network model was developed and it shows the development of management guidelines in neonatal necrotizing enterocolitis. The model can be a valuable adjunct to clinical decision and the development of management guidelines in neonatal necrotizing enterocolitis.

485 PREDICTING THE LIKELIHOOD FOR SURGICAL INTERVENTION IN NEONATAL NECROTIZING ENTEROCOLITIS USING A BAYESIAN NETWORK MODEL

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Purpose of Study: The decision to whether an infant suffering from neonatal necrotizing enterocolitis (NEC) requires surgical intervention can be challenging. Our aim in this study was to develop a Bayesian network model capable of predicting the likelihood of surgical intervention in patients with NEC based on clinical variables demonstrative of intestinal perforation and gangrene.

Methods Used: With IRB approval, we undertook chart reviews of 164 infants with NEC treated operatively and non-operatively at our institution from 1998 to 2008. Patient demographics, physical examination findings, illness severity, radiological findings, laboratory values, and outcomes were extracted. Variables which are associated with bowel perforation and/or gangrene were used as inputs for the Bayesian network model. The network was then trained separately with sets of 25, 50, and 75 cases, with each set being randomly selected from the total of 164 cases. For each training set, the network was then tested for sensitivity, specificity, and accuracy in predicting the likelihood of infants requiring operative versus non-operative treatment.

Conclusions: The network had a predictive sensitivity of 62%, a specificity of 72%, and an accuracy of 68% (a cutoff point selected to yield highest accuracy) when trained with 25 cases. When trained with 50 cases, the sensitivity, specificity, and accuracy were 69%, 83%, and 78%, respectively. With a training set of 75 cases, these values were 70% (sensitivity), 97% (specificity), and 86% (accuracy). These values demonstrate that the predictive performance of the network improved with increasing number of training cases.

Conclusions: A Bayesian network model was developed and it shows promising ability to predict the likelihood of requiring surgical intervention in cases of NEC. The model can be a valuable adjunct to clinical decision and the development of management guidelines in neonatal necrotizing enterocolitis.

486 VIDEO-ASSISTED THORACIC SURGERY AS A SAFE ALTERNATIVE FOR THE RESSECTION OF PULMONARY METASTASES: A RETROSPECTIVE COHORT STUDY

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Purpose of Study: Video-assisted thoracic surgery (VATS) has become a preferred method for benign surgical conditions, yet still remains controversial for malignancies. The purpose of this study was to review our results of pulmonary metastasectomies using both open thoracotomy and VATS techniques.

Methods Used: Patients with previous oncological history were retrospectively enrolled. Patients were divided into 2 groups, based on the surgical approach used for the initial pulmonary metastasectomy. Data for operations performed from 1986 to 2006 were collected by chart review. Primary outcomes were overall survival (OS) and recurrence free survival (RFS), evaluated using Kaplan Meier analysis. A non-inferiority margin was set at 0.2.

Summary of Results: A total of 280 surgical procedures were performed on 186 patients, of which 228 were completed using open thoracotomy and 52 using VATS. From 171 eligible individuals (100M, 71F, median age 53), there were 135 patients in the thoracotomy group (79%; 82M, 53F; median age 49), and 36 patients in the VATS group (21%; 18M, 18F; median age 58.5). Primary cancers were mainly: 81 sarcoma (47%), 26 colorectal adenocarcinoma (15%), and 22 renal cell carcinoma (13%). Median postoperative follow-up was 26.2 months. Disease Free Interval-1 (DFI) was 27.5 months for thoracotomy, and 24.6 months for VATS (P = 0.79). Median OS was 53.2 months for thoracotomy, and 30.1 months for VATS (P = 0.03). The actuarial 5-year OS rates were 69.6% for VATS and 58.8% for thoracotomy. The estimated difference in 5-year OS is 10.8%. Second occurrences were noted in 59 thoracotomy (median DFI-2: 14.8 months) and 10 VATS (median DFI-2: 12.4 months) patients. Median RFS was 24.8 months for thoracotomy and 25.6 months for VATS. Actuarial 5-year RFS rates were 51% in thoracotomy, and 67% in VATS (P = 0.27).

Conclusions: The 5-year overall survival of VATS is equivalent to thoracotomy, and VATS patients have a longer recurrence free survival. In cases of pulmonary metastases, VATS is an acceptable alternative that is both safe and efficacious. Based on our experience, it is permissible to use VATS resection in these circumstances: small tumor, fewer nodules, single lesion, age ≤53, unilateral, tumor size amenable to wedge resection, and non-recurrent disease.

487 ANATOMY OF IRREDUCIBLE METACARPOPHALANGEAL DISLOCATION

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Purpose of Study: The aim of this work is to develop a cadaveric model of MP dislocation that closely simulates the clinical situation, and study the
anatomy of the different structures around the MP joint and their contribution to irreducibility of the dislocation.

Methods Used: Fourteen fresh frozen cadaveric hands were divided into two groups. In group 1, five hands were dissected and irreducible dislocation was created by dividing proximal attachment of volar plate. In group 2, nine specimens were used to produce irreducible dislocation of MP joint of index finger by impact loading with MTS machine and structures responsible for irreducibility were studied.

Summary of Results: MP joint was dislocated only when proximal attachment of volar plate was ruptured and its attachment to DTML was partially severed. DTML with its partially intact attachment with the volar plate acted as tight continuous band dorsal to metacarpal head thus making the dislocation irreducible. The flexor tendons were displaced unlarly, with the A2 pulley intact and tethering the tendon between the second and third metacarpal heads. The natalary ligament was distant from the dislocation and had no contribution to the irreducibility. The superficial transverse metacarpal ligament was superficial to the neck of the metacarpal and did not contribute to the irreducibility of the dislocation. Complete release of the volar plate from DTML allowed easy reduction of the dislocation.

Conclusions: Previous attempts at creating a dorsal MP irreducible dislocation were limited to manual dissection with volar approach and forcefully hyperextending the joint by open surgical dissection. We present a model for an irreducible dislocation that more closely resembles the clinical situation than manual dissection. Our findings from both groups show that both the STML and natalary ligament do not contribute to irreducibility after MP dislocation. The volar plate with partially intact attachment to DTML is the primary contributor to reduction in irreducible dislocation of MP joint of a finger. Complete division of the lumbricals or flexor tendons does not allow reduction of dislocation. Kaplan’s theory of a noose forming around the metacarpal head was not observed in this study.

488 RATE OF PSEUDARTHROSIS IN PATIENTS WITH ANTERIOR CERVICAL DISECTOMY AND FUSION
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Purpose of Study: Anterior Cervical Discetomy and fusion (ACDF) is a procedure used to treat patients with cervical radiculopathy. One serious complication associated with ACDF is pseudarthrosis (non-union). Several factors may contribute to pseudarthrosis including choice of bone graft and medical co-morbidities. This study examines the influence of diabetes mellitus, rheumatoid arthritis and graft choice on pseudarthrosis following ACDF.

Methods Used: A retrospective review was done using a commercially available online database of insurance billing records of orthopaedic patients. These records were then cross-referenced using the International Classification of Diseases, 9th Revision (ICD-9)/CPT codes. Patient records were further stratified by graft type (structural autograft, allograft, intervertebral cage) and presence of medical co-morbidities (diabetes Mellitus, rheumatoid arthritis) based on concurrent entry of ICD-9/CPT codes.

Summary of Results: A total of 31,038 patients in the database underwent ACDF from Q1/2004-Q2/2007, including 16,258 (52.4%) single-level and 14,780 (47.6%) multi-level ACDF patients. Autograft usage declined from 10.9-5.9% from 2004-2007, while intervertebral cage usage increased from 25.7-41.0%. Instrumentation was used in 28,198 patients (90.9%), more frequently in multi-level (95.1%) than single-level ACDF (86.7%). Intraoperative microphone was used in 3,904 patients (12.9%). Microscope usage increased from 5.8-15.2% from 2004-2007, and was greatest in the West (18.8%) compared to other regions (11.3-13.2%). Neurophysiologic monitoring was used in 4,886 patients (15.7%). Usage of neurophysiologic monitoring increased from 13.0-18.3% from 2004-2007, and was lowest in the Midwest (9.2%) compared to other regions (17.5-19.0%).

Conclusions: There is wide variability in technique among surgeons performing ACDF. Surgeons in certain geographic regions clearly show certain preferences. Additionally, there are several clear trends in the technical aspects of the procedure. Future studies should better elucidate the reasons for regional variability and overall trends.

490 DESIGN AND VALIDATION OF A HIP JOINT FATIGUE TEST FRAME FOR THE BIOMECHANICAL EVALUATION OF HIP FRACTURE CONSTRUCTS
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Purpose of Study: Although fatigue testing is commonly used to evaluate and compare fracture fixation, there is not a standardized method for biomechanical testing of hip fracture implants. The purpose of this study was to design, construct and validate a fatigue test machine that mimics the physiologic loading pattern of the hip joint during ambulation while simultaneously measuring implant failure in a quantitative manner.

Methods Used: The fatigue test frame was designed and optimized using Solidworks® CAD software. The completed fixture uses a 2.5” pneumatic cylinder to apply load to the femoral head of a fractured and implanted synthetic bone analog (Sawbones®) while a second 1.5” cylinder cycles the femoral head through flexion (30°) of ACDF patients (RA). The total load on the head was 12° relative to the center axis of the femur. The force acts on the femoral head via an anatomically correct acetabulum. As in normal gait, the load is only applied during flexion resulting in a swing phase (no load) during extension. Data are acquired at 10,000 Hz via a load cell and displacement transducer, which measure the applied load and femoral head displacement, respectively. Failure was defined as 5 mm of femoral head displacement. To validate the construct, five initial samples were tested up to failure or 40 k cycles. Cycle rate is adjustable but was maintained at approximately 1 Hz. A progressive loading protocol was implemented to simulate progressive weight bearing as the patient recovers.

Summary of Results: The load pattern recorded during cycling closely approximates the loads on the femoral head that have been recorded in vivo with instrumented hip prostheses. The peak load was increased from an initial
PLG scaffolds containing known masses of LPA were fabricated using a gas foaming/particulate leaching method. The kinetics of LPA release were quantified by measuring released inorganic phosphate into the media. The osteogenic and proangiogenic capacity of sustained LPA release was examined by stimulating murine MLO-A5 late osteoblasts/early osteocytes and human microvascular endothelial cells (HMVECs), respectively. Cells were seeded at 7500 cells/cm², and transwells containing scaffolds loaded with 0, 1, 5, 10 or 25 µg LPA were placed above adherent cells. Osteogenic potential was assessed by quantifying intracellular alkaline phosphatase (ALP) activity, total protein and DNA content after 7 days in reduced serum-containing basal media. The proangiogenic potential of LPA was measured by quantifying HMVEC proliferation using a Coulter Counter after 3 days of exposure to scaffolds in growth factor deficient basal media.

Summary of Results: All scaffolds demonstrated an initial burst of LPA release over 24 hrs followed by a sustained discharge for the rest of the 7 day study period. We did not observe significant differences in ALP activity for any LPA dosage, but increasing concentrations of incorporated LPA resulted in enhanced MLO-A5 proliferation, with 25 µg LPA yielding a significant increase in DNA content compared to no LPA (P < 0.05, n = 4). HMVEC mitogenic response was significantly enhanced for cells exposed to at least 5 µg LPA compared to no LPA (P < 0.05, n = 4).

Conclusions: The data demonstrate that LPA can be incorporated within scaffolds for sustained release while retaining its bioactivity. The mitogenic effect of LPA suggests that this molecule may not induce osteogenic differentiation in cells of the osteoblastic lineage, but may instead act to enhance the local microenvironment through angiogenesis and neovascularization.

492 SUSTAINED RELEASE OF LYSOPHOSPHATIDIC ACID FROM POLY(LACTIDE-CO-GLYCOLIDE) SCAFFOLDS FOR ENHANCED OSTEOGENESIS

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Purpose of Study: Lysophosphatic acid (LPA) is an important mediator of cell survival, proliferation and angiogenesis. This bioactive phospholipid is significantly less expensive than conventional growth factors used to promote osteogenesis. By incorporating LPA into previously characterized poly(lactide-co-glycolide) (PLG) scaffolds, we hypothesized that LPA can be locally delivered at controllable rates while maintaining desirable stimulatory effects on cells of the endothelial and osteoblastic lineages.

Methods Used: PLG scaffolds containing known masses of LPA were fabricated using a gas foaming/particulate leaching method. The kinetics of LPA release were quantified by measuring released inorganic phosphate into the media. The osteogenic and proangiogenic capacity of sustained LPA release was examined by stimulating murine MLO-A5 late osteoblasts/early osteocytes and human microvascular endothelial cells (HMVECs), respectively. Cells were seeded at 7500 cells/cm², and transwells containing scaffolds loaded with 0, 1, 5, 10 or 25 µg LPA were placed above adherent cells. Osteogenic potential was assessed by quantifying intracellular alkaline phosphatase (ALP) activity, total protein and DNA content after 7 days in reduced serum-containing basal media. The proangiogenic potential of LPA was measured by quantifying HMVEC proliferation using a Coulter Counter after 3 days of exposure to scaffolds in growth factor deficient basal media.

Summary of Results: All scaffolds demonstrated an initial burst of LPA release over 24 hrs followed by a sustained discharge for the rest of the 7 day study period. We did not observe significant differences in ALP activity for any LPA dosage, but increasing concentrations of incorporated LPA resulted in enhanced MLO-A5 proliferation, with 25 µg LPA yielding a significant increase in DNA content compared to no LPA (P < 0.05, n = 4). HMVEC mitogenic response was significantly enhanced for cells exposed to at least 5 µg LPA compared to no LPA (P < 0.05, n = 4).

Conclusions: The data demonstrate that LPA can be incorporated within scaffolds for sustained release while retaining its bioactivity. The mitogenic effect of LPA suggests that this molecule may not induce osteogenic differentiation in cells of the osteoblastic lineage, but may instead act to enhance the local microenvironment through angiogenesis and neovascularization.

493 VARIATIONS IN OUTCOMES OF TOTAL KNEE REPLACEMENTS

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Purpose of Study: Variations exist in the outcomes for total knee arthroplasty (TKA) patients. The objective of our study is to determine if there are variations in outcomes for total knee arthroplasty patients between three UCLA affiliated hospitals: UCLA-Westwood (academic), UCLA-Harbor (county) and UCLA-Santa Monica (private).

Methods Used: Data was collected from patients undergoing total knee arthroplasty surgeries performed at UCLA Medical Center-Westwood (N = 76), UCLA-Harbor (N = 91) and UCLA-Santa Monica (N = 25) from 1/1/2003-12/31/2004. Quality of care was examined pre-operatively, intra-operatively and post-operatively through evidence-based indicators we developed based on the RAND-Modified Delphi expert panel methodology. The level of adherence with recommended care at the three affiliated hospitals was compared.

Summary of Results: Rates of adherence - Westwood 71% (95% CI 69-73%), Harbor 55% (95% Confidence Interval 54-56%) and Santa Monica 70% (95% CI 68-73%) Harbor was found to be statistically different from Santa Monica and Westwood with a P-value < 0.001. Westwood and Santa Monica were also similar in regards to patient ethnicity with a majority of their patients being White (61% and 75% respectively). Harbor TKA patients were predominantly Hispanic accounting for 64% of all TKA’s. There were no significant population differences between Asian and Black patients across each hospital.

Conclusions: No significant difference was observed between Westwood and Santa Monica. However, there was a statistically significant difference in rate of adherence to recommended care between Harbor and two other UCLA- affiliated hospitals. This supports further investigation into the underlying causes of this variation as well as its effect on outcomes.

Western Student Medical Research Forum
Student Scientific Session XII
8:30 AM
Saturday, January 31, 2009

494 CAROTID IMT: COMPARING ANALOG AND RADIO FREQUENCY MEASUREMENTS

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Purpose of Study: Elevated carotid intimal-media thickness (CIMT) is an independent risk factor for coronary artery disease. At present, CIMT is measured by an analog technique that is a derivative of the radio frequency (RF) signal obtained through ultrasound. In conjunction with BioSound Esato, direct radio frequency measurement of CIMT, a theoretically more accurate and less machine sensitive measurement is now possible. A formal comparison between RF and Analog CIMT measurements is required for proper interpretation of the new RF CIMT measurements.

Methods Used: In order to compare RF and Analog CIMT measurements, 84 (168 pairs of measurements) clinically indicated patients were measured with both techniques consecutively between February and July 2008. Similar portions of the carotid were measured by both techniques to minimize the effect of intra-artery variation in lipid deposition or thickening of the intima, and 29 of the 168 pairs were excluded due to measurement difficulties.

Summary of Results: For the included patients, the analog CIMT mean was 542 microns, and the RF CIMT mean was 520 microns. The mean difference between the analog and RF measurements was 22 microns and the results were significant to a p value of approximately zero (P = 0.0000002).

Conclusions: Though the RF measurements were significantly smaller by 22 microns, the difference was not uniform, as 32 of the 139 measurement pairs had greater RF values than analog values. This study was primarily limited by sample size, and on occasion, by image quality. The results of this study begin to develop a frame of reference through which the new RF CIMTs can be interpreted.

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THE EFFECTS OF MUSCLE PARALYSIS ON TIBIAL BONE MORPHOMETRY AT ONE MONTH AND ONE YEAR IN SKELETALLY MATURE RATS

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Purpose of Study: Botox induced muscle paralysis provides a useful model to study skeletal and muscle physiology under conditions which mimic complete denervation. As the popularity of neuromuscular inhibitors increase, it is essential to better understand their side effects on skeletal morphometry.

Methods Used: This study consisted of an in-vitro analysis of seven sets of skeletally mature male Sprague-Dawley rat tibias. All rats received a one-time 6 units/kg botox injection into the tibialis anterior muscle mid-belly of the right hindlimb. The rats were divided into two groups. One group was sacrificed four weeks post paralysis and the second group was sacrificed one year post paralysis. The dissected rat tibias were scanned and analyzed using a Scanco uCT20 scanner. Bone morphometry was analyzed at three locations of the rat tibia: proximal metaphysis, mid-diaphysis and distal metaphysis.

Summary of Results: Bone loss in the proximal metaphysis resulted in a decrease of bone volume to total volume ratio (BV/TV) by 14% one month post-paralysis and 3.4% decrease one year post paralysis. In the distal region, BV/TV decreased 4.1% and 6.0%, in the one month and one year groups, respectively. Changes in total volume, bone volume, trabecular number, trabecular thickness, trabecular spacing between the one month group and the one year group were not significant, nor were changes comparing the botox injected limb to the contralateral limb. In the mid-diaphysis region, there was a 9.2% increase in endocortical volume in the one month group.

Conclusions: Botox induced muscle paralysis of the tibialis anterior muscle produced significantly less bone loss than was hypothesized based on findings from a previous study of calf muscle paralysis. Possible explanations for these findings include muscle mass, contact surface area with the tibia, muscle action during gait and amount of sensory innervation. Findings from this study provide supportive evidence that botox-induced muscle paralysis may cause bone resorption by altering the mechanical environment of the bone and blocking local sensory neuron innervation. The mass, action, an innervation of paralyzed muscle all seem to influence the amount and pattern of bone loss.

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BONY CT SCAN CHANGES ASSOCIATED WITH IMPROVEMENT IN SLEEP APNEA IN PATIENT UNDERGOING LEFORT III DISTRACTION

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Purpose of Study: Lefort III distraction is a recognized treatment for sleep apnea associated with midface hypoplasia. In some patients apnea remains untreated despite successful linear advancement. The purpose of this study was to characterize the bony CT changes occurring in a cohort of patients undergoing Lefort III distraction and compare them to improvement in sleep apnea measures. Our hypothesis was that degree of advancement relative to skull base was related to successful treatment of sleep apnea.

Methods Used: We reviewed records of 13 consecutive patients with syndromal midface hypoplasia but no tracheostomy who underwent Lefort III distraction (mean age 8.8 years) and had pre-op apnea hypopnea index (AHI) >5. Favorable treatment outcome was determined by a post-distraction AHI<5. Linear and angular measurements of bone landmarks selected as being independent of neck position or intubation were generated from pre and post-operative CT scans.

Summary of Results: Nine patients had favorable apnea treatment outcome with a pre-op AHI average of 20 that decreased to an average of 3.5 post-distraction. Four patients did not have improvement in apnea with a pre-op AHI of 18 and a post-op average of 20. Linear distance and percentage increase from PNS to skullbase was not significantly different between the two groups. SNA however increased 18 degrees in the treated group vs 6 degrees in the persistent apnea group (24% vs 7% increase respectively). Pre-op and post-op % change in palate plane relative to skull base was not significant between the two groups.

Conclusions: SNA describes a change in maxillary position relative to skull base. Minimal change in this relationship was a consistent finding in the four patients with minimal improvement in sleep apnea despite successful linear advancement. These findings suggest that significant change in SNA relation is a positive indicator for improvement in sleep apnea measures following the Lefort III distraction procedure.

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CHARACTERIZATION OF LYMPHOID AGGREGATES FOUND IN LYMPHATIC MALFORMATIONS USING IMMUNOHISTOCHEMISTRY

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Purpose of Study: Normal lymphoid tissue includes T-lymphocytes, B-lymphocytes, and lymphatic vasculature. A marker for T-lymphocytes is CD3. One marker for B-lymphocytes is CD19. A lymphatic vessel marker is podoplanin. We performed immunohistochemistry using these known lymphoid tissue markers to characterize lymphoid aggregates found in lymphatic malformations.

Methods Used: Specimens: Surgical specimens obtained from Department of Pathology Seattle Children’s Hospital through an IRB approved protocol.

Immunohistochemistry: Specimens stained were formalin-fixed, paraffin-embedded tonsil and lymphatic malformations. Antigen retrieval was performed using heat-treatment with citrate pH 6. After appropriate blocking, primary antibodies for CD3, CD19 and Podoplanin were incubated overnight. Peroxidase-peroxidase-conjugated secondary antibodies were detected with diaminobenzoamide. Sections were counterstained with hematoxylin, dehydrated and mounted in DPX. Antibodies were diluted according to manufacturer’s recommendation. Negative controls containing secondary antibody only were performed.

Photomicrographs: Images were obtained using a Nikon Eclipse E400 microscope with SPOT RT Slider digital camera and SPOT software.

Summary of Results: A representative example from one lesion was analyzed. CD19 shows staining of B-lymphocytes within the lymphoid aggregates. Podoplanin reveals lymphatic vasculature surrounding the lymphoid aggregate. CD3 shows no T-lymphocytes within lymphoid aggregates. Positive controls with tonsil sections were stained with CD3 and CD19. Negative controls contained secondary antibody only.

Conclusions: Lymphoid aggregates within lymphatic malformations are predominantly comprised of B-lymphocytes. The finding of a difference in lymphocyte composition may have implications in the pathogenesis of these lesions. This information may also contribute to improvements in LM treatment. This is a pilot study that needs further investigation involving a larger sample size and more lymphoid cell markers.
Case Report: Whole genome scanning technologies such as array-based comparative genomic hybridization (array CGH) have facilitated the detection of interstitial copy number alterations in up to 10% of individuals with cognitive impairment of unknown etiology. In 2006 Koolen and colleagues described three individuals with a microdeletion at 17q21.31 who had a distinctive pattern of malformation including ptosis, low set ears, a distinctive tubular nose with a bulbous nasal tip, and a broad chin. Since this report, 25 cases have been described confirming the distinctive phenotype. Affected individuals have significant hypotonia and variable degrees of cognitive impairment. The microdeletion occurs in a region of the genome that harbors a 900-kb inversion polymorphism (H2 haplotype), which is present in 20% of Europeans. The inversion directly orients low copy repeats that immediately flank the breakpoints in the deleted region. All microdeletion to date have occurred on the H2, rather than the H1 (non-inversion) background. The natural history of microdeletion 17q21.31 is currently being elucidated.

We have recently diagnosed an 8-year-old girl with de novo microdeletion 17q21.31. She was referred for genetic reevaluation when a dilated aortic arch was discovered in the course of evaluation of a possible arthrythmia. Aortic dilatation has not been described in other patients. The purpose of this report is to suggest that aortic root measurements should be assessed in individuals with microdeletion 17q21.31.

499 DIABETES AND HYPERTENSION PREVALENCE 20 YEARS FOLLOWING EXTRACORPOREAL SHOCKWAVE LITHOTRIPSY (ESWL)


Purpose of Study: ESWL is a mainstay of therapy in the treatment of kidney stones. It has been suggested that ESWL may predispose patients to diabetes (DM) and hypertension (HTN). In our study, the prevalence of DM and HTN in patients treated with ESWL 20 years ago was compared to that of the provincial population.

Methods Used: We performed telephone surveys on 727 patients who underwent ESWL between 1985-1989. Due to difficulty in identifying patients who had never been treated with ESWL for stone disease, our study group was compared to the B.C. prevalence of DM and HTN. In 1989, ESWL protocol was changed from an unmodified Dornier HM3 (single shockwave high intensity) to a modified HM3 (dual shockwave low intensity).

Summary of Results: The response rate was 37.3%. Patients were ineligible due to incorrect address (202), refusal/ability to consent (35), unreachable (114), deceased (43), unsure of diagnosis (3), diagnosis prior to ESWL (14), and other reasons (61). The mean age was 65.4 years and BMI was 27.2 kg/m². There was a greater proportion of overweight and obese patients in the study group compared to the provincial average. There was an increase in the likelihood of DM in males who underwent ESWL (OR: 2.07 95% CI 1.9-3.9) P < 0.0001. Univariate and multivariate survival analysis did not show any independent effect of gender or type of lithotripter in likelihood of DM diagnosis. Incidence of HTN was increased in both sexes: Male OR: 1.91 95% CI: 1.39-2.62; Female; OR: 2.19 95%CI: 1.45-3.32. See table.

Conclusions: There appears to be no relationship between DM development and the type of lithotripter used. Because this study lacks proper controls, the increased prevalence of DM in males cannot be solely attributed to ESWL. DM itself is a risk factor for stone disease. Results suggest that an association may exist between ESWL therapy and HTN development for both males and females.

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Diabetes Prevalence (%)</th>
<th>Hypertension Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Single shockwave high intensity</td>
<td>28.7</td>
<td>20.0</td>
</tr>
<tr>
<td>Dual shockwave low intensity</td>
<td>14.9</td>
<td>11.6</td>
</tr>
<tr>
<td>Study groups pooled (1985-1995)</td>
<td>23.2</td>
<td>16.1</td>
</tr>
<tr>
<td>Provincial B.C Average (Age 55-74 years)</td>
<td>10.1</td>
<td>9.1</td>
</tr>
</tbody>
</table>

500 PROGRAMMED CELL DEATH-1 INTERACTION WITH PROGRAMMED CELL DEATH LIGAND REGULATES NEURONAL CELL DEATH IN THE MOUSE RETINA

N.M. Gandhi1, C. Sham2, L. Chen1,4, X. Yang1, A.H. Sharpe4, G. Freemantle1, J. Braun2, L. Gordon1,6, 1University of California at Los Angeles, Los Angeles, CA; 3University of California at Los Angeles, Los Angeles, CA; 4University of California at Los Angeles, Los Angeles, CA; 5Harvard Medical School, Boston, MA; 6Harvard Medical School, Boston, MA and 7Greater Los Angeles VA Healthcare, Los Angeles, CA

Purpose of Study: During retina maturation, retinal ganglion cell (RGC) undergo neuronal culling via programmed cell death. We observed that the immune receptor, programmed cell death-1 (PD-1), typically found in lymphocytes, is constitutively expressed in adult mouse RGCs. PD-1 expression varies during retinal development, peaking during the postnatal period of RGC culling. Antibody blockade of PD-1 at P0 enhances RGC survival and decreases caspase-3 apoptotic pathway activity. Concordantly, there is a transient early developmental defect in RGC culling in PD-1-/- mice. During development, we predict one or both known PD-ligands will be expressed and PD-L1/L2 double knockout (DKO) mice to have increased RGCs, due to defective developmental culling, as observed in the PD-1-/- mice.

Methods Used: See Poster

Summary of Results: We measured PD-L1 and PD-L2 gene expression by RT-PCR in retinas from groups of 3 mice, over the first week of development. Both PD-L1 and PD-L2 expression are observed through P7, peaking at P4. Immunofluorescence staining revealed maximal PD-L2 protein expression at P7, localized in the ganglion cell layer (GCL) and inner nuclear layer (INL) of the rat retina. Immunofluorescence staining of mature PD-L1/L2 DKO retinas revealed an increased number of RGCs and total GCL cellularity, as compared to PD-1-/- and wildtype mice. Furthermore, PD-L1/L2 DKO mice were observed to have abnormal INL decompaction by H&E.

Conclusions: There is evidence for PD-ligand transcriptional regulation during development, as well as PD-ligand protein expression within the retina. Collectively, these findings support that PD-1/PD-ligand interaction regulates neuronal cell death in the mouse retina.

501 MOUSE MODEL OF MULTIPLE SCLEROSIS

C.M. Biggs1,2, H.L. Atkins1 1Ottawa Health Research Institute, Ottawa, ON, Canada and 2University of British Columbia, Vancouver, BC, Canada

Purpose of Study: The progressive accumulation of disabilities in Multiple Sclerosis (MS) is thought to be mediated by an auto-destructive immune reaction. A clinical trial currently underway uses chemotherapy to remove the dysfunctional immune system followed by immune reconstitution using purified autologous hematopoetic stem cells (HSC). Microenvironment alterations due to transplant chemotherapy or recipient age may explain the persistent naive CD4 T lymphopoeita despite recovery of early lymphoid precursors seen in HSC transplant recipients. In order to overcome the limitations to experimentally probing the reconstituted immune system of MS patients, we are developing a murine xenograft model system in which to study lymphocyte dynamics caused by microenvironmental changes before and after HSC transplantation.

Methods Used: Three NOD/SCID/B2m(null) immunodeficient mice were injected with 10^7 healthy control human PBMCs intravenously (IV), intraperitoneally (IP), or ½ IV & ½ IP. After 4-6 weeks, mice were sacrificed and spleen and blood samples analyzed by flow cytometry.

Summary of Results: The IP injected mouse demonstrated the best engraftment with human lymphocytes composing 29% of circulating and 73% of spleen lymphocytes. Immunodeficient mice will support significant engraftment of human lymphocytes. This may be a promising model for dissecting changes in the immune system associated with MS remission following HSC transplantation.

502 CHARACTERISTICS OF SLEEP DISTURBANCE AMONG ORTHOPEDIC PATIENTS DURING POST-ACUTE REHABILITATION

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0.001). Further research is needed to evaluate methods to improve sleep quality during this critical period of rehabilitation and recovery.

Summary of Results: There were 739 responses from 86 programs. Delivery experience varied widely. For R1s number of deliveries attended averaged 24.8 (SD 26.2 range 0-240). For R2s number of deliveries over 2 years averaged 49.4 (SD 42.1 range 2-294). For R3s number of deliveries over 3 years averaged 59.9 (SD 43.3 range 1-275). There was no difference by 5 geographic regions. Community hospital (n = 10) residents had more deliveries (mean = 95.8) than either university-based (n = 65 mean = 52.6) or community hosp./univ.-affiliated (n = 121 mean = 61.0). Programs with 46-59 residents averaged 75.4 deliveries compared to 44.9 for programs with 60-126 residents. There was wide variability in number of deliveries depending on individual program attended. A composite score of resident comfort level in leading delivery room resuscitation correlated with number of deliveries attended (P = 0.01 Figure).

Conclusions: Newborn resuscitation is an integral part of pediatric practice, yet no mandatory minimum experience is required during residency. We found wide variation in delivery room experience across programs. Comfort with leading resuscitation correlated with greater experience.

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PEDIATRIC RESIDENT ATTENDANCE AT DELIVERIES

D. Patel1, J.L. Martin2,3, C. Alessi2,31western University of Health Sciences, College of Osteopathic Medicine of the Pacific, Pomona, CA; 2Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA and 3David Geffen School of Medicine, Los Angeles, CA

Purpose of Study: Older orthopedic patients endure invasive and complex surgical procedures after which they commonly receive physical and occupational therapy in post-acute care settings. In this study, we sought to characterize sleep disturbance for orthopedic patients over age 65.

Methods Used: Within a larger study of sleep during post-acute rehabilitation, 98 patients admitted after orthopedic procedures (47 elective; 51 non-elective procedures) completed study assessments, including 1 week of wrist actigraphy (to measure sleep/wake) and the Pittsburgh Sleep Quality Index (PSQI was used to assess subjective sleep quality; scores >5 indicate disrupted sleep). The PSQI was administered twice: once to assess sleep quality prior to the health event precipitating hospitalization (pre-morbid) and a second time to assess sleep during the post-acute rehabilitation stay.

Summary of Results: Table 1 describes sleep quality for all orthopedic patients (n = 98) and for those receiving rehabilitation after elective (e.g., hip replacements; n = 47) vs. non-elective (e.g., fracture after an injurious fall; n = 51) procedures.

Conclusions: Patients reported significantly worse sleep during the post-acute rehabilitation stay compared to their pre-morbid sleep quality (P < 0.001). Further research is needed to evaluate methods to improve sleep quality during this critical period of rehabilitation and recovery.

Sleep measures [mean (SD)] during the post-acute rehabilitation stay.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole Group</th>
<th>Elective (n=47)</th>
<th>Non-Elective (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSQI total score, pre-morbid</td>
<td>5.7 (4.1)</td>
<td>5.7 (3.9)</td>
<td>5.7 (4.3)</td>
</tr>
<tr>
<td>PSQI total score, during rehabilitation stay</td>
<td>8.7 (4.3)</td>
<td>9.2 (4.0)</td>
<td>8.2 (4.6)</td>
</tr>
<tr>
<td>Evening bed time</td>
<td>21:43 (0:55)</td>
<td>21:42 (0:53)</td>
<td>21:44 (1:07)</td>
</tr>
<tr>
<td>Morning wake up time</td>
<td>6:54 (9:52)</td>
<td>6:36 (0:51)</td>
<td>7:10 (0:49)</td>
</tr>
<tr>
<td>Nighttime hours of sleep*</td>
<td>4:57 (1:58)</td>
<td>5:00 (2:00)</td>
<td>4:53 (1:57)</td>
</tr>
<tr>
<td>Nighttime percent sleep*</td>
<td>54.8 (21.4)</td>
<td>57.1 (21.9)</td>
<td>52.6 (20.9)</td>
</tr>
<tr>
<td>Nighttime number of awakenings*</td>
<td>15.5 (7.5)</td>
<td>14.5 (6.6)</td>
<td>16.4 (8.2)</td>
</tr>
<tr>
<td>Daytime percent sleep*</td>
<td>12.9 (10.0)</td>
<td>11.4 (8.3)</td>
<td>12.7 (10.6)</td>
</tr>
</tbody>
</table>

* Determined from wrist actigraphy: nighttime = bed time to wake up time; daytime = wake up time to bed time

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A REVIEW OF THE ROLE OF VITAMINS IN PHOTOAGING

J. Ahdout1, J. Zussman2, J. Kim2 1David Geffen School of Medicine at UCLA, Los Angeles, CA and 2David Geffen School of Medicine at UCLA, Los Angeles, CA

Purpose of Study: With the rise of the cosmeceutical industry, numerous formulations have surfaced with claims of reducing the clinical manifestations of photoaging. Many of these products capitalize on the positive connection the public makes with vitamins, especially with respect to their antioxidant capabilities. An impressive amount of basic science and clinical research has been conducted in both an attempt to discover novel strategies for preventing detrimental sun damage and also to validate the addition of vitamins to skincare products. The purpose of this study is to objectively evaluate studies assessing the utility of individual vitamins in modifying the process of photoaging.

Methods Used: In this review, we will systematically examine the evidence supporting the use of vitamins in oral and topical formulations and provide a brief summary of the pathogenesis of photoaging.

Summary of Results: There is variable evidence both supporting and refuting the role of individual vitamins in the treatment of photoaging.

Conclusions: It is essential to provide our patients with substantiated counseling regarding the efficacy of commercial assertions.

Resident’s Forum

9:00 AM

Saturday, January 31, 2009

506

PERCUTANEOUS CORONARY INTERVENTION OF LEFT MAIN CORONARY ARTERY DISEASE IN PATIENTS WITH HIGH SURGICAL RISK

M. Shannugasundaram, J. John, Y. Huang, T. Hagerty, R. Arsanjani, H. Thai Sarver Heart Center, University of Arizona, Tucson, AZ

Purpose of Study: Left Main coronary artery disease (LM CAD) is associated with a high risk of cardiac death due to left ventricular dysfunction and arrhythmias. Percutaneous coronary intervention (PCI) has lately been proposed as an alternative to coronary artery bypass graft surgery (CABG) for LM CAD, especially in high risk patients. The predictors of outcome after PCI of LM CAD, however, remain largely unclear.

Methods Used: A retrospective case review was performed to select all patients who underwent left main interventions at our institution between Jan 2005 and May 2008. Demographics, Society of Thoracic Surgeon (STS) score, indications for PCI, procedural success and 30 day mortality data were collected. Regression analysis was used to identify predictors of 30 day mortality.

Summary of Results: A total of 23 patients were included in this analysis. The mean age was 69.4 ± 7.6 years. The incidence of diabetes was 47.8%, hypertension was 91.3% and the mean left ventricular ejection fraction was 48.1 ± 13.15%. The mean STS score was 7.5 ± 11.4%. Cardiogenic shock was present in 4 patients (17.4%), 12 patients (52.2%) had prior CABG. There were 4 in hospital deaths (17.4%), with 3 of the 4 the patients presented in...
cardiogenic shock (75%), with the fourth patient death related to sepsis. There was 1 death (5.2%) in the 30 day follow up with unclear reason. There was no post procedure myocardial infarction or target vessel revascularization even at 30 day follow up. On Logistic regression analysis the only significant predictor of mortality was the pre procedure STS score with an odds ratio of 1.18 ($P = 0.03$).

**Conclusions:** The review of our data suggests that percutaneous coronary intervention is a viable alternative to CABG in high surgical risk patients with LM CAD. It also suggests that the STS score can be effectively used for risk stratification prior to left main PCI in high surgical risk patients with LM CAD.

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**506 GLOBAL HEALTH INITIATIVES: VALUE AND RELEVANCE TO RESIDENCY TRAINING**


**University of British Columbia, Vancouver, BC, Canada and Makerere University, Kampala, Uganda**

**Purpose of Study:** Over the years the field of medicine has drastically evolved. With globalization, medicine is no longer limited by geographical borders, making international health and social responsibility areas of importance for the modern day physician. In addition a holistic understanding of medicine now encourages a multidisciplinary approach to optimal healthcare, necessitating skills in effective teamwork and team leadership. These concepts however, are currently not incorporated into the curriculum of conventional residency training. The purpose of this study is to determine if embarking on a global health initiative as a resident team leader is a useful component of residency training, providing practical experience in global health and team building.

**Methods Used:** A multidisciplinary team of 3 medical students, 3 undergraduates, 1 masters student, 1 paediatrician and 1 paediatric resident travelled to an aboriginal community in Hartley Bay, Canada and 4 rural communities outside Kampala, Uganda to participate in Brighter Smiles (a global health initiative focused on improving paediatric oral health). As resident team leader, responsibilities included organization pre-trip, coordinating logistics of each community visit with local collaborators, allocating project supplies funds and participation in project delivery. In addition a clinical component involved working at Hartley Bay Health Clinic and Mulago Hospital, Kampala.

**Summary of Results:** Brighter Smiles provided an opportunity to practice medicine in local, rural communities and resource-limited, developing world hospitals, expanding knowledge and skills of clinical medicine. The importance of cultural sensitivity was also learned, valuable for practicing medicine in multicultural Canada. The project encouraged team work both as team leader and player, allowing one to appreciate the diverse skills of a multidisciplinary team.

**Conclusions:** A wealth of knowledge and experience about life and medicine exists outside of the conventional academic centres where residents train. Participation in a global health initiative involving local communities and communities abroad is an invaluable resident experience, fostering team building and creating doctors with a more comprehensive understanding of health and its broader determinants.

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**507 DRUG SUSCEPTIBILITY TRENDS AMONG COMMUNITY ACQUIRED AND HOSPITAL ACQUIRED SOFT TISSUE INFECTIONS**

A.D. Kirk, S. Mirhosseini, B. Aghani

**UC Irvine, Orange, CA**

**Purpose of Study:** Soft tissue infections caused by S. aureus have become a major cause of morbidity among children. The purpose of this study was to compare the trend of drug susceptibility among S. aureus isolates from soft-tissue infections among the pediatric population between 2 time periods, 2001-03 versus 2004-06.

**Methods Used:** Records of patients who had S. aureus isolated from soft tissues were reviewed to determine whether they were community acquired (CA) or hospital acquired (HA). Drug susceptibilities of the isolates were recorded and compared for the 2 time periods.

**Summary of Results:** Of 47 skin and soft-tissue (SST) isolates in 2001-03 and 90 SST isolates in 2004-06, 20% and 40% were resistant to oxacillin ($P = 0.013$), respectively. Comparing the two time periods, erythromycin resistance remained high (>80%) and did not change significantly for the MRSA isolates, but increased from 25% to 53% for the HA-MSSA isolates ($P < 0.05$). There was also a trend toward an increase in clindamycin-resistance (10% vs. 22%, $P = 0.076$); the most increase was among the HA-MSSA isolates (6% vs. 26%). Clindamycin-resistance remained low (<10%) among CA-MSSA isolates.

**Conclusions:** Soft tissue infections caused by S. aureus are increasing among the pediatric population. Because of differences in drug-susceptibilities, distinction of community versus hospital acquired infections is important to determine the appropriate empiric therapy.

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**508 MANAGEMENT OF LIVER ABSCESS IN THE NEONATE**

A. Weiner, D.A. Gremse, P. Patamasuson

**University of Nevada SOM, Las Vegas, NV**

**Purpose of Study:** Neonatal hepatic abscess is a relatively rare condition that is associated with risk factors such as umbilical venous catheterization, home births, systemic infections, abdominal surgery, and immunodeficient states. Recommended management includes long term antibiotic therapy with or without percutaneous or open drainage. We report the presentation and treatment outcomes of two neonates with hepatic abscesses.

**Methods Used:** We reviewed the medical records of two neonates with hepatic abscess to identify risk factors, diagnostic evaluation, and treatment outcomes.

**Summary of Results:** Patient 1 was born at 24 weeks gestation. Necrotizing enterocolitis (NEC) occurred on the 29th day of life. The patient was treated with antibiotics × 7 days and feedings were restarted but abdominal distention developed. Liver abscesses were diagnosed on the 46th day of life. Abdominal ultrasound revealed two echogenic foci of 1.3 × 0.7 and 1 × 0.5 cm in the liver. The liver abscesses were treated with IV vancomycin and meropenem × 6 weeks. Patient 2 was born at term with perinatal asphyxia (APGARS 0/7/9 @ 1/5/10 min). The patient developed NEC on the 12th day of life. He was NPO on antibiotics × 14 days and subsequently developed abdominal distention. Abdominal CT showed two fluid collections in the hepatic parenchyma measuring 2.8 × 3 cm and 2.7 × 2.3 × 2.2 cm. Liver abscess was treated with vancomycin and meropenem × 6 weeks and his abscesses resolved.

**Conclusions:** Based upon our experience we propose that medical management alone can be considered as an alternative to surgical drainage and antibiotics when treating neonatal liver abscesses.

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**509 LOW ALBUMIN/GLOBULIN RATIO AS A RISK FACTOR FOR THE OCCURRENCE OF CORONARY ARTERY DISEASE**

S. Puttaswamy, H. Bhukthavatsalam, P. Singh, S. Sinnapunyagam

**Coney Island Hospital, Brooklyn, NY**

**Purpose of Study:** Conditions like autoimmune disorders (e.g. SLE) gammopathy (e.g. multiple myeloma) liver and kidney diseases are well known risk factors for coronary artery disease (CAD). Globulin (G) is significantly increased in these conditions. As the ratio of albumin/globulin (A/G) decreases the viscosity of blood increases which could explain the risk...
of Acute Coronary Syndrome (ACS). The purpose of this study was to investigate the relationship between A/G and CAD.

Methods Used: It was a retrospective study, reviewing electronic medical records of 100 subjects of age group 50-75 years admitted during 2005-2007. Two groups were compared for their A/G value. Group 1 of 50 subjects (1st episode of ST Elevation Myocardial Infarction and Non ST Elevation Myocardial Infarction with significant coronary occlusion) with group 2 of 50 subjects (normal coronaries). Subjects with Diabetes, Chronic Kidney Disease, Malignancy, Connective disorders were excluded from the study. The study used regression analysis and t-test to see statistically significant difference.1.45 was taken as the cut off A/G ratio

Summary of Results: Analysis showed statistically significant difference between the two groups for A/G (P = 0.0001), A alone (P < 0.0001), G alone (P = 0.6931) and total protein (P = 0.0001). There was also statistically significant difference between the two groups when both sex were matched, for male A/G (P < 0.0001), A alone (P < 0.0001) and in female A/G (P = 0.0252), A alone (P < 0.0001), except for G in both the sex. Using logistic regression analysis it was noted that the probability of suffering disease increases with the decrease of the A/G ratio, odds ratio(OR) = .023 in male and female combined, OR = .006 in men and OR = .049 in female.

Conclusions: From this it can be concluded that there is an inverse relationship between A/G and occurrence of coronary artery disease. This could help in risk stratifying patient for acute coronary syndrome. Further prospective studies need to be done to see if A/G could be used as a marker for ACS.

<table>
<thead>
<tr>
<th>A/G VALUE</th>
<th>FEMALE</th>
<th>MALE</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP 1 AVERAGE STD COUNT</td>
<td>1.21 ±0.26 16</td>
<td>1.23 ±0.24 34</td>
<td>1.22 ±0.25 50</td>
</tr>
<tr>
<td>GROUP 2 AVERAGE STD COUNT</td>
<td>1.42 ±0.29 28</td>
<td>1.51 ±0.26 22</td>
<td>1.46 ±0.28 50</td>
</tr>
</tbody>
</table>

510 PERMANENT PACEMAKERS IN HEART TRANSPLANT PATIENTS

B. Kim, M. Hamilton, J. Kobashigawa David Geffen School of Medicine at UCLA, Los Angeles, CA

Purpose of Study: Conventionally, the need for permanent pacemaker (PPM) placement after heart transplantation is thought to be benign and assumed mainly due to preoperative amiodarone use. However, we hypothesize that these patients may in fact have worse outcomes and the purpose of the current study was to examine the outcomes of patients who require PPM post-transplant.

Methods Used: Between January 2000 and December 2005, we reviewed 346 heart transplant patients. 45 patients had PPMs implanted post-transplant: early implants (>30 days, range 7-30 days, n = 15) and late implants (>30 days, range 85-2506 days, n = 10). Control patients were matched 5:1 to PPM patients (by age, sex, CMV mismatch status). Control patients were also matched for time from transplant to PPM implant, which was the start of the follow-up period. Pre-transplant amiodarone use was seen in 3/15 of the early PPM group and 1/10 in the late PPM group. Five-year survival and non-fatal major adverse cardiac events (NF-MACE, myocardial infarction, heart failure, percutaneous intervention, stroke, peripheral vascular disease) was assessed.

Summary of Results: Compared to early controls, early PPM patients had decreased 5-year survival (53.3% vs. 81.3%, P = 0.014) and decreased freedom from NF-MACE (66.7% vs. 93.3%, P = 0.002). 5/7 deaths in the early PM group were due to immunologic causes (rejection, N = 3 and infection, N = 2). However, freedom from cardiac allograft vasculopathy (CAV, >30% stenosis by angiogram) was similar in the early PPM group and early controls (P = 0.34). In the late PPM group vs. late controls, 5-year survival (80.0% vs. 90.0%, P = 0.38), freedom from CAV (90.0% vs. 88.0%, P = 0.89) and freedom from NF-MACE (80.0% vs. 96.0%, P = 0.067) were comparable. For both the early and late PPM groups, no patients were PPM dependent at 1-year post implant.

Conclusions: Early PPM requirement after heart transplant is a marker for decreased 5-year survival, with the majority of deaths due to infection or rejection. This suggests that an immune mechanism may be responsible for the early PPM requirement. Heightened awareness is essential in monitoring this high-risk population.

511 MUSIC INSPIRES HEALTH: MULTIMEDIA AND HIV/STI PREVENTION

B.H. Levy1, E. Wershba2, E.J. Levy3 1University of Arizona, Tucson, AZ; 2Phoenix Children’s Hospital, Phoenix, AZ and 3Emory University, Atlanta, GA

Purpose of Study: Residents and medical students at the University of Arizona, Emory University, and the University of Virginia recently organized a new national health education campaign called “Music Inspires Health” aimed at teaching high school and college students about HIV and STI prevention. We conducted online surveys at colleges around the country for 3 years to assess which health education topics students felt like their peers needed to learn more about during high school and college. We wanted to identify which celebrities college students trust to present accurate health information. Finally, our goal was to determine which multimedia education methods would be most effective.

Methods Used: A national online survey was created and administered on www.surveymonkey.com between 2006-2008. Questions for our research study were written by medical students, physicians, and public health experts on our national medical advisory board. College students enrolled in the study by agreeing to an informed consent form and filling out demographic descriptions. We recruited students with campus posters and emails from student government organizations. Survey answer choices were jumbled at random by the website for each responder to prevent order bias. A sampling of the college campuses that participated included: University of Arizona, UCLA, UC Berkeley, University of Virginia, Emory, University of Georgia, Morehouse, Georgia Tech, Northwestern, and the University of Florida.

Summary of Results: Consistent condom use was the most important topic chosen by college students. Will Smith, U2, and Dave Matthews Band were the best musicians to teach adolescents about HIV/STD Prevention. 1) Flash Animation and 2) Entertaining Health Education Short Films were the two most important multimedia strategies that college students chose to teach their peers about health. 93% of college students surveyed wanted health education campaigns to use more flash animation on their websites. 84% of college students believed that entertaining short films should be used to empower young adults to make healthier decisions.

Conclusions: This research study fine-tuned plans for our 2008 national health education concert tour and a multimedia based health education website.

512 LUCIO’S PHENOMENON COMPLICATED BY PULMONARY TB

V.D. Hernandez1, S. Huerta2, J. Cisneros1 1University of Juarz Durango, Durango, Mexico; 2University of Texas Southwestern Medical Center, Dallas, TX and 3Social Security Mexican Institute, Durango, Mexico

Case Report: Background: Lucio’s phenomenon is a form of lepromatous leprosy characterized by painful erythematous lesions of the skin. It is typically observed in untreated cases of leprosy and its clinical manifestations may be complicated by other infections. Case Report: In the present report, we discuss a 52-year-old man, with a 10 days previous diagnosed with leprosy, which was being treated with Thalidomide, dapsone, rifampin, clofazimine. The patient first presented with sudden onset of palpable, maleolar, and bilateral hand edema. This rapidly evolved into dermatosis characterized by the formation of papulous lesions in face, arms, thorax and groin, which were very pruriginous. His past medical history was negative for allergies, or a history of blood transfusions. On physical examination, he was febrile with a temperature of 38°C, and tachypnic with a heart rate of 115 BPM. Laboratory analysis showed eosinophilia (48%), and anemia with a hemoglobin of 7.3 mg/dL. The papulous lesions rapidly transformed into purulent ulcers within 10 hour of their appearance. During the second day of admission, he still was febrile and new oral mucosa ulcers developed, which were characterized by pseudomembranes. His symptoms continued to worsen and dyspnea, and productive green cough developed. Chest X-ray demonstrated lesions consistent with Pulmonary TB. Treatment was then changed to target mycobacterium TB as well as leprosy. His dermal lesions began to form scars and the symptoms improved following a week of antibiotic treatment and supportive measurements including blood transfusion. Discussion: Lucio’s phenomenon is a rare form of leprosy whose clinical presentation and
513 QUALITATIVE ASSESSMENT OF FACTORS AFFECTING FRUIT AND VEGETABLE INTAKE AMONG ADOLESCENTS AT RISK OF FOOD INSECURITY

J. Ng, K.C. Harris BC Children’s hospital, Vancouver, BC, Canada

Purpose of Study: Poor diet contributes to the growing epidemic of childhood obesity. Obesity is associated with coronary heart disease, diabetes and reduced life span. Low fruit and vegetable (FV) intake is one component of poor diet in children and is more prevalent in food insecure children and adolescents. Little is known about the factors influencing FV intake in Canadian schoolchildren. The purpose of this study was to determine what factors influence FV intake in Canadian adolescents at risk of food insecurity in order to help design an intervention study to improve diet.

Methods Used: A focus group was conducted in children 13-16 years old. Based on previous research done in the United States and Europe, we developed an interview guide to facilitate the focus group. Two trained and facilitators moderated the focus group. Discussion focused on personal factors (taste preferences, health beliefs, knowledge and awareness), school factors (availability, peer influences, food policy), and family food environment (family influences, availability). Data from the focus group were independently reviewed by 2 investigators. In cases of discrepancy, data records were reviewed until consensus was reached.

Summary of Results: Twenty-one adolescents, aged 13 to 16 years, volunteered to participate. Twenty of 21 were from First Nations groups. Taste preference and cost were the most common personal factors influencing FV intake. The most important school factor was greater accessibility to tasty, cheaper and unhealthy foods compared with FV choices. At home, parental involvement was the most influential factor. Many children did not believe that ill-effects from poor diet were relevant to their personal well-being. This was despite having family who suffered from diet-related diseases.

Conclusions: School-based FV programs in food insecure areas should be designed to address factors that influence FV intake. Poor diet contributes to the growing epidemic of childhood obesity. Obesity is associated with coronary heart disease, diabetes and reduced life span. Low fruit and vegetable (FV) intake is one component of poor diet in children and is more prevalent in food insecure children and adolescents. Little is known about the factors influencing FV intake in Canadian schoolchildren. The purpose of this study was to determine what factors influence FV intake in Canadian adolescents at risk of food insecurity in order to help design an intervention study to improve diet.

514 TREATING CONGENITAL PORTOSYSTEMIC SHUNTS IN NEWBORNS

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Purpose of Study: Congenital portosystemic shunts (CPSs) likely arise from developmental errors in the subcardinal-vitellobiumbical venous systems. Treatment strategies are controversial. We report 3 newborns with CPSs who received different treatments.

Methods Used: Case 1: A prenatal fetal echocardiogram (Echo) demonstrated an abnormal venous connection between the portal sinus with the right atrium. At 20 days-of-age, an Echo noted a persistent CPS between the portal sinus and right atrium. An MRI confirmed the pathology. Because of increasing biventricular hypertrophy and pulmonary hypertension, we performed interventional cardiac catheterization (ICC) and occluded the CPS with two Amplatz vascular plugs.

Case 2: A 5-day-old underwent an Echo that showed moderate biventricular hypertrophy and a CPS connecting the portal sinus to the inferior vena cava. At 25 days-of-age, we performed an ICC because of persistently abnormal liver function and occluded the CPS with a 5/4 Amplatz ductal device.

Case 3: A prenatal Echo in a 33-week fetus with trisomy 21 showed mild cardiomegaly, a dilated inferior vena cava, absent ductus venosus, and a CPS between the portal sinus and the inferior vena cava. A postnatal Echo confirmed the findings. Over a 3-month follow-up, the CPS decreased in size, laboratory testing remained normal, and the patient did not require intervention.

Summary of Results: We report 3 newborns with congenital portosystemic shunts: two symptomatic treated with Amplatz vascular plug occlusion, and one asymptomatic not needing intervention.

Conclusions: Persistent symptomatic CPSs may need to be eliminated. CPSs can be occluded with vascular plugs delivered during ICC, even in newborns. Asymptomatic patients should be followed closely and treated conservatively.

515 TGF-ß2 CAN BE PRESENT IN INFANT FORMULA, RESISTS DIGESTION IN VITRO AND IS BIOLOGICALLY ACTIVE

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Purpose of Study: TGFß2 is present in human milk and is believed to be important for IgA production and oral tolerance induction. Concentrations are much lower in bovine milk, but by utilizing milk protein sources high in TGFß2, formula content of TGFß2 can be increased considerably. The purpose of this study was to investigate whether TGFß2 in human milk and formula can resist proteolysis under conditions similar to those in the infant gut.

Methods Used: Human milk and infant formula were exposed to pepsin at pH 5.0, 3.5 or 2.0 (reflecting increasing maturity of the infant gut) at 37°C for 30 min, neutralized to pH 7.0 by bicarbonate and incubated for 30 min with pancreatic enzymes. TGFß2 in original samples, pepsin digests and pepsin+pancreatin digests was analyzed by enzyme-linked immunosorbant assay (ELISA). TGFß2 signal through cell surface receptors with serine/threonine kinase activity to intracellular signaling components known as Smads, which in turn translate to the nucleus leading to assembly of the transcriptional apparatus of target genes. The Smad2 Redistribution Assay utilizes the MDA-MB-468 cell line and TGFß2-induced Smad2 translocation is monitored by translocation of a GFP-Smad2 fusion protein from the cytoplasm to the nucleus. The assay response is read using the Cellomics ArrayScan VTI HCS system.

Summary of Results: The level of TGFß2 in infant formula was variable (113-429 pg/ml), but in some cases exceeded that of these particular human milk samples (285-518 pg/ml). Digestion with pepsin at pH 2.0 or 3.5 substantially increased the immunodetectable TGFß2 in formula by ~250-400%, and digestion with pancreatic enzymes increased it even further (to ~400-600%). Pepsin digestion at pH 5.0 resulted in lower levels of TGFß2. This strongly suggests that acidification and/or proteolysis play important roles in liberation of immunodetectable TGFß2. Additionally, the TGFß2 in these digests (pepsin+pancreatin) was highly bioactive as measured by the Smad2 Redistribution assay.

Conclusions: TGFß2 present in infant formula continues to be immuno-detectable and retains activity following in vitro digestion, strongly suggesting that TGFß2 can survive in the infant gut and exert its bioactivities.

516 EVIDENCE OF INCREASED FETAL ANGIOGENESIS/ VASCULOGENESIS IN A RAT MODEL OF DIABETIC PREGNANCY

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Purpose of Study: Pregnancies complicated with diabetes are associated with a hypermetabolic state, hypoxia and over-expression of VEGF, a potent mitogen for embryonic angiogenesis and vasculogenesis. VEGF is regulated by sVEGFR-1, an endogenous negative regulator in the VEGF signaling pathway. The effects of maternal diabetes on VEGF/sVEGFR-1 signaling in the fetus have not been studied. We examined the hypothesis that VEGF/sVEGFR-1 signaling is altered in the fetal compartment of pregnancies complicated with diabetes mellitus.

Methods Used: Three groups of pregnant rats were studied: 1) Non-diabetic control (CTL); 2) Diabetic, non-treated (DNT); and 3) Diabetic insulin-treated (DIT). For groups 2 and 3, diabetes was induced in non-pregnant rats
Percentage of 65 mg/kg IV). Once diabetes was confirmed by blood glucose and urinary ketone levels, the rats were implanted with either insulin or placebo pellets subcutaneously, prior to mating. C-section was performed at gestation day 20 for fetal blood glucose; and VEGF, sVEGFR-1, and 8-isoPGF2α (a biomarker for oxidative stress) in amniotic fluid (AF), placenta (PL), and fetal membranes (FM).

Summary of Results: Mean fetal body and organ weights were higher in the DNT group compared to the CTL (P < 0.05) and TXT (P < 0.01) groups. However, mean PL weight was lower in both diabetic groups (P < 0.01). Mean fetal blood glucose (mg/dL) was elevated in the DNT group (408.7 ± 21.9, P < 0.001) and TXT (231.7 ± 11.6, P < 0.001) compared to CTL (162.2 ± 15). VEGF was higher in PL of both diabetic groups, but a greater elevation was seen in the DNT group (P < 0.01). sVEGFR-1 was elevated in PL and FM of both diabetic groups (P < 0.01), but was higher in FM of DNT group. sVEGFR-1 was lower in AF of DNT group (P < 0.05). Oxidative stress was increased in both diabetic groups (P < 0.05).

Conclusions: In poorly controlled diabetes, a high fetal glucose environment will result in hypoxia, increased oxidative stress, and enhanced VEGF/sVEGFR-1 signaling. Interaction between these mechanisms may explain in part, the pathophysiology of the diabetic-exposed fetus.

517 EXPLORING THE WEIGHT-NEUTRAL EFFECTS OF INSULIN DETEMIR VS. INSULIN GLARGINE IN TYPE 1 DIABETES
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Purpose of Study: Insulin detemir is a neutral, soluble long-acting insulin analog that has been shown to result in less weight gain in type 1 diabetes when compared to other long acting insulin formulations. One possible mechanism for this weight neutrality is the lipophilicity conferred by its 14-carbon fatty acid chain, which may allow for improved central nervous system activity and enhanced satiety. We hypothesize that type 1 diabetes subjects will consume fewer calories when allowed to eat to satiety following a 24 hour fast after 3 weeks of basal-bolus therapy with insulin detemir compared to 3 weeks of a basal-bolus regimen with insulin glargine. Additional endpoints include validated hunger and satiety scores, indirect calorimetry, body composition by bioelectrical impedance, and the serum hunger and satiety factors PYY, leptin and ghrelin.

Methods Used: We recruited ten e-peptide negative type 1 diabetic patients with BMI less than 31 kg/m2, HbA1C values less than 11%, and no active complications to participate in a randomized, double-blind, crossover study to evaluate the effects of insulin detemir on appetite and satiety. Subjects administered equivalent doses of either insulin detemir or glargine twice daily for at least 3 weeks, after which time they were admitted to the UNM CTSC and were fasted for 24 hours following a standard ADA meal. On the morning of day 2, resting energy expenditure and body composition were assessed. After 24 hours of fasting, subjects were presented with a "buffet style" study meal consisting of a 10,000 calorie food array and were allowed to eat until satiety. Rapid acting insulin was administered only after the study meal was completed. Timed samples for leptin, ghrelin, and PYY were obtained before and after the study meal, and glucose and insulin were measured every 2 hours. Hunger and satiety surveys were also obtained. Upon completion, subjects crossed over to the alternative study insulin for at least 3 weeks and were then readmitted to repeat the above protocol.

Summary of Results: Two subjects have completed the study and five subjects are currently enrolled. Ten subjects will have completed the study by January, 2009.

Conclusions: Study data will be unblinded and the results will be presented at the meeting.

518 REPLACE MED-MAL WITH OMIn
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Purpose of Study: Analyze the effectiveness of the US medical malpractice system.

Methods Used: Literature review of both financial and other outcomes data. Summary of Results: The US medical malpractice system (med-mal) is a complete failure. It is intended to accomplish two goals: deter negligence and “make the victim whole.” Med-mal accomplishes neither. The public expects med-mal to improve quality and to help those injured during medical care. Med-mal fails to fulfill these expectations.

Errors are common and most cause no lasting harm. The majority of patients injured during medical care receive no compensation. Most adverse patient impacts are not due to negligence. Many adverse patient impacts are preventable. Med-mal hinders or outright prevents learning. Med-mal creates large, non-value-adding expenses.

Conclusions: Modifying our current med-mal system will not produce what the Public expects. We need a new system based on no-fault policy. Legal precedents exist in both auto insurance and divorce. A proposal is made for an Office of Medical Injuries (OMIn) with four Divisions: Compensation; Dissolution; Improvements; and Oversight. Liability (blame) would have no place in their deliberations.

Since everyone would benefit from an OMIn, everyone should pay into the new system, in a fashion similar to social security. It is estimated that OMIn will cost ~20% of what the current med-mal system consumes and will substantially raise GDP.

Allowing med-mal to fade away, replaced by OMIn, will achieve what the Public needs: help for those injured during health care; enhanced medical quality; reduced costs; and improved productivity.