YALE JOURNAL OF BIOLOGY AND MEDICINE 82 (2009), pp. 181-229.

Yale University School of Medicine Thesis Abstracts — 2009

Use of Antidepressant Medications and the Subsequent Course of Depressive Symptoms Among Older Adults. Janet Jalal Abou. Yale University School of Medicine, New Haven, Connecticut.

Antidepressant medications are commonly prescribed for older adults with depressive symptoms who may not have a major depressive disorder. Yet the effect of antidepressants on depressive symptoms in this population over time is largely unknown.

We sought to determine whether the use of antidepressant medications is associated with a reduction in the severity of depressive symptoms over time.

Participants included 754 community-dwelling adults, aged 70+ years, who were followed at 18-month intervals for 90 months. Depressive symptoms were assessed using the 11-item CESD scale, with a higher score indicating worse depressive symptoms. A linear mixed effects model, adjusted for demographic features, number of chronic conditions, cognitive status, and physical frailty, was used to evaluate the effect of antidepressant use on change in depressive symptoms score over time. In addition, among people with clinically significant depressive symptoms (i.e., CESD score > = 20), we evaluated whether antidepressant use was associated with a transition to a non-depressed state (CESD score < 20) using a Generalized Estimating Equations (GEE) model.

At baseline, participants taking an antidepressant (n = 75) had higher mean CESD scores than those not taking an antidepressant (15.1 + 9.2 vs. 8.5 + 8.3; $p < 0.001$) and were more likely to be female ($p < 0.001$). Average unadjusted CESD change scores ranged from -3.4 to 1.7 and 0.4 to 1.5 among those taking, and not taking, an antidepressant, respectively (for the different 18-month intervals). Adjusted CESD scores worsened, on average, for participants taking an antidepressant as compared with those not taking an antidepressant. These differences were statistically significant between baseline to 18 months ($p = 0.03$), 36 to 54 months ($p = 0.02$), and 72 to 90 months ($p = 0.01$). The longitudinal findings indicated that CESD scores worsened by 2.2 points, on average, among participants taking an antidepressant as compared with those not taking an antidepressant, although this difference was not statistically significant ($p = 0.14$). Among participants with clinically significant depressive symptoms, use of antidepressants was not associated with transitioning to a non-depressed state (OR = 0.85, 95 percent CI 0.5-1.4).

Our findings raise concerns about the effectiveness of antidepressant medications, as prescribed in clinical practice. Additional research is needed to better understand the real-world use and benefit of antidepressants among older adults.

Comparison of Four Different Embolic Materials for Uterine Artery Embolization in Post-Procedure MRI Enhancement. Steven D. Abramowitz, Gary M. Israel, Shirley M. McCarthy, Jeffrey S. Pollak, Robert I. White Jr., and Michael G. Tal. Department of Radiology, Yale University School of Medicine, New Haven, Connecticut.

The aim of this study was to assess embolic agent equivalency in uterine artery embolization (UAE) using post-procedure MRI enhancement of uterine fibroids in patients embolized using Embosphere Microspheres, (EM) Contour SE spheres (CSE), Poly-Vinyl Alcohol particles (PVA), and Bead Block spheres (BB).

Eighty-four women with six-month MRI follow-up constituted this retrospective study. Within this group, 25 women were treated with PVA, 23 were treated with CSE, 19

were treated with EM, and 17 were treated with BB. Pre- and post-procedure MRI exams were analyzed for the total number of fibroids present in the uterus of each patient, and the percentage individual fibroid enhancement of each fibroid was scored in quartile intervals. The overall percentage change in enhancement was then calculated for each patient. Bivariate analysis using Generalized Linear Modeling and one-way ANOVA was used to assess differences in infarction by different embolic materials.

Of patients treated with PVA or EM, there was a mean reduction in enhancement by 76.60 percent and 83.07 percent, respectively, compared to a mean reduction of 52.53 percent and 49.78 percent in patients treated with CSE or BB, respectively. There was a statistically significant difference between CSE or BB and EM or PVA.

Patients treated with BB or CSE demonstrate a reduced degree of infarction on follow-up MRI than those patients treated with PVA or EM.

Improving the Plight of Fallen Dancers: Lessons Learned from the Netherlands.

Mary E. Air. Medical Center for Dancers and Musicians, Medisch Centrum Haaglanden Westeinde, The Hague, Netherlands; Yale University School of Medicine, New Haven, Connecticut. (Sponsored by Thomas D. Stewart, Section of Psychiatry Consultation, Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut).

Despite facing exceptionally high physical and psychological stressors, dancers in most parts of the world represent a marginalized and often neglected patient population. This study examined the physical, psychological, and health care access challenges of injured dancers in the Netherlands, a country that has remained grossly underrepresented in the performing arts medicine research literature, despite having a unique tetrad of universal health care access, a robust performing arts industry, leading clinical care in performing arts medicine, and tight-knit systems of networks and referrals between dance and medical institutions. The purpose of this study was to determine the degree of psychological distress among injured dancers and whether this distress persisted or resolved with resolution of the physical injury. Therefore, the Brief Symptom Inventory (BSI)®, a well-known and highly validated tool, was used to screen for psychopathology in 154 pre- and post-retirement age injured Dutch dancers. In addition, a cross-sectional, descriptive survey and chart review were performed in this group to identify clinical features of dancers who were at highest risk for elevated distress and determine the physical outcomes of injured dancers in the Netherlands, their health care seeking behavior, and their perceptions of the medical industry when injured.

Dutch dancers suffered a low injury and surgery rate compared to available data from other countries, but the epidemiology of the injuries was similar. Dancers suffered an average of 1.5 injuries, most often to the knee or foot-ankle complex (30 percent each). The surgery rate was 4 percent (six of 154 dancers). Most injuries were chronic ($M = 20.6 \pm 25.3$ months), overuse-type injuries, and 40 percent of dancers did not know where or how the injury occurred. Pain and artistic compromise emerged as distinct entities of the injury process, with artistic compromise representing a variable of greater magnitude and duration than somatic pain.

Logistical and perceptual restrictions to health care were not reported by dancers in the study; only three younger (< 35 years) foreign dancers lacked a primary care physician. No dancer reported monetary or insurance hindrances or fear of going to the doctor. A small percentage of the younger group (18 percent), but none of the older dancers, reported that they felt the doctor would not understand them ($\chi2 = 2.2$, $df = 1$, $p = 0.14$). The majority of dancers were satisfied or very satisfied with their medical treatment before and after presenting to the dance medicine specialist (67 percent older dancers, 52 percent younger, $\chi2 = 1.19$, $df = 1$, $p = 0.2$; 100 percent older dancers, 93 percent younger dancers, $\chi2 = 1.46$, $df = 1$, $p = 0.2$, respectively). Dancers in both age groups most often sought first treatment from either a physiotherapist (36-40 percent) or a medical doctor (39-41 percent). The primary reason for not seeking treatment from a physician first was that dancers already had access to a phys-

iotherapist and thought that treatment was sufficient. This attitude was opposite to reports of dancers' antagonistic perceptions of medical providers reported elsewhere.

Upon psychological screening, injured Dutch dancers performed poorly on the BSI, which revealed a high degree of persistent, elevated psychological distress in the study population. Sixty percent of dancers scored high enough for referral to a psychiatrist for at least one psychological dimension, 80 percent scored above the average of the normative Dutch adult outpatient population (dimensional score 5, $Z > 1.0$ S.D.), and 20 percent scored "highly distressed" on a global measurement of psychological well-being (GSI score 6 or 7, $Z > 2$ S.D.). Additionally, dancers who met criteria for referral were referable for multiple clinical dimensions ($M = 4.00$). These findings were independent of age, gender, dance style, anatomic injury, professional experience, pain, and perceived level of artistic compromise due to injury. Somatic, cognitive, interpersonal sensitivity, paranoid, and anxious symptoms were the grounds for most referrals. However, overall, there was little change in the psychological profiles of dancers and number of clinically significant dimensions, despite injury resolution (3.9 ± 4.0 vs. 4.0 ± 2.9 dimensions, $p = 0.9$). On group analysis, clinical reduction in scores post-injury treatment was seen in phobic (50 percent reduction), somatic (44 percent), hostile (38 percent), and paranoid dimensions (38 percent); yet, on individual analysis, the number of dancers who changed from referable to non-referable status after injury resolution was equivalent to those who showed no change in their need to be referred ($n = 7$, 41 percent vs. $n = 6$, 35 percent). Student dancers emerged as a patient population with a particularly high level of persistent distress.

These results suggest that in this study population, in which injured dancers displayed improved physical outcomes, health care seeking behavior, and doctor-dancer relationships than dancers in other parts of the world, high psychological distress was nevertheless a latent, if not independent, feature of the injury process. In the Netherlands and abroad, physicians, dance institutions, and instructors should be cognizant of overt and latent psychological distress among dancers and take measures to mitigate it, including increased education for patients and providers, increased support services at dance academies, and increased funding for research into the etiology of the distress.

Radical Prostatectomy vs. Intensity Modulated Radiation Therapy in the Management of Localized Prostate Cancer. Ayal Aaron Aizer. Yale University School of Medicine, New Haven, Connecticut.

Purpose: To determine whether radical prostatectomy (RP) or intensity modulated radiation therapy (IMRT) to ≥72 Gy, plus hormonal therapy if indicated, results in improved biochemical disease free survival (BDFS) in localized prostate adenocarcinoma.

Methods and Materials: A consecutive sample of 556 patients who underwent RP ($n = 204$) or IMRT ($n = 352$) at two referral centers between 1997 and 2005 was analyzed. Patients were stratified into prognostic groups based on clinical stage, Gleason score, and pretreatment prostate specific antigen (PSA) level as outlined by schemes designed by Memorial Sloan Kettering (MSK) and the National Comprehensive Cancer Network (NCCN). The outcome used in this study was BDFS. Median follow up in the RP and IMRT cohorts was 46 months and 40 months, respectively.

Results: IMRT patients had more advanced and aggressive disease at baseline ($p < .001$). No difference was found in five-year BDFS rates between RP and IMRT in the favorable prognosis (92.8 percent vs. 85.3 percent, $p = .20$) or the MSK intermediate prognosis (86.7 percent vs. 82.2 percent, $p = .46$) subsets. A difference favoring IMRT was seen in the NCCN intermediate prognosis (70.7 percent vs. 83.3 percent, $p = .03$), MSK poor prognosis (38.4 percent vs. 62.2 percent, $p < .001$), and NCCN poor prognosis (37.0 percent vs. 56.8 percent, $p = .005$) subsets. Within the entire cohort, after adjustment for confounding variables, Gleason score ($p < .001$) and clinical stage ($p < .001$) predicted BDFS, but treatment modality ($p = .06$) did not. Within the MSK poor prognosis subset, treatment modality ($p = .006$) was predictive of BDFS, favoring IMRT.

Conclusion: Biochemical disease free survival is similar between RP and IMRT for patients with a good prognosis. Patients with a poor prognosis, and some with an intermediate prognosis, may benefit from IMRT to ≥72 Gy plus hormonal therapy.

The Role of Maternally Derived Human Metapneumovirus (hMPV) Specific Antibodies in the Protection of Infants Against Infection. Carolyn Avery, Kristina DePeau, Eugene Shapiro, Jeffrey Kahn, and Marietta Vazquez. Section of Infectious Diseases, Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

The aim was to determine whether the concentration of maternally derived serum neutralizing antibodies against human metapneumovirus (hMPV) in cord blood correlated with the development and severity of hMPV infection in infants during the first year of life. This was a prospective, community-based, cohort study at the Yale Pediatric Primary Care Center. Subjects were enrolled at birth, and an aliquot of cord blood was obtained to measure the concentration of maternally derived hMPV antibody by ELISA. Results were divided into quartiles. Subjects were followed longitudinally for one year. When they presented with respiratory symptoms to a medical provider, a nasal wash was obtained to screen for the presence of hMPV by RT-PCR and a clinical severity score was given based on vital signs, work of breathing, and disposition. At one year of age, a serum sample was obtained from subjects to measure the concentration of hMPV antibody. Multivariable logistic regression was performed to determine the risk ratios for the likelihood of hMPV infection in each antibody quartile. This is an ongoing study. To date, 554 infants have enrolled (84 percent of those eligible) and 142 (25 percent) have completed one year of follow-up. Two hundred thirty-five infants have presented with respiratory symptoms on 363 occasions. Of nasal specimens tested, 12/209 samples (5.7 percent) were PCR+ for hMPV. Of serum samples tested, 28/142 (19.7 percent) were ELISA+ for hMPV infection at one year. There was no statistical significance between antibody quartile and risk of hMPV infection in the first year of life. Twenty percent of this cohort had serologic evidence of hMPV infection at one year of age. At present, the study is underpowered and further analysis on the complete data set will better answer the stated hypothesis.

High Rates of Undiagnosed Pulmonary Tuberculosis and Barriers to Diagnosis and Care Among TB and HIV Co-infected Patients in a Rural South African Hospital: A Cross-Sectional Cohort Study. Palav Babaria. Yale University School of Medicine, New Haven, Connecticut.

Tuberculosis (TB) is the leading cause of mortality among HIV-infected patients in South Africa. Symptoms of active TB may be subtle in HIV patients and go unrecognized in early illness, creating an opportunity for nosocomial TB transmission. Late presentation and delayed diagnosis of TB also contribute to increased mortality and community-based TB transmission. In an effort to identify active TB promptly, screening for TB must be integrated into routine HIV care, and barriers to seeking care must be addressed.

We prospectively initiated a standardized TB screening program at a rural HIV clinic to determine the prevalence of unsuspected TB and drug-resistant TB. All HIV clinic patients at a rural hospital in Tugela Ferry, South Africa, were screened for TB symptoms, and those with one or more TB symptoms (e.g., cough, night sweats, fever) were enrolled and submitted sputum samples for microscopy, mycobacterial culture, and drug-susceptibility testing (DST). We also administered a questionnaire to all inpatient and outpatient participants based on the Information, Motivation, and Behavioral Skills (IMB) model in order to identify barriers to TB diagnosis and care.

Among 263 HIV-infected ambulatory patients enrolled, 52 (20 percent) were culture-positive for TB and 24 (9 percent) were smear-positive. Among 46 patients with available DST results, 13 (5 percent of 263 screened) were resistant to at least isoniazid and rifampin (MDR TB) and seven of these (3 percent) met criteria for XDR TB. Patients with TB were

more likely to be male (p = .01), without a prior history of TB (p = .02), and had lower median CD4 counts (p < 0.001). Patients presented with similar symptoms irrespective of TB status, except for weight loss, which was significantly greater among those with TB. Twenty-seven percent of all patients reported delaying seeking care for >4 weeks. Delay was associated with male gender (p = 0.02), not being on ARVs (p < 0.001), and being seen elsewhere for treatment (p = 0.003). Among 480 patients who completed the IMB questionnaire, 387 (81 percent) thought TB was treatable and 231 (48 percent) thought that having TB meant you also had HIV. Almost all felt that they could disclose their TB (97 percent) or HIV (88 percent) status to a family member. However, several barriers to seeking care were identified: 294 (61 percent) stated they lived too far to be treated and 263 (55 percent) lacked finances for transport to the hospital.

This study demonstrates a high prevalence of active TB, particularly MDR and XDR TB, among HIV clinic patients in rural South Africa. These unrecognized TB cases raise concern for nosocomial TB transmission among vulnerable HIV patients and underscore the need for active TB case finding and infection control measures. The majority of patients also identified barriers for accessing care, including distance to hospital and lack of transport money. These findings support further strengthening of TB and HIV programs, particularly decentralized TB screening and care.

A Role for RAGE System Activation in Preterm Birth. Margaret Ann Baumbusch. Yale University School of Medicine, New Haven, Connecticut.

The receptor for advanced glycation end products (RAGE) is a multiligand pattern recognition receptor involved in transducing endogenous damage associated stimuli into inflammatory responses. Advanced glycation end products (AGEs), HMGB1 (amphoterin), and S100 proteins, such as S100B, are prototype RAGE ligands, while soluble RAGE (sRAGE), a product of RAGE activation, acts as a ligand scavenger and RAGE inhibitor. We propose that RAGE may play important yet distinct pathogenic roles in both inflammation-induced preterm birth and preeclampsia and that while inflammation-induced preterm birth associates with fetal RAGE activation, preeclampsia induces a maternal state of RAGE activation. We sought to identify the putative stimuli and implications for the opposing types of RAGE activation in these two leading causes of prematurity. Biological samples from two cohorts of prospectively enrolled women were analyzed. In women with symptoms of preterm birth who were assessed to rule out intra-amniotic infection, we measured amniotic fluid for HMGB1 and cord blood for HMGB1 and S100B. For ex vivo validation of our findings, HMGB1 also was measured in tissue explants subjected to endotoxin. From women assessed clinically to rule out preeclampsia, blood and urine of three subgroups (severe preeclampsia, healthy controls, and chronic hypertension but no preeclampsia) were used to determine levels of AGE and HMGB1 as potential stimuli for RAGE activation. Immunohistochemistry on reproductive tissues was used on select cases in both cohorts for cellular localization and validation of immunoassay findings. We found that HMGB1 levels are increased in amniotic fluid of women with intra-amniotic inflammation and preterm birth, and the likely source is the damaged amniochorion, as demonstrated by explant experiments and immunohistochemistry. Cord blood levels of HMGB1 correlate with the extent of fetal inflammation and S100B but not with either the level of intra-amniotic infection or amniotic fluid HMGB1, indicating that other RAGE axis modulating molecules may play a role. We confirmed that severe preeclampsia is associated with elevated sRAGE, a product of RAGE activation, but that neither serum AGE nor HMGB1 levels mirrored the changes in sRAGE. In contrast, women with severe preeclampsia and especially those with HELLP and/or eclampsia had significantly elevated HMGB1 excretions that correlated directly with circulating sRAGE.

In conclusion, this research provides evidence for a biologically relevant role of HMGB1 in driving the distinct types of RAGE activation in two major obstetrical complications leading to prematurity. Heightened fetal HMGB1-RAGE axis activation may play a role in intra-amniotic inflammation, while a maternal HMGB1-RAGE system may contribute to the pathogenesis of preeclampsia.

Development of a Novel Biofedelic Skull-Neck-Thorax Model Capable of Quantifying Motions of Aged Cervical Spine. Naseem Neon Beauchman. Yale University School of Medicine, New Haven, Connecticut.

Study Design: An *in vitro* biomechanical study.

Objectives: The objectives were to develop a new biofidelic skull-neck-thorax model capable of quantifying motion patterns of the cervical spine in the presence of a halo-vest; investigate the effects of vest loosening, superstructure loosening, and removal of the posterior uprights; and evaluate the ability of the halo-vest to stabilize the neck within physiological motion limits.

Summary of Background Data: Previous clinical and biomechanical studies have investigated neck motion with the halo-vest only in the sagittal plane or only at the injured spinal level. No previous studies have quantified three-dimensional intervertebral motion patterns throughout the injured cervical spine stabilized with the halo-vest or studied the effect of halo-vest components on these motions.

Methods: The halo-vest was applied to the skull-neck-thorax model. Six osteoligamentous whole cervical spine specimens (occiput through T1 vertebra) were used that had suffered multiplanar ligamentous injuries at C3/4 through C7/T1 during a previous protocol. Flexibility tests were performed with normal halo-vest application, loose vest, loose superstructure, and following removal of the posterior uprights. Average total range of motion (RoM) for each experimental condition was statistically compared ($P < 0.05$) to the physiological rotation limit for each spinal level.

Results: Cervical spine snaking was observed in both the sagittal and frontal planes. The halo-vest, applied normally, generally limited average spinal motions to within average physiological limits. No significant increases in average spinal motions above physiological were observed due to loose vest, loose superstructure, or removal of the posterior uprights. However, a trend toward increased motion at C6/7 in lateral bending was observed due to loose superstructure.

Conclusions: The halo-vest, applied normally, effectively immobilized the cervical spine. Sagittal and frontal plane snaking of the cervical spine due to the halo-vest may reduce its immobilization capability at the upper cervical spine and cervicothoracic junction.

Relationship Between Pre-Operative Statin Use and Post-Operative Infectious Complications in General and Non-Cardiac Surgery. Johnathan Alexander Bernard. Yale University School of Medicine, New Haven, Connecticut.

Objective: Characterize the impact of pre-operative statin use on post-operative infectious complications and 30-day post-operative mortality in general and non-cardiac surgery patients.

Background: The lipid-lowering effects of statins have been well documented for the treatment of coronary artery disease. There has been mounting evidence to support use of statins for their pleiotropic effect. Among these, immune system modulation, improved endothelial function, attenuation of sepsis, and organ protection are particularly relevant to the surgical patient. However, the pleiotropic effects of statins are poorly understood post-operatively in general and non-cardiac surgery patients.

Design: Retrospective observational study conducted to test the hypothesis that pre-operative statin use leads to a risk reduction of post-operative infectious complications (POIC) (any occurrence of surgical site infection, deep surgical site infection, wound dehiscence, pneumonia, urinary tract infection, sepsis, or septic shock) and would reduce the risk of 30-day post-operative mortality, while identifying independent risk factors for POIC. To do so, the ACS NSQIP database at a 777-bed academic medical center was merged with pharmacy data and electronic medical records at the same institution from January 1, 2006, to January 1, 2008.

Results: Two thousand five hundred eighty-four patients underwent major general and non-cardiac surgery during the study time period. Five hundred seventy-eight of these patients were on statin therapy before admission and continued statin therapy after surgery. Two hundred twenty-four POIC occurred. Best-fit logistic regression models demonstrated that ASA classification, length of operation, and emergent status of case were associated

with an increase in POIC. Patients receiving statins, when adjusted for ASA classification, length of operation, and case emergency, did not have a reduced risk of POIC, with an AOR of 0.978 (95 percent CI 0.58 – 1.63, p = 0.93). Statin use was, however, associated with a reduction in 30-day post-operative mortality (OR 0.45; 95 percent CI 0.23 – 0.87, p = 0.019).

Conclusion: Pre-operative statin therapy reduces the risk of 30-day mortality, but its effect on reducing POIC after general surgery remains to be proven. Further research is needed to evaluate the role of preoperative statin therapy and its pleiotropic effects in surgical patients.

Lactate Clearance Predicts 28-Day Survival Among Patients with Severe Sepsis and Septic Shock. Sundeep Ram Bhat. Yale University School of Medicine, New Haven, Connecticut.

Severe sepsis and septic shock comprise a significant number of emergency department (ED) admissions annually. With the advent of early goal-directed therapies, early identification and intervention have become paramount in this population. Few studies, however, have examined the role of serum lactate as a predictor of mortality or endpoint to resuscitation among this population. We aimed to show that improved lactate clearance is associated with decreased 28-day in-hospital mortality. We retrospectively examined data from the Yale Sepsis Registry for patients with severe sepsis or septic shock who had lactate levels that were measured initially in the ED and subsequently when the patient arrived on the floor. This study received Institutional Review Board approval. Lactate clearance was calculated as a percentage, and comparison between patients who cleared lactate and those who did not were made for mortality data, as well as baseline characteristics and interventions required between the two groups. Two hundred seven patients (110 male) with mean age and standard deviation (SD) of 63.17 ± 17.9 years were examined. One hundred thirty-six patients (65.7 percent) were diagnosed with severe sepsis, and 71 patients (34.3 percent) had septic shock. Of those with identified sources of infection, pneumonia was the most common (54 patients, 26.1 percent). There were 171 patients in the clearance group, and 36 patients in the non-clearance group, all of whom had a mean time of 9 hours 8 minutes ± 4 hours 6 minutes between lactate measurements. Twenty-eight-day mortality rates were 15.2 percent (26 patients) in the lactate clearance group and 36.1 percent (13 patients) in the non-clearance group ($p < 0.01$). Vasopressor support within 72 hours of admission was initiated among 61.1 percent (22 patients) in the non-clearance group, compared with 36.8 percent (63 patients) in the clearance group ($p < 0.01$). Mechanical ventilation was required for 36.3 percent (62 patients) in the clearance group and 66.7 percent (24 patients) in the non-clearance group ($p = 0.001$). Rates of severe sepsis, mean number of SIRS and organ dysfunction criteria, and initial creatinine were similar between the two groups; however, only 86.1 percent (31 patients) in the non-clearance group received intravenous fluids in the ED, compared with 98.8 percent (169 patients) in the clearance group ($p = 0.002$). In the non-clearance group, 33.3 percent (12 patients) had chronic obstructive pulmonary disease (COPD), compared with 15.2 percent (26 patients) in the clearance group ($p < 0.05$). The mean Mortality in Emergency Department Sepsis (MEDS) scores were 8.78 ± 3.96 for the clearance group and 10.4 ± 4.48 for the non-clearance group (95 percent CI, -3.1 to -.14, $p < 0.05$). These results show significantly higher mortality rates among patients who do not clear their lactate in the ED. Additionally, these patients require vasopressor support and mechanical ventilation more often. Lactate clearance was significantly associated with receipt of fluids and also may reflect a lower MEDS score. Our findings suggest lactate clearance could be used as an endpoint for ED resuscitation and in stratifying mortality risk among patients with severe sepsis or septic shock. Future studies might seek to prospectively validate these findings and incorporate multivariate analysis to determine factors affecting lactate clearance.

Quantifying the Effects of Degeneration and Other Patient Factors on Lumbar Segmental Range of Motion. Jesse Emory Bible. Yale University School of Medicine, New Haven, Connecticut.

Prior studies have investigated the roles of age and degeneration on lumbar segmental range of motion (ROM) only using univariate analyses. However, multivariate analyses also

are required to differentiate the multiple factors that may affect ROM and quantify their relative effects.

The purpose of this study was to assess lumbar spine segmental ROM with flexion/extension (F/E) radiographs and determine the relation to clinical variables. This involved retrospectively reviewing 376 patients who presented to our clinic with lumbar or radicular complaints and had F/E radiographs taken. One hundred eighteen patients were excluded for previous surgery, sacralized L5, scoliosis, fracture, spondylolisthesis, poor radiographic exposure, radiographic technical difficulties, or unavailable weight/height. The radiographic series of the remaining 258 patients were analyzed, including 137 females and 121 males with ages ranging from 18 to 92 years.

Degeneration was evaluated for each lumbar segmental level from the neutral lateral film using a modified Kellgren scale (KS). This scale assigns a numerical grade from 0 to 4 based on the presence of radiographic markers of degeneration (osteophytes, endplate sclerosis, intervertebral space narrowing) and has been used in large cross-sectional studies. The interobserver reliability of Kellgren Score (KS) and segmental ROM were evaluated for three observers. Multivariate regression analyses were performed for each level. The predicting variables evaluated were: KS at the level of interest; KS at the level above; KS at the level below; age; gender; weight; height; BMI; and smoking. Significance was defined as $p < 0.05$.

Interobserver reliabilities for assessing KS (ICC 0.70) and segmental ROM (ICC 0.80) were good to excellent. In the multivariate analyses, age had a significant negative association with ROM at L1/L2, L2/L3, L3/L4, and L4/L5. BMI had a significant negative association with ROM at L2/L3, L3/L4, and L4/L5. KS at the level of interest had significant negative association with ROM only at L5/S1. KS at adjacent levels, gender, weight, height, and smoking did not have a significant association with ROM at any level.

The results of this study provide the clinician with insight into factors that influence segmental lumbar ROM. Age was the strongest statistical predictor of ROM and associated with declining motion, amounting to an approximate 3 degree decrease in total sagittal lumbar ROM in the superior four segments every 10 years. Given our findings that age is the strongest predictor of lumbar ROM analyzed, we can now appreciate a natural history of declining lumbar ROM with age that is independent of degenerative disease. Further, factors related to general body habitus, such as BMI, may be more important predictors of lumbar motion than previously recognized. When controlling for these factors, degenerative disease itself seems to have a lesser role in effecting lumbar ROM than previously accepted.

Demineralized Bone Matrix Variability for Posterolateral Lumbar Spinal Fusion in the Athymic Rat. Debdut Biswas. Yale University School of Medicine, New Haven, Connecticut.

Study Design: Posterolateral lumbar spine fusions in athymic rats.

Objectives: To compare fusion rates of different production lots of demineralized bone matrix (DBM) to a dose response curve of rhBMP-2 in inactive DBM for posterolateral lumbar spinal fusion in an athymic rat model.

Summary of Background Data: Demineralized bone matrix (DBM) preparations are available as bone graft supplements. Substantial variability in osteoinductive potential has been reported between different DBM products as well as between production lots of the same product. To date, no studies have correlated the osteoinductive indexing of a DBM product to *in vivo* performance in inducing spinal fusion.

Methods: Single-level intertransverse process fusions were performed in 109 athymic nude rats. Fusion sites were prepared and implanted with no graft, iliac crest autograft, or 0.2 cc per bone graft alternative. Alternatives included inactive BioSet DBM (0,0) or one of two production lots of BioSet DBM with different pre-implant osteoinductive activities: DBM Donor A(2,1 BioSet) and DBM Donor B(4,1 BioSet); and inactive 0,0 BioSet DBM plus 0.35 μg, 0.85 μg, 1.70 μg, or 10 μg of rhBMP-2. Animals were euthanized at six weeks post-operatively. Fusion masses were assessed by manual palpation, radiography, and histology.

Results: At six weeks, manual palpation revealed a fusion rate with autograft of 25 percent, with 0,0 BioSet of 0 percent, with DBM Donor A of 17 percent, and with DBM Donor B of 36

percent. Radiographic and histologic analyses demonstrated statistically significant differences between fusion rates for DBM Donor A and Donor B. The dose response of rhBMP-2 with the 0,0 BioSet carrier had fusion rates of 45 percent, 91 percent, 90 percent, and 100 percent, respectively, the latter three significantly higher than autograft and both production lots of BioSet DBM ($p < 0.05$).

Conclusions: Differences between the ability of two variably osteoinductive BioSet DBM products to induce fusion in an athymic rat posterolateral lumbar spine fusion model were observed. The results of this preclinical animal study may compel the spine surgeon to more carefully evaluate the osteoinductive capacity of DBM products prior to their use in clinical scenarios.

Optimal Needle Angle for Lumbar Puncture in Children as Determined by Ultrasonography. Rebecca E. Bruccoleri and Lei Chen. Section of Pediatric Emergency Medicine, Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

The objective was to find the optimal angle to perform lumbar punctures in children ages 0 to 12 years. We hypothesized that there is a consistent angle in different stages of development. Children ages 0-12 who presented to the Yale-New Haven Children's Hospital at a low acuity level or in need of a lumbar puncture and their siblings were eligible for the study. A lumbar puncture was not required as part of the treatment plan for participation in the study. The goal enrollment was 10 to 20 subjects in each of the following age groups: 0-12 months (group 1), 12-36 months (group 2), and 3-12 years (group 3). Ultrasound images of the L3-L4 and L4-L5 lumbar space were taken with a SonoSite 180 ultrasound and high frequency linear probe in the lateral recumbent and sitting positions. The angle from the interspinous space to the skin was measured on printed images using a protractor. A p-value of less than or equal to 0.05 was considered significant. Thirty-eight subjects were enrolled in the study. For the final analysis, 36 subjects with data were included. For the lateral recumbent position, there were 13 subjects in group 1, 10 subjects in group 2, and 12 subjects in group 3. For the sitting position, there were nine subjects in group 1, 10 subjects in group 2, and 12 subjects in group 3. The mean angles in the lateral recumbent and sitting positions were as follows in each group: group 1: 47.8 (+/-8.2) degrees and 51.1 (+/-8.5) degrees, group 2, 58.8 (+/-6.8) degrees and 59.6 (+/-5.5) degrees, group 3: 60.5 (+/-6.6) degrees and 61.9 (+/-4.0) degrees. The results of each group are significantly different in both positions (p-value = 0.00183 and 0.0108 in the lateral recumbent and sitting positions, respectively). However, groups 2 and 3 are not significantly different in both positions (p-value = 0.510 and 0.391 in lateral recumbent and sitting positions, respectively). The optimal angle for lumbar puncture is statistically different and more acute in infants than older children. Future directions include determining if these angles, when given to clinicians, result in increased success rates of lumbar punctures.

Mindfulness Training and Stress Reactivity in Substance Abuse: A Randomized, Controlled Pilot Study. Justin A. Chen and Judson A. Brewer. Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut.

There is substantial evidence for the central role of stress in the inception and maintenance of substance use disorders. The use of mindfulness training (MT) has demonstrated promise in a number of stress-related conditions. However, no studies to date have compared MT to empirically validated treatments such as cognitive behavioral therapy (CBT) for substance use disorders or assessed its impact on response to stress provocation. The specific aim of this investigation was to engage in the first randomized, controlled trial of a manualized mindfulness-based therapy for the treatment of substance use disorders. The hypotheses to be tested were: MT would be tolerated equally as effectively as CBT in terms of retention rates and subjective measures of treatment tolerability; participants undergoing MT would demonstrate reduced reactivity on both subjective and objective measures during stress provocation as compared with CBT; and participants undergoing MT would have reduced substance use as compared with CBT following completion of the intervention. Thirty-six individuals with

alcohol and/or cocaine use disorders were randomly assigned to receive group MT or CBT in an outpatient community setting. After treatment completion, subjective and physiologic responses to personalized stress provocation were measured by self-report, skin conductance, heart rate, and heart rate variability. Subjects exposed to MT demonstrated reduced psychological and physiological indices of stress during provocation compared with subjects exposed to CBT, as evidenced by the laboratory paradigm conducted post-treatment among those who completed treatment. There were no significant differences in retention, treatment satisfaction, or abstinence rates between individuals assigned to MT vs. CBT. This pilot study provides preliminary evidence for the use of MT in targeting stress for substance use disorders.

Megakaryoctye-Bone Cell Interactions: The Role of Gap Junctions, Maturation, and Longevity. Wendy A. Ciovacco, Carolyn G. Goldberg, Amanda F. Taylor, Justin M. Lemieux, Henry J. Donahue, Ying-Hua Cheng, Mark C. Horowitz, and Melissa A. Kacena. Department of Orthopaedic Surgery, Indiana University School of Medicine, Indianapolis, Indiana.

Research shows that megakaryocytes (MKs) can enhance bone volume by increasing osteoblast (OB) proliferation and inhibiting osteoclast (OC) formation. This cumulative work first explores the role of gap junction intercellular communication (GJIC) in MK-OB interactions and, secondly, examines the effect of MK maturation state and MK number on skeletal homeostasis. In both studies, cell lineages were cultured as described below. In the gap junction (GJ) study, we used real-time PCR to test for MK expression of connexin 43 (Cx43), the predominant GJ protein found in bone cells. A dual-label parachute assay and FACS analysis assessed GJIC between MKs and OBs. Proliferation and differentiation assays of OBs cultured with and without MKs were performed. Here we demonstrate that: MKs express Cx43; MKs can functionally communicate with OBs via GJIC; the addition of two distinct GJ uncouplers inhibits this communication; inhibiting MK-mediated GJIC further enhances the ability of MKs to stimulate OB proliferation; and blocking GJIC does not result in MK-induced reduction of OB differentiation. In the second study, increasing numbers of MKs were co-cultured with bone cells to see if increased MK number correlated with increased OB proliferation and decreased OC formation. In addition, MKs were separated using flow cytometry into three subpopulations based on maturation and effects on OB proliferation, and OC formation were assessed. Finally, longevity studies on wild type and mutant MKs were also conducted. In the second study we show that: increased MK number corresponds with increased OB proliferation and decreased OC formation; MK maturation stage does not alter the effect of MKs on bone cell lineages beyond the megakaryoblast stage; and GATA-1 deficient MKs survive longer than wild-type controls. Thus, we demonstrate a novel interaction between two cell lineages only recently shown to be functionally connected and take steps toward understanding how MKs exert their osteogenic effects.

Predictors of Early Adult Outcome in Pediatric-Onset Obsessive-Compulsive Disorder. Brittany G. Craiglow, Michael H. Bloch, Angeli Landeros-Weisenberger, Philip A. Dombrowski, Kaitlyn E. Panza, Bradley S. Peterson, and James F. Leckman. Child Study Center, Yale University School of Medicine, New Haven, Connecticut.

This study was conducted in order to determine childhood clinical predictors of early adult outcome in pediatric-onset obsessive-compulsive disorder (OCD). We specifically hypothesized that OCD symptom dimensions and comorbid tic disorders would be associated with persistence of obsessive-compulsive (OC) symptoms into early adulthood. The study followed a longitudinal cohort design in which 45 of 61 eligible children with OCD were reassessed in early adulthood, an average of nine years following a baseline childhood assessment. Main outcome measures included expert-rated OC symptom severity and time to remission of OC symptoms. Baseline clinical characteristics were evaluated in terms of their impact on early adulthood OC symptom severity and time to remission of OC symptoms. Forty-four percent of subjects were determined to have subclinical OC symptoms at follow-up. Absence of a comorbid tic disorder and presence of prominent hoarding symptoms were

associated with OC symptom persistence. In our best-fitting multivariate Cox Proportional Hazard model female gender, younger age at childhood baseline assessment, older age of OCD onset, more severe childhood OC symptoms, and comorbid oppositional defiant disorder were also independently associated with persistence of OC symptoms into early adulthood. Our results suggest that a significant proportion of patients with pediatric-onset OCD will remit by early adulthood. The presence of comorbid tics was associated with a favorable outcome, while primary hoarding symptoms were associated with persistent OCD.

From Mueller to Miller: Determining Standards for Decisions Regarding Critically Ill Newborns. Tanaz Farzan Danialifar. Section of Neurology, Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut. (Sponsored by Geoffrey Miller.)

The controversy surrounding selective non-treatment of critically ill newborns has been ongoing for more than three decades. Since ancient times, ill, premature, or deformed infants have been treated discriminatorily, and infanticide has been a historically acceptable practice. With medical, moral, and legal progress, infanticide has disappeared and been replaced with selective non-treatment. This raises new ethical concerns such as best interests, quality of life, wrongful life, and parental autonomy, as well as legal questions regarding medical neglect, privacy, discrimination, and the limits of the federal government. Through an examination of relevant medical and legal literature, mass media publications, and both state and federal court decisions, this paper will provide a historical overview of the development of the ethical and legal principles guiding neonatal decision-making. In addition to a review of the historical contexts for treatment decisions regarding vulnerable infants, a discussion of several landmark medical-legal cases will establish the current standards for neonatal decision-making. This historical overview reveals the shortcomings of past and current legislation and the dissonance between current practice, public opinion, and the law.

Creating a Path for High Quality Care: Implementation of the Mini-CEX in a Student-Run Clinic. Paul Daniel Di Capua. Yale University School of Medicine, New Haven, Connecticut.

Purpose: This study examines the utility of implementing the mini-CEX at a student-run primary care clinic. The mini-CEX is a validated tool for clinical skills feedback and evaluation. The implementation of the mini-CEX sought to improve quality standards in providers' clinical skills and, therefore, to set a model for continuous quality improvement in medical education.

Hypothesis: The primary hypothesis tested is that a minimum of three mini-CEXs per week will produce a positive "utility" for both students and faculty.

Methods: A needs-based analysis focus group solicited opinions on the mission and function of the clinic from the student-providers. The mini-CEX was then presented as a feedback tool that could create a more structured learning environment. After the providers agreed to a trial implementation of the mini-CEX, the faculty at the clinic was instructed on observation and feedback using the mini-CEX. During the trial study, the authors collected a copy of all mini-CEX forms, which were used to document the number of evaluations per week, characteristics of the visit, and the feedback given. Interviews conducted during the trial study with both students and faculty were documented on a weekly basis. The utility of the mini-CEX was determined according to a previously published model, which examines the reliability, validity, educational impact, acceptability, cost, and feasibility.

Results: The student-providers agreed to the trial implementation of the mini-CEX in their clinic. During the trial period, there was a mean of 3.82 (median = 3) evaluations. Interviews with faculty revealed a lack of experience in observing trainees with patients but also increased attention to the teaching they could provide the students. Interviews with students revealed frustration at the lack of consistency in the teaching, but appreciation of the feedback process.

Conclusions: The mini-CEX was successfully implemented in this student-run clinic. The feasibility is evidenced in the number of weeks in which the minimum of three evaluations was performed. The positive feedback during and after the trial period from both faculty and students evidences the acceptability of the mini-CEX. The implementation of a feedback and evaluation tool by students for students represents a movement in structuring clinical education in a self-regulatory manner to ensure higher quality clinical skills by future physicians.

Percutaneous Renal Artery Revascularization in Patients with Atherosclerotic Renal Artery Stenosis and Chronic Kidney Disease. Laura E. Dichtel, Faina Gurevich, and Aldo J. Peixoto. Section of Nephrology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

The impact of percutaneous renal artery angioplasty and stenting (PTRAS) for treatment of atherosclerotic renal artery stenosis (ARAS) is not fully understood, especially in patients with chronic kidney disease (CKD). We performed a retrospective cohort study of patients with significant ARAS and moderate-to-severe chronic kidney disease (estimated GFR 15-60 ml/min/1.73m2) who were treated medically or with PTRAS. The primary endpoint of this study was change in renal function over the first year after treatment. Secondary endpoints included hemodynamic outcomes, antihypertensive medication doses, end stage renal disease (ESRD), and death. We reviewed all patients with a diagnosis of significant ARAS and impaired GFR treated between 1997 and 2007 in the Veterans Affairs Connecticut Healthcare System (VACHS). One hundred eighteen patients met inclusion criteria (71 medical treatment, 47 PTRAS), with an average follow-up of 34 months. The Student's t-test was used to compare baseline characteristics, as well as renal and hemodynamic endpoints between the two treatment groups. The cohort had a mean age of 73 ± 9 years and average baseline GFR of 37.2 ± 14.9 ml/min/1.73m2. Demographic, clinical, and laboratory characteristics at baseline were similar between the two groups, with the exception of higher diastolic blood pressure in the stent group at baseline (75 vs. 70 mmHg, $p = 0.028$). No statistically significant difference was found between the two treatment groups for any renal endpoints. After a steady decline in GFR in both the medical treatment and stent groups during the 12 months preceding diagnosis (-4.2 vs. -4.0 ml/min/1.73m2, $p = 0.911$), GFR stabilized in both groups over the year following diagnosis (decline in GFR of -1.6 vs. -1.4 ml/min/1.73m2, $p = 0.938$). Multivariate models did not reveal an association between treatment modality and percent change in GFR during follow-up. No difference was found in blood pressure outcomes at 12 months between the medical and stent groups. Antihypertensive therapy, measured in defined daily doses (DDDs), was significantly higher in the medical treatment group at 12 months (4.5 vs. 3.5 DDDs, $p = 0.048$), but lost significance thereafter. In addition, the number of deaths was significantly higher in the stented group on univariate analysis, although this did not remain significant with multivariate Cox analysis. No difference was found between treatment groups in the development of ESRD. These data suggest that, among patients with ARAS and CKD, medical therapy and renal artery stenting are comparable in stabilizing renal function.

Development and Localization of Spike-Wave Seizures in Animal Models. Damien Jon Ellens. Yale University School of Medicine New Haven, Connecticut.

Animal models allow for detailed investigation of neuronal function, particularly invasive localization and developmental studies, not possible in humans. This thesis will review the technical challenges of simultaneous EEG-fMRI and epileptogenesis studies in animal models, including issues related to anesthesia, movement, signal artifact, physiology, electrode compatibility, data acquisition, and data analysis, and review recent findings from simultaneous EEG-fMRI studies in epilepsy and other fields.

Original research will be presented on the localization of neuronal networks involved during spike-and-wave seizures in the WAG/Rij rat, a model of human absence epilepsy. Simultaneous EEG-fMRI at 9 Tesla, complimented by parallel electrophysiology, including

multiple unit activity (MUA), local field potential (LFP), and cerebral blood flow (CBF) measurements were employed to investigate the functioning of neuronal networks. This work indicates that while BOLD signal increases in the somatosensory cortex and thalamus during spike-wave discharges (SWD) are associated with MUA, LFP, and CBF increases, BOLD signal decreases in the caudate are associated with CBF decreases, a relatively larger increase in LFP, and smaller increase in MUA.

Complementing the localization studies, original research also will be presented on the development of spike-and-wave epilepsy in the C3H/Hej mouse, a model that will allow for more advanced genetic and molecular investigation. This work shows seizure development progressing though immature, transitional, and mature stages.

The Greek God of Healing Asclepius and Goddess of Health Hygeia: A Double-Gendered Double-Deity Model. Caroline Wagner Engel. Section of the History of Medicine, Yale University School of Medicine, New Haven, Connecticut. (Sponsored by Dr. John Harley Warner, PhD.)

The ancient Greeks worshipped both a god of healing, Asclepius, and a goddess of health, Hygeia. When one examines ancient Greek sculptural representations of Asclepius and Hygeia, a difference in portrayal becomes readily apparent. This art historical essay explores the distinctive ways in which these two characters were illustrated and hypothesizes that their differing roles as healer vs. health served as the foundation for, and hence correspond with, these artistic discrepancies. The avenues from which this contrast is examined include familial relationship, gender, physical representation, and the treatment of their attributes.

The analysis of ancient Greek art herein presented supports the hypothesis that Hygeia was a health nurturer and Asclepius was a hands-on healer. While Hygeia was worshipped in a preventative manner with the goal of keeping that patron healthy, Asclepius was the hierarchically superior father who was prayed to, for healing, when one was suffering. Asclepius, as a man dominating over health and healing, is visually depicted in seated position with increased musculature, a stern facial expression, and handling a snake; Hygeia is delicately represented as a woman who is slim, feminine, and smooth-skinned.

This essay demonstrates that an examination of ancient Greek sculpture supports Asclepius and Hygeia's distinct, yet complementary, roles, as healer and health nurturer.

Becoming the Doctor I Want to Be: The Professional Development of Internal Medicine Residents. Merritt McLean Evans. Yale University School of Medicine, New Haven, Connecticut.

Background: Several studies have suggested that the current medical training environment may include experiences that compromise trainees' professional development. Little work has been done to explore this evolution during internship.

Methods: Interns in the Yale University Internal Medicine Residency Programs were asked to evaluate their professional development during internship through a qualitative study involving two open-ended written surveys and a focus group interview. Participants were identified in June 2003 during the annual Professionalism Workshop that occurs during internship orientation. Participating interns completed an initial survey asking them to describe the physician each aspired to be. In February 2004, interns attended a follow-up Professionalism Workshop. Prior to the workshop, participating interns completed a second survey, which asked them to evaluate their progress toward achieving their previously stated aspirations. Following this workshop, interns were divided into three groups for a focus group interview. Each facilitator followed the same script, probing the personal and professional changes interns noticed in themselves during internship. Interviews were taped and transcribed. Data were analyzed using the constant comparison method by at least two investigators, who achieved consensus regarding the extracted themes. Twenty-four interns from the primary care, traditional, and medicine-pediatrics residencies participated, and 19 completed all parts of the study.

Results: On the initial surveys, interns demonstrated great concordance in describing physician characteristics to which they aspire, such as being compassionate (N = 19), competent

(N = 19), and an effective communicator (N = 10). On the follow-up survey and in the focus groups, none of the interns said they were failing to become the doctor they would like to be. In the focus group discussion, interns believed they were on track to attain their professional ideals, although the constraints of internship forced them to delay focusing on certain aspirations, with more emphasis on developing certain competencies (e.g., technical proficiency and medical knowledge) instead of others (such as interpersonal skills). Themes that emerged from the interns' descriptions of how they struggled to sustain their professional development included acceptance of the role of intern (as distinct from an ideal of physician); the necessity of constricting their responsibilities to their patients given the limitations of internship; increased emphasis on self-care and self-awareness; and pride in the skills they mastered.

Conclusions: Our interns entered residency with professional ideals consistent with most professionalism statements. Although interns were frustrated by parts of their educational experience, they still believed they were on track to become the doctors they wanted to be. However, they felt that they postponed development of interpersonal skills while emphasizing technical and knowledge aspects of care. Further research should evaluate more senior physicians to see if they still delay attainment of certain ideals, achieved their ideals, or altered them in favor of more attainable ones. If professional development remains compromised, the factors preventing physicians from achieving their ideals should be clarified and modified.

Novel Severity Measurement of Infant Skull Deformities. Samer M. Fadl. Yale University School of Medicine, New Haven, Connecticut.

Over the last decade, physicians have noted a rise in the prevalence of plagiocephaly. This sudden increase, combined with the variability in presentation of infant head deformities, makes the management of these cases often difficult. Currently, assessment for treatment is largely based solely on subjective determination of the severity of the patient's skull malformation. Existing cephalometric techniques, such as external caliper measurements are commonly used; however, these techniques still contain inaccuracies, due to movement of an infant during measurement, soft tissue compression by the calipers, and lack of precise defined landmarks [10]. Given that no type of normalized measurement exists to identify objectively the severity of a patient's skull deformity, the grading and selection of treatment modality largely has been relegated to experienced plastic surgeons and neurosurgeons. We report a novel measurement that utilizes both CT scan and digital images combined with basic geometry to determine, objectively, the severity of an infant's skull deformity, enabling all physicians to better decide what therapeutic intervention to employ.

Temporal Evolution in the Histopathologic Diagnosis of Borderline Melanocytic Lesions. Jason E. Frangos, Lyn Duncan, and Alexa B. Kimball. Departments of Dermatology and Dermatopathology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. (Sponsored by Dr. Robert Tigelaar, Department of Dermatology, Yale University School of Medicine, New Haven, Connecticut.)

While the incidence of cutaneous malignant melanoma has risen steeply over the past half century, increases in the mortality rate have been relatively modest. In an effort to understand this discrepancy, we sought to determine whether a shift toward more malignant diagnoses may have been made by dermatopathologists (DPs) diagnosing severely dysplastic nevi over 20 years. Forty biopsy slides of dysplastic nevi [28] and thin melanomas [12] from 1988 to 1990 were obtained from the pathology files of the Massachusetts General Hospital (MGH). All DPs that had rendered an original diagnosis for any of the 40 slides as well as the current staff in the MGH Dermatopathology department were invited to re-evaluate the slide-set. Three original DPs and three current MGH staff DPs re-read the slide-set. The mean number of melanoma diagnoses by the six study participants was 19.7 (median = 19.5), an increase of 64 percent from the original number of melanoma diagnoses in the slide set [12]. For lesions originally diagnosed as

"Melanoma," study participants had a high level of agreement between each other (kappa = 0.74) and between each rater and the original diagnosing DP (kappa = 0.86). For lesions originally diagnosed as "Not Melanoma," study participants had a low level of agreement between each other (kappa = 0.22) and a low level of agreement between each rater and the original diagnosing DP (mean kappa = 0.39). The results of this study indicate that a small set of DPs at a major academic institution tended to read prior non-malignant diagnoses of borderline melanocytic lesions as malignant but not to revise prior diagnoses of malignant melanoma as benign.

Photoplethysmographic Waveform Analysis During Lower Body Negative Pressure Simulated Hypovolemia as a Tool to Distinguish Regional Differences in Microvascular Blood Flow Regulation. Nicholas J. Galante, Lars J. Grimm, Aymen A. Alian, Nina S. Stachenfeld, Kirk H. Shelley, and David G. Silverman. Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this investigation was to explore modulation of the photoplethysmographic (PPG) waveform in the setting of simulated hypovolemia as a tool to distinguish regional differences in regulation of the microvasculature. The primary goal was to glean useful physiological and clinical information as it pertains to these regional differences in regulation of microvascular blood flow. This entailed examining the interplay between the cardiovascular, autonomic nervous, and respiratory systems in the functional hemodynamic regulation of microvascular blood flow to both central (ear, forehead) and peripheral (finger) sites.

We monitored 10 healthy volunteers (men and women, ages 24-37) non-invasively with central and peripheral photoplethysmographs and laser Doppler flowmeters during Lower Body Negative Pressure (LBNP). Waveform amplitude, width, and oscillatory changes were characterized using waveform analysis software (Chart, ADInstruments). Data was analyzed with the Wilcoxon Signed Ranks Test, paired t-tests, and linear regression.

Finger PPG amplitude decreased by 34.6 ± 17.6 percent ($p = 0.009$) between baseline and the highest tolerated LBNP. In contrast, forehead amplitude changed by only 2.4 ± 16.0 percent (p = NS). Forehead and finger PPG width decreased by 48.4 percent and 32.7 percent, respectively. Linear regression analysis of the forehead and finger PPG waveform widths as functions of time generated slopes of -1.113 ($R = -0.727$) and -0.591 ($R = -0.666$), respectively. A 150 percent increase in amplitude density of the ear PPG waveform was noted within the range encompassing the respiratory frequency (0.19-0.3Hz) ($p = 0.021$) attributable to changes in stroke volume. We also noted autonomic modulation of the ear PPG signal in a different frequency band (0.12 – 0.18 Hz).

The data indicate that during a hypovolemic challenge, healthy volunteers had a relative sparing of central cutaneous blood flow when compared to a peripheral site, as indicated by observable and quantifiable changes in the PPG waveform. These results are the first documentation of a local vasodilatation at the level of the terminal arterioles of the forehead that may be attributable to recently documented cholinergic mechanisms on the microvasculature.

The Regulation of DCDC2, A Candidate Gene for Dyslexia. Christopher J. Gibson and Jeffrey R. Gruen. Departments of Pediatrics, Genetics, and Investigative Medicine, Yale University School of Medicine, New Haven, Connecticut.

Within the human genome, genetic mapping studies have identified 10 regions of different chromosomes, known as DYX loci, which are genetically linked with dyslexia. The gene DCDC2, located within the DYX2 region on chromosome 6p22, has been shown to be genetically associated with dyslexia in several independent studies. Functional assays of DCDC2 indicate that it may help guide the migration of neurons during early brain development. DCDC2 polymorphisms that display the strongest association with dyslexia are located in a highly GC-rich region in intron 2 known as BV677278. These polymorphisms contain several transcription factor binding sites, including the canonical 8-base recognition

site for PEA3, a transcription factor known to modulate neuronal migration in mice. We hypothesized that BV677278 is an enhancer element for DCDC2 that regulates its expression level, location, or timing and that PEA3 regulates DCDC2 expression by binding BV677278. To test these hypotheses, we showed that PEA3 binds to regions within BV677278 and that siRNA knockdown of PEA3 appears to delay the expression of DCDC2 during neuronal differentiation in mouse cells. We concluded that PEA3 was a viable candidate transcription factor for DCDC2 with the ability to bind to BV677278. Taken together, these data suggest a possible mechanism by which BV677278 polymorphisms alter PEA3 binding and DCDC2 expression, which in turn may modulate neuronal migration and affect the risk of dyslexia.

Medical Students' Exposure and Response to Error on the Wards. Kimberly B. Gold. Yale University School of Medicine, New Haven, Connecticut.

Medical errors are common and cause extraordinary costs. Errors should be openly discussed and learned from, but medical schools have been slow to adopt curricula on medical errors and training on how to respond to errors. Since error disclosure remains incomplete, students may be lacking both formal and informal education in error management. Our aims were to describe students' knowledge about medical errors and error reporting, their attitudes toward medical errors and error reporting, their exposure to various types of errors, and their disclosure patterns. A survey instrument was developed using previously validated questions, and new questions were developed using the results of a focus group. The survey was refined by leading survey experts and a pilot test with students. The study sample consisted of students who had completed their third year of medical school at a single institution. Ninety-nine useable surveys were received for a response rate of 48 percent. Many students (91.9 percent) witnessed at least one error during their clerkships that resulted in harm to the patient. The most common types of errors witnessed by students included errors from failed medication reconciliation (73.5 percent), incorrect diagnoses (67.7 percent), missed diagnoses (66.7 percent), and poor or incomplete handoff (65.65 percent). The services during which the most students reported witnessing errors resulting in harm were Medicine, OB-GYN, and Surgery. There were significant gaps in students' knowledge about errors and error reporting. For example, 17.2 percent of students did not feel confident that they know what constitutes a medical error, and 69.7 percent did not feel confident that they know how to report an error. The majority of students (83.84 percent) said that they had not received training on how to respond to errors they observe. Training was significantly associated with students' knowing how to report an error ($p = .006$) and knowing which errors to report ($p = .02$). None of the 16 students who reported having formal training said that they did not report an actual error because they were unsure about whether something was an error. More than a quarter of students (27.94 percent) who witnessed an error that remained undisclosed or unacknowledged did not tell anyone about the error. Their reasons for not telling anyone include being unsure of whether it was an error (64.3 percent), fear that their team would be upset with them (42.9 percent), being unsure of who to tell (42.9 percent), not thinking the information would help the patient (39.3 percent), and fear of a bad evaluation or grade (28.6 percent). Over a quarter (27.6 percent) of the students thought it would be likely or very likely that their grade and evaluation would have been negatively affected, and 61 percent felt it would be likely or very likely that their residents and/or attending physician would have been upset with them if they reported an undisclosed error to the patient or patient's family on their last rotation. The involvement of the attending physician after a minor ($p = .003$) or major ($p < .001$) error significantly predicted positive actions, such as open explanations to the patient and open educational discussion among the team. Medical students frequently witness errors but perceive a culture in which transparency is not the goal. Because training significantly increased students' comfort with errors, there should be more training and education in handling errors for physician trainees at all levels. Since active responses to errors by attending physicians lead to positive actions

after errors occurred, we should continue to train and recruit faculty who will act as positive role models for medical students with respect to safety and disclosure.

Blame and Medical Errors: Allocation of Blame for Medical Errors among Physicians, Nurses, and Administrators at an Academic Medical Center. Stephen Elliot Gordon. Yale University School of Medicine, New Haven, Connecticut.

Despite significant efforts among health care leaders in the past two decades to move away from the so-called "culture of blame," individual blame for medical errors is still a significant presence in health care settings. Furthermore, little is understood about how individuals assign blame and what differences, if any, exist between different health care professionals in how they assign individual blame.

This study tested three hypotheses regarding the allocation of blame for medical errors. Hypothesis No. 1: Despite a shift toward systems-based thinking, health care professionals will blame individuals rather than the system for medical errors. Hypothesis No. 2: Even when given the exact same information, health care professionals will allocate blame or accountability for medical errors differently, depending on their role in the health care system. Hypothesis No. 3: In general, health care professionals will allocate blame disproportionately toward other professions rather than blame their own professions.

We conducted a detailed survey centered on a set of three standardized cases, each involving fictitious clinical vignettes during a single patient admission. Each case involved multiple medical errors, each of which was necessary but insufficient in isolation to result in the adverse outcome. For each case, respondents allocated blame for the medical errors among four root causes that corresponded to nurses, physicians, and hospital administrators. A self-blame ratio was calculated that examined the extent to which people disproportionately assigned blame to their own profession compared to the level of blame assigned to them by other respondents.

Overall, when given specific cases, respondents placed more blame on individuals than on systemic factors. Respondents placed more blame on physicians than on nurses, and hospital administrators placed more blame on the system and culture (non-individual factors) than either physicians or nurses placed on these factors. Respondents' role within the health care system was of significant predictive value in determining how they would assign blame for standardized cases. ANOVA of the mean values of blame allocation across all three cases demonstrated statistically significant differences by respondent's position for blame allocation to nurses ($p = .004$) and blame allocation to the hospital system ($p = .017$), but not for blame allocation to physicians or blame allocated to hospital culture ($p = .256$ and $p = .333$, respectively). Self-blame scores averaged above 1.00 ($1.20 \pm .50$, $N = 85$), indicating that respondents in general placed more blame on their own professions than others placed on them. This held true across all three groups, but was the most pronounced with nurses ($1.40 \pm .48$, $N = 24$), moderately pronounced with administrators ($1.09 \pm .34$, $N = 38$), and the least pronounced with physicians ($1.17 \pm .67$, $N = 23$). ANOVA of differences between groups was statistically significant ($p = .049$).

Conclusions: Respondents placed more blame on individuals than non-individuals; role within the hospital was a significant predictor of blame allocation. Overall, respondents tended to blame their own professions more than others blamed them.

Autologous Stem Cell Transplantation in Elderly Patients with Non-Hodgkin's Lymphoma. Joel Robert Green. Yale University School of Medicine, New Haven, Connecticut.

Clinical trials investigating autologous stem cell transplantation (ASCT) historically have excluded elderly patients due to the risk of treatment-related morbidity related to the administration of high dose chemotherapy. While the availability of this procedure continues to expand, the elderly still represent a population for which the role of ASCT needs to be

fully defined. Two hundred one patients who underwent autologous stem cell transplantation (ASCT) for non-Hodgkin's lymphoma (NHL) at a single institution following BEAM conditioning between January 1, 2000, and December 31, 2007, were retrospectively identified from the Yale University School of Medicine Bone Marrow Transplant Database. Sixty-seven patients were older than 60 years at the time of transplantation (median age 65, range 60-75) and were compared to a matched group of 134 patients transplanted during the same time period. These groups were extremely well matched for all demographics such as gender, NHL histology, performance status, and comorbidities. Most patients had advanced stage disease at diagnosis and were transplanted at first or second remission. Diffuse large B-cell and mantle cell lymphoma were the most common subtypes, but other subtypes were represented. The elderly group experienced significantly more serious toxicities within the first 100 days (63 percent) when compared to the control group (42 percent). However, there were no statistical differences ($p < 0.0001$) between the groups regarding specific organ system toxicities. The one-year non-relapse mortality (3 percent) was not significantly different when compared to the younger cohort (1 percent). At a median follow-up of 31 months, the median overall survival is 85 months in the elderly group; at a median follow-up of 33 months in the younger group, the median overall survival has not yet been reached. The overall survival at three years is 74 percent and 75 percent respectively ($p = 0.91$). The disease-free survival at three years is 48 percent in the elderly group compared to 58 percent in the control group ($p = 0.66$). By univariate analysis, age >60 years (RR 3.1, 95 percent CI 1.7 – 5.7, $p = 0.004$) was the only factor predictive of developing a serious toxicity from ASCT within the first 100 days. HCT-CI score (RR 2, 95 percent CI 1 – 4, $p = 0.043$) was the only factor associated with significantly worse overall survival. Autologous stem cell transplantation can be performed safely in selected patients older than 60 years with chemosensitive NHL. Although elderly patients appear more likely to develop acute toxicities, the outcomes are similar to that of younger patients with respect to non-relapse mortality, disease-free survival, and overall survival.

Personal Accounts of Endometriosis: Online Narratives of Lives Shaped by Pain. Veronique Anne Sabine Griffith. Yale University School of Medicine, New Haven, Connecticut.

Endometriosis is a chronic disease characterized by the presence of endometrial implants outside the endometrial cavity. Because of its chronicity and lack of cure, the experience of endometriosis goes well beyond physical symptoms and has a significant impact on the psychosocial aspects of affected patients' lives. Given this extensive impact on the patients' quality of life, it is surprising how little attention has been given by the medical profession to exploring the mechanisms used by endometriosis patients to cope with this disease. One such important mechanism is the use of online support groups.

This qualitative study focused on the use of online support groups by patients afflicted with endometriosis. Two online groups were accessed, and 28 posts from 27 patients were analyzed in detail in an attempt to understand how the patients used the groups and what matters they discussed. The following four major themes emerged from the analysis: the quest to legitimize the endometriosis illness experience and the search for support; the search for medical information; descriptions of the effect the disease has on the patients' lives (known as the illness experience); and efforts of group members to interact effectively with non-group members not suffering from the disease and, therefore, lacking this unique illness experience.

The results indicate that the patients were often dissatisfied with the treatment they had received from medical professionals who generally focused on the physical manifestations of the disease. The group's communications reflected a broader understanding of the illness experience that was frequently ignored by medical professionals. These results lead to the notion, deserving of further study, that the endometriosis peer groups may be an important adjunctive measure in the armamentarium of endometriosis treatment. In addition, the findings suggest that the training of physicians in the management of patients with endometriosis needs to be re-conceptualized to emphasize treatment of both the disease and its psychosocial impact on the patients.

The Effect of Left- Vs. Right-Sided Contrast Infusion on Attenuation in Chest CT Angiograms. Lars J. Grimm, Daniel Cornfeld, and Hamid R. Mojibian. Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut.

This study assesses if the arm of contrast infusion influences attenuation of the main pulmonary artery in CT angiograms to evaluate for pulmonary emboli. With IRB approval, 407 consecutive CT angiograms performed to exclude pulmonary emboli were reviewed. Patient characteristics, study details, and interpretation results were collected. After exclusion criteria were applied, 100 studies from each of our three scanners (4, 16, and 64 slice) remained. A reader, blinded to injection side, reviewed the images and recorded the attenuation of the main pulmonary artery. The average post-contrast attenuation in the main pulmonary artery was similar if infused through the right (275.4 HU) or left (275.0 HU) arm when controlling for confounders with a multiple regression analysis ($p = 0.82$). There was no statistical difference ($p > 0.05$) in the number of scans with attenuation less than 250 (45.9 percent right, 42.9 percent left), 200 (25.0 percent right, 29.0 percent left), or 150 HU (11.6 percent right, 12.3 percent left) and no difference in the number of scans interpreted as indeterminate (1 percent right, 4 percent left) or non-diagnostic (3 percent right, 3 percent left). Main pulmonary artery attenuation is not dependent on the arm of infusion when evaluating mean attenuation, attenuation beneath thresholds of 250, 200, or 150 HU, or indeterminate or non-diagnostic interpretations for patients undergoing a CT angiogram of the chest to rule out pulmonary emboli.

Thinking Outside The Black Box: Current Policies and Problems with the FDA's Highest Drug Safety Warning. Kylene Halloran. Yale University School of Medicine, New Haven, Connecticut.

Based on data collected from clinical trials and post-approval surveillance systems, the Food and Drug Administration (FDA) issues warnings to communicate increasingly dangerous and/or preventable risks to doctors and their patients. The black box warning, the highest of all warnings issued by the FDA, emphasizes risks the FDA has deemed are critical to safe use of the drug. The warning has numerous implications for pharmaceutical companies and physicians. The purpose of this thesis is to discuss the infrastructure of the adverse effect detection system, the effects of the Food and Drug Amendments Act (FDAAA) of 2007, and the need for the FDA to reevaluate the black box warning system.

Recent studies and public scandals have demonstrated that the warning system is flawed, from the information on which the FDA drug safety advisory committees base their decisions to the methods by which they communicate their findings. Most critically, the warnings often go unheeded by doctors due to inconsistencies in the warning system and the language and methods by which this information is communicated.

The FDAAA of 2007 addresses many of these underlying issues. Mending these dysfunctional systems will undoubtedly strengthen the advisory committee's ability to properly assess safety issues. However, even if data gathering systems are perfected, doctors most likely will not abide by an inconsistent warning system that inflates or downgrades safety information. Only when the warnings accurately reflect the risk-benefit profile of a medication will health care providers regain trust in the FDA's ability to identify, label, and communicate these issues.

Barriers to Interpreter Use in the Medical Clinical Encounter. Luz Evelyn Jimenez. Yale University School of Medicine, New Haven, Connecticut.

The Limited English Proficiency (LEP) population in the United States requires interpreters in order to receive appropriate medical care. However, interpreters are not used consistently in clinical encounters. This study aims to identify the barriers that interfere with providing this service, as well as to propose some possible ways to overcome these barriers. A systematic review of the literature was conducted using Medline, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and PsycINFO. Twenty articles that

presented barriers to interpreter use were identified. These barriers referred to either professional interpreters or ad hoc interpreters, or were general barriers. The barriers to professional interpreter use most frequently identified were related to cost and most of the cost-related barrier citations were found in studies conducted in the United States. The barriers to ad hoc interpreter use most frequently identified were related to concern about the interpreters' ability to interpret. I determined that the appropriate provision of interpreters to the LEP community would require four elements: the consistent use of professional interpreters and the elimination of ad hoc interpreter use; research into the possible financial benefits that may arise from increased interpreter use and how the cost of providing interpreters may be offset by the widespread benefits of using them; professionalization of interpreter services with quality assurance, standardized training, and evaluation of interpreters; and increased education and training for patients and providers about the language services that are available, how to access them, and how to work with an interpreter efficiently and effectively. One possible solution that would allow the implementation of all of the above elements is a national interpretation service.

A Survey of Radiology Practices' Use of After-Hours Services. Adam Harris Kaye. Yale University School of Medicine, New Haven, Connecticut.

Purpose: To identify the characteristics of and the motives behind radiologists' use, or lack thereof, of after-hours services.

Methods: From August 2005 to June 2006, 300 non-specialty hospitals randomly selected from the 2005 American Hospital Association Directory of Hospitals were contacted by phone, email, and mail, with an attempt made to speak to the chief of radiology. We obtained 115 responses, a 38.3 percent response rate, including 64 from practices that used an external after-hours service. Responses were analyzed using descriptive statistical analyses.

Results: Practices cited convenience as the most important reason for using after-hours services, value for recruiting ranked second, and shortage of radiologists for off-hours coverage ranked third. Three-fourths of practices said they receive 5 percent or fewer of their reads from these services. Two-thirds of practices paid the service about as much as they collected or more. Approximately 40 percent of respondents utilized an after-hours service that was located internationally. Of these, 56 percent said that the international radiologists used were either all Americans or mostly Americans, and 40 percent did not know the proportion of foreigners. Regardless, in-state licensure of all interpreting teleradiologists is essentially universal.

Conclusions: Most radiology groups that use after-hours services do so for convenience rather than shortage of staff to provide coverage. Most practices send a very small percentage of their studies to the services. While services located overseas are commonly used, there is little evidence of radiologists at these services who are not American or American-trained.

Copy Number Variant Analysis of Patients with Malformations of Cortical Development. Luis Enrique Kolb. Yale University School of Medicine, New Haven, Connecticut.

Copy Number Variants (CNVs) are DNA fragments approximately 1 kilobase (kb) to several megabases in size for which copy-number differences have been revealed by the comparison of two or more genomes. The Human Genome Project has led to the identification of close to 1,500 of these variable regions covering 12 percent of the human genome. Even though many of these variants are considered to be benign, some of these genomic rearrangements have been found to cause diseases, including several nervous system disorders such as Charcot-Marie-Tooth, Williams-Beuren Syndrome, and Prader-Willi syndrome.

In this study, we performed copy number variant analysis on 252 patients with cortical malformations. Cortical malformations represented in our cohort included patients with cortical dysplasia [95], lissencephaly [33], heterotopia [10], pachygyria [8], and polymicrogyria [20], among other diseases.

Two disease-causing copy number variants were identified, and those two diseases are the focus of this manuscript: a diffuse villous hyperplasia of the choroid plexus and cerebellar atrophy with pachygyria.

Diffuse villous hyperplasia of the choroid plexus is a rare cause of hydrocephalus not amenable to shunting alone. Tetrasomy of the short arm of chromosome 9 was identified using high-resolution genomic array mapping, broadening the phenotype of this described entity to include diffuse villous hyperplasia of the choroid plexus.

Congenital ataxia with cerebellar hypoplasia is a heterogeneous group of disorders that presents with motor disability, hypotonia, incoordination, and impaired motor development. A homozygous deletion in the VLDLR gene was identified using high density single nucleotide polymorphism (SNP) microarrays in a Turkish family with two siblings affected with cerebellar atrophy and pachygyria. Previous identification of VLDLR mutations in a Turkish family with quadrupedal gait led to various speculations ranging from "reverse evolution" to cultural influences. Discovery of disease causing homozygous deletions in a new Turkish family, which maintained bipedal movement, constitutes significant evidence against these speculations.

Is Papilledema in HIV/AIDS Patients with Cryptococcal Meningitis Related to Mortality? Ninani E. Coyne Kombo and Oathokwa Nkomazana. Department of Ophthalmology, Princess Marina Hospital, Gaborone, Botswana. (Sponsored by Susan Forster, Department of Ophthalmology, Yale University School of Medicine, New Haven, Connecticut.)

Once simply thought of as an obscure yeast affecting very few people worldwide, Cryptococcus has established itself as one of the most common fungal causes of death and morbidity since the beginning of the HIV/AIDS pandemic. Seventeen percent of the general population and 35 percent of pregnant women between the ages of 15 and 35 in Botswana have HIV/AIDS, thus cryptococcal meningitis has a high incidence in that country.

This study sought to determine whether papilledema is related to mortality in HIV/AIDS patients with cryptococcal meningitis. The secondary goals were the estimation of the incidence of visual loss and the description of the risk factors for developing vision loss, other ocular complications associated with cryptococcal meningitis, and ocular complications of HIV infection unrelated to cryptococcal infection.

The setting of the study was Princess Marina Hospital, a tertiary referral center, in Gaborone, Botswana. From June to August 2008, 14 patients were enrolled in the study and one dropped out; their ages ranged from 16 to 52 years (median 37 years). The mean CD4+ level of the participants was 72 cells/μL (range 10 to 206 cells/μL, median 45 cells/μL).

Twelve of 13 participants reported visual symptoms, the most common being blurry vision, photophobia, and tearing. Ocular findings related to elevated intracranial pressure secondary to cryptococcal meningitis were ophthalmoplegia (3/13), papilledema (2/13), and optic disc atrophy (3/13). No participants presented with complete blindness, nor did they become completely blind during their hospitalization. The in-hospital mortality in this study was 30.8 percent (four of 13 patients). Only one of the four patients that died had papilledema, another had optic atrophy, and two had a relapse of cryptococcal meningitis.

There was no cryptococcal infection of the eye observed. Non-cryptococcal related findings were: clinically diagnosed ocular surface neoplasia (OSSN) in one patient (OD), molluscum contagiosum papules on the eyelids of two patients, and a pterygium and a pingueculum each in one patient.

In conclusion, our data, in agreement with other studies, indicates the high in-hospital mortality (30.8 percent) of cryptococcal meningitis in HIV/AIDS patients and the low prevalence of intraocular cryptococcal infection. A larger study needs to be completed to further investigate the relationship between papilledema and mortality. This study is the beginning of new and important ophthalmologic research that needs to be carried out in Botswana. This research will benefit ophthalmologists and health care providers in Botswana. In addition,

it has the potential to inform other sub-Saharan nations that have similar HIV/AIDS and cryptococcal meningitis rates.

Febrile Infants and Common Respiratory Viruses: Epidemiology and Clinical Implications. Caleb Bosler Korngold. Yale University School of Medicine, New Haven, Connecticut.

Fever in infants younger than two months causes a significant number of emergency department visits and is particularly worrisome because of the potential for serious infection. Management of febrile infants is problematic because clinical observation is not a reliable indicator of serious bacterial illnesses (SBI) such as bacteremia, meningitis, and urinary tract infection (UTI). Numerous investigators have proposed methods of screening laboratory tests to ascertain the risk of SBI in febrile infants. These screening tests could potentially avoid an invasive and costly sepsis work-up, which usually includes complete blood count (CBC), blood culture, urinalysis, urine culture, and lumbar puncture. We conducted a prospective, cross-sectional study that examined the prevalence of rhinovirus (RV) and coronavirus (CoV), which are two of the most common causes of upper respiratory infections in the first year of life, and human metapneumovirus (hMPV), which is a common cause of bronchiolitis, in infants younger than two months. This study also examined whether febrile infants with RV were more or less likely to also have a SBI than infants without a viral respiratory infection. **Methodology**: Fever was defined as rectal temperatures greater than 37.9 C or a historical fever greater than 100.3 F. Nasal swabs were tested with reverse transcriptase polymerase chain reaction (RT-PCR) techniques for rhinoviruses (RV), human metapneumovirus (hMPV) and coronaviruses (CoV). Nasal samples also were tested for RSV, influenza A and B, parainfluenza types 1, 2 and 3, and adenovirus via direct fluorescent antibody (DFA). **Conclusion**: Rhinovirus (RV) was the most commonly detected respiratory viral pathogen in our cohort (14 percent of 98 total enrolled patients). Coronovirus (CoV) and human metapneumovirus (hMPV) were both detected in only one patient (1 percent) each. RV occurred predominantly in the summer (79 percent). This study showed no difference between the incidence of serious bacterial illness (SBI) in patients with or without RV infection ($p = 0.84$).

Patient Perspectives on Dissatisfaction: A Qualitative Analysis of Expectations for Hospital Care. Alicia V. Lee, John P. Moriarty, Christopher P. Borgstrom, and Leora I. Horwitz. Section of General Internal Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

The measurement of patient satisfaction has taken a prominent role in the assessment of health care quality. Patient dissatisfaction, however, is not well understood. While the concept of satisfaction often proves vague and difficult to accurately measure, experiences with dissatisfaction are more tangible. In order to more fully understand dissatisfaction and its relationship to patients' expectations, we conducted a qualitative analysis of patient suggestions for improvements in hospital care.

Data were obtained from telephone interview surveys of adult patients discharged from Yale-New Haven Hospital between July 1, 2007, and June 30, 2008. Patients were asked: "If there was one thing we could have done to improve your experience in the hospital, what would it have been?" We randomly selected 10 percent of survey respondents and analyzed answers to this question using standard qualitative analytic techniques.

Nine hundred seventy-six of 9,764 surveys were randomly selected; 439 (45.0 percent) included at least one suggestion in response to the study question. We identified six major domains of dissatisfaction. These domains corresponded to six implicit expectations for quality hospital care: 1) safety; 2) treatment with respect and dignity; 3) minimized wait times; 4) effective communication; 5) control over the physical environment; and 6) high quality amenities. Further, each expectation was associated with unique emotional responses. Respectively, patients felt: 1) unsafe (7.7 percent); 2) disrespected (6.0 percent); 3) anxious and/or abandoned (15.8 percent); 4) confused and mistrustful (7.4 percent); 5)

confined and imposed upon (15.6 percent); and 6) disappointed (6.9 percent) when expectations were not met.

Dissatisfaction with hospital care was found to largely result from discrete episodes when expectations for care were not met. The expectations that emerged from our qualitative analysis represent patient-generated priorities for quality improvement in hospital care, which have previously not been adequately measured. Certain aspects of patient expectations were found to be in accordance with current quality improvement initiatives, while other aspects were found to be inadequately addressed.

Inventing New CARs: Analysis of Chimeric Antigen Receptor Gene-Targeted T cells Modified to Overcome Regulatory T cell Suppression in the Tumor Microenvironment. James C. Lee. Yale University School of Medicine, New Haven, Connecticut.

Human T cells may be genetically modified to express targeted chimeric antigen receptors (CARs). We have previously demonstrated that T cells modified to express a CAR specific to the B cell tumor antigen CD19, termed 19-28z, successfully eradicate systemic human CD19+ tumors in SCID-Beige mice. While these results are encouraging, this xenogeneic tumor model fails to address potential limitations of this therapeutic approach in the clinical setting wherein these modified T cells encounter a hostile tumor microenvironment. Specifically, these models fail to address potential effector T cell inhibition mediated by endogenous regulatory T cells (Tregs). To investigate the role of inhibitory Tregs, we initially assessed the *in vitro* function of CAR-modified T cells in the context of Tregs. We found that CD19-targeted T cell proliferation and cytotoxicity were inhibited by purified natural Tregs. To further assess the role of these Tregs *in vivo*, we isolated and genetically modified Tregs to express the CD19-targeted 19z1 CAR. We verified specific trafficking of targeted Tregs to CD19+ tumors *in vivo* and demonstrated that 19z1 Tregs wholly inhibit anti-tumor function of subsequently injected 19-28z effector T cells even at low Treg to effector T cell ratios (1:8). In order to overcome this limitation, we assessed whether the addition of a pro-inflammatory cytokine *in vitro* could overcome Treg inhibition. Indeed, the addition of exogenous IL-12 mediated resistance of 19-28z T cells to Treg inhibition. In light of this data, we generated a bicistronic retroviral vector containing both the 19-28z CAR as well as the murine IL-12 fusion gene (19-28z IRES IL-12). Significantly, we found that 19-28z/IL-12+ T cells exhibited enhanced proliferation *in vitro* as well as resistance to Treg mediated inhibition when compared to 19-28z+ T cells. Finally, we demonstrate that 19-28z/IL-12+ T cells overcome Treg inhibition *in vivo* in our SCID-Beige Treg tumor model. In conclusion, tumor targeted T cells modified to express IL-12 demonstrate significantly enhanced *in vivo* anti-tumor efficacy in the presence of Tregs that are similarly targeted to the site of tumor. These results validate utilization of IL-12 secreting tumor targeted T cells in future clinical trials.

Horizontal Deviation of Retinal Nerve Fiber Layer Peak Thickness with Stratus Optical Coherence Tomography in Glaucoma. Jennifer C. Lee and M. Bruce Shields. Department of Ophthalmology and Visual Sciences, Yale University School of Medicine, New Haven, Connecticut.

Nasal/temporal peak contour shifts from the normative database observed on the Fast retinal nerve fiber layer (RNFL) scan are a common occurrence. We hypothesize that this is because of the wide distribution of peak contours due to anatomical variation and not necessarily related to glaucoma. Therefore, these displacements may lead to misclassification as glaucoma under current commercial optical coherence tomography (OCT) criteria. The purpose of this study was to evaluate the prevalence of these shifts with Stratus OCT and possible associations with demographic or glaucoma-related variables.

This was a retrospective case series of glaucoma patients and glaucoma suspects (one eye per patient) who underwent a Fast RNFL thickness study with the Stratus OCT. A study

was considered to have a clinically significant horizontal deviation if there was a shift greater than 20° from the normative database in both superior and inferior peaks. A second cut-off value of 12° also was used to examine smaller deviations. A linear regression model was used to assess correlations of demographic and glaucoma-related variables between eyes, with and without significant deviations.

Of 400 subjects screened, 273 met the inclusion criteria. Thirty-nine eyes (14.3 percent) had clinically significant horizontal deviation using the 20° cut-off (95 percent CI 10 percent-19 percent), while 122 (44.7 percent) met the definition with the 12° cut-off (95 percent CI 38 percent-51 percent). Additionally, 121 eyes (44.3 percent) had a >20° horizontal shift of either the superior or inferior peak (95 percent CI 38 percent-51 percent). There was no correlation between the demographic or glaucoma-related variables and the horizontal deviation of peak contours.

This study suggests that significant horizontal deviation of peak RNFL contours with the Stratus OCT Fast RNFL is common and emphasizes the need for caution when interpreting the influence of such deviations on clock hour segment thinning. It is not possible with this technology to distinguish between scan circle misalignment (horizontal or vertical) and anatomical variation as the explanation for the finding, and further study with newer technology is needed.

Curcumin Protects Against Renal Ischemia by Activating the Unfolded Protein Response and Inducing HSP70. Sarah Angeline Lee. Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to establish whether curcumin protects renal proximal tubule cells against ischemic injury, determine if this postulated cytoprotective effect is mediated through the upregulation of HSP70, and investigate whether the mechanism by which curcumin induces HSP70 expression and confers its protective effect is through activation of the Unfolded Protein Response. LLC-PK1 cells were cultured on collagen-coated filters to mimic conditions of *in vivo* renal proximal tubule cells and induce cell polarization. Injury with and without curcumin treatment was studied by using chemically induced ATP-depletion, which mimics renal ischemic injury. Cell injury was assessed using a TUNEL assay in order to evaluate DNA cleavage associated with ischemia-induced apoptosis and actin staining used to assess cytoskeletal disruption. Renal ischemic damage was further investigated by assessing detachment of the Na-K ATPase from the basolateral membrane as a measurement of loss of cell polarity. Cells were incubated with curcumin in a dose- and time-response fashion and subsequent levels of HSP70 expression were assessed. Cells were then incubated with AEBSF, an inhibitor of the Unfolded Protein Response (UPR), and both HSP70 and BiP/GRP78 (an ER resident chaperone that is up-regulated by the UPR) expression levels were evaluated. Results demonstrated that treatment with curcumin during two hours of injury results in significantly less injury-related apoptosis and cytoskeletal disruption compared to control injured cells. It was demonstrated that curcumin induces HSP70 in both a dose- and time-response fashion. Moreover, curcumin treatment resulted in profound stabilization of Na-K ATPase on the basolateral membranes as there was significantly less Na-K ATPase detachment in cells treated with curcumin during two hours of injury compared to control injured cells. Finally, treatment with AEBSF inhibited HSP70 up-regulation in curcumin-treated cells as well as inhibiting the GRP78 over-expression otherwise demonstrated in curcumin-treated cells. Protection of proximal tubule cells against renal ischemic injury by curcumin was therefore indicated to be mediated by the activation of the UPR through which HSP70 is up-regulated. Curcumin's activation of the UPR and induction of HSP70 explains the stabilization of Na-K ATPase on the cytoskeleton and also provides a potential mechanism explaining many of curcumin's therapeutic and protective qualities.

Mechanisms of Hematopoietic-Mesenchymal Cell Activation. Justin Michael Lemieux. Yale University School of Medicine, New Haven, Connecticut.

As the prevalence of osteoporosis is expected to increase over the next few decades, the development of novel therapeutic strategies to combat this disorder becomes clinically imperative. These efforts draw extensively from an expanding body of knowledge pertaining to the physiologic mechanisms of skeletal homeostasis. To this body of knowledge, we contribute that cells of hematopoietic lineage may play a crucial role in balancing osteoblastic bone formation against osteoclastic resorption. Specifically, our laboratory previously has demonstrated that megakaryocytes can induce osteoblast proliferation *in vitro*, but do so only when direct cell-to-cell contact is permitted. To further investigate the nature of this interaction, we have effectively neutralized several adhesion molecules known to function in the analogous interaction of megakaryocytes with another cell-type of mesenchymal origin — the fibroblast. Our findings implicate the involvement of fibronectin/RGD-binding integrins including α3β1 (VLA-3) and α5β1 (VLA-5) as well as glycoprotein IIb (CD41), all of which are known to be expressed on megakaryocyte membranes. Furthermore, we demonstrate that IL-3 can enhance megakaryocyte-induced osteoblast activation *in vitro*, as demonstrated in the megakaryocyte-fibroblast model system. Taken together, these results suggest that although their physiologic and clinical implications are very different, these two models of hematopoietic-mesenchymal cell activation are mechanistically analogous.

Clinical-Pathologic Features and Long-Term Outcomes of Tubular Carcinoma of the Breast Compared with Invasive Ductal Carcinoma. Gene-Fu F. Liu. Yale University School of Medicine, New Haven, Connecticut.

Purpose: The purpose of our study is to evaluate our institutional experience of treating Tubular Carcinoma of the Breast (TC) and Invasive Ductal Carcinoma (IDC) with Breast Conservation Therapy (BCT), consisting of conservative surgery (CS) and radiation therapy (RT), and to compare clinical-pathologic features and long-term outcomes.

Materials and Methods: A review of our institution's tumor registry from 1975 to 2007 was performed, followed by a central pathology review of available slides, yielding 71 cases of Stage I/II TC and 2238 cases of Stage I/II IDC treated with BCT.

Results: Clinical-pathologic features and outcomes were then analyzed by subtype to detect significant differences. The median follow-up was seven years. The TC cohort presented more frequently with pT1 disease (97 percent vs. 80 percent, $p = 0.0007$), pN0 disease (95 percent vs. 74 percent, $p = 0.0004$), hormone-receptor positivity (ER+: 89 percent vs. 62 percent, $p = 0.0001$; PR+: 81 percent vs. 52 percent, $p = 0.0001$), and HER-2 negativity (89 percent vs. 71 percent, $p = 0.04$). Clinical outcomes also favored the TC cohort, with lower rates of breast cancer-related death (1 percent vs. 10 percent; $p = 0.0109$) and distant metastasis (1 percent vs. 13 percent; $p = 0.0028$), and higher rates of 10-year overall (90 percent vs. 80 percent; $p = 0.033$), cause-specific (99 percent vs. 86 percent; $p = 0.011$), and disease-free (99 percent vs. 82 percent; $p = 0.003$) survival. There was a non-significant trend toward improved breast relapse-free survival for the TC cohort (95 percent vs. 87 percent; $p = 0.062$) but no difference in nodal relapse-free survival or contralateral breast relapse-free survival (all p-values > 0.05) between the cohorts.

Conclusion: Our institutional experience suggests that TC, when compared to IDC, is associated with more favorable clinical-pathologic features and comparable, if not superior, outcomes following BCT, suggesting the appropriateness of a conservative approach to this rare subtype.

Aesthetics of the Female Breast: Correlation of Pluralistic Evaluations with Volume and Surface Area. Yuen-Jong Liu. Yale University School of Medicine, New Haven, Connecticut.

The goal of cosmetic and reconstructive breast surgery is to fashion symmetric breasts with aesthetically acceptable shapes. Breast shape is largely determined by volume of tissue

and surface area of the skin envelope. Values for breast surface area have never been published in the literature. The investigators developed an inexpensive, non-invasive optical method to objectively measure breast volume and surface area. The aims were to validate the method, assess the accuracy of visual inspection by plastic surgeons, determine ideal anthropomorphic measurements, and derive a mathematical relationship between volume and surface area for an aesthetically acceptable shape.

In the novel method, an optical grid was projected onto each breast and two images were captured in order to create a computerized three-dimensional model from which volume (V), surface area (A), and maximum vertical projection (Z) were calculated. The method was used to measure volume and surface area of the breasts of female volunteers. Anthropomorphic measurements also were recorded. Images of their breasts were arranged into a computerized survey, and plastic surgeons, cosmetic patients, and reconstructive patients were interviewed for aesthetic feedback.

The method was validated on geometric shapes and female breasts. Simple geometric shapes ($n = 22$) were analyzed, and the actual V, A, and Z were compared with the imaged values using least-squares linear regression. There was excellent correlation in all three parameters ($R > 0.995$, $p < 10^{-14}$). The mean differences in V, A, and Z were 28 ± 28 mL (mean +- SD), 2 ± 9 cm^2, and 0.4 ± 0.5 cm, respectively. Female breasts ($n = 14$) were analyzed, and the actual V and A were measured using plaster casts. Based on least-squares linear regression, there was excellent correlation between the imaged values and actual values ($R > 0.992$, $p < 10^{-11}$), and the mean differences in V and A were 32 ± 22 mL and 3 ± 11 cm^2, respectively.

The breasts of 109 female volunteers were measured and included for aesthetic evaluation. Two hundred fifty-two plastic surgeons, 15 cosmetic patients, and 25 reconstructive patients submitted totals of 3641, 368, and 437 evaluations, respectively. On average, plastic surgeons underestimated volume by 7 percent ± 49 percent (mean ± SD) and overestimated surface area by 15 percent ± 69 percent. Ideal anthropomorphic measurements and volume to surface area ratios were calculated and compared to previously published values. Cosmetic patients were most attentive to insufficient cleavage, and reconstructive patients were most attentive to severe asymmetry.

For the first time, an optical method was demonstrated to measure volume and surface area with accuracy. When applied to the breast, measurement errors were small and clinically insignificant. Plastic surgeons were more accurate in estimating volume than surface area, though showing significant inconsistencies in both parameters from one breast to the next. Ideal anthropomorphic measurements were similar among plastic surgeons and breast surgery patients. Reconstructive patients preferred higher volume to surface area ratios than plastic surgeons and cosmetic patients.

A Prognostic Index for Predicting Lymph Node Metastasis in Minor Salivary Gland Cancer. Shane Lloyd. Yale University School of Medicine, New Haven, Connecticut.

We hypothesized that lymph node involvement in minor salivary gland cancers is associated with clinical and pathological factors commonly available to the clinician after a typical initial workup. Our aim was to identify these factors using a dataset that allowed us to compile the largest series of minor salivary gland cancers in the published literature. Using this dataset, we also aimed to characterize the distribution of histological types by primary site, identify the predictors of the use of external beam radiation therapy and neck dissection, and examine the effect of lymph node involvement on survival. Using the SEER database, we identified 2,667 minor salivary gland cancers with known lymph node status from 1988 to 2004. Univariate and multivariate analyses were conducted to identify factors associated with the use of neck dissection, the use of external beam radiation therapy, and the presence of cervical lymph node metastases. Kaplan Meier survival curves were constructed to examine the effect of lymph node involvement on survival. Four hundred twenty-six (16.0 percent) patients had neck nodal involvement. Factors associated with neck nodal

involvement on univariate analysis included increasing age, male gender, increasing tumor size, high tumor grade, T3-T4 stage, adenocarcinoma or mucoepidermoid carcinomas, and pharyngeal site of primary malignancy. On multivariate analysis, four statistically significant factors were identified, which included male gender, T3-T4 stage, pharyngeal site of primary malignancy, and high-grade adenocarcinoma or high-grade mucoepidermoid carcinomas. The proportions (and 95 percent confidence intervals) of patients with lymph node involvement for those with 0, 1, 2, 3, and 4 of these prognostic factors were 0.02 (0.01-0.03), 0.09 (0.07-0.11), 0.17 (0.14-0.21), 0.41 (0.33-0.49), and 0.70 (0.54-0.85) respectively. Grade was a significant predictor of metastasis for adenocarcinoma and mucoepidermoid carcinoma but not for adenoid cystic carcinoma. Overall survival was significantly worse at five, 10, and 15 years for patients with lymph node involvement on presentation. A prognostic index using the four clinicopathological factors listed above can effectively differentiate patients into risk groups of nodal metastasis. The precision of this index is subject to the limitations of SEER data and it should be validated in further clinical studies.

Disease Predilection and Molecular Heterogeneity of the Murine Aorta are Intrinsic to the Vessel Wall. Sheng-fu Larry Lo. Yale University School of Medicine, New Haven, Connecticut.

Vascular diseases such as atherosclerosis or aneurysmal disease preferentially affect different parts of the arterial system. Despite this heterogeneous pattern of disease within the arterial system, the contribution of different smooth muscle cell phenotypes to this pattern has not been well studied. We investigated aortic disease susceptibility and epigenetic differences within different regions of the murine aorta. Quantitative analyses showed increased numbers of atherosclerotic plaques and larger aneurysms in the ascending aorta compared to the descending thoracic aorta in apoE$^{-/-}$ and fbn1$^{C1039G/+}$ mice, respectively. Interferon-γ and transforming growth factor-β responses, which are characteristic of these disease processes, were greater in the ascending vs. descending thoracic aorta. There was differential gene expression within the aorta, and a "Hox code" was found for the murine arterial vasculature along the anterior-posterior axis. Transplantation of ascending and descending thoracic aortic segments to the abdominal aorta of syngeneic recipients confirmed that the propensity for atherosclerotic disease and the expression of selective molecular markers were innate properties of the vessel wall and not dependent on regional hemodynamic factors or paracrine signals from surrounding tissues. The epigenetic changes were also stable in cultured cells despite identical *in vitro* conditions. Our work supports the concept of intrinsic differences between vascular smooth muscle cells from various arteries that may play a role in disease pathogenesis.

Searching for Genes That Matter in Acute Kidney Injury: A Systematic Review. Jonathan Chun Ting Lu. Yale University School of Medicine, New Haven, Connecticut.

Background and Objectives: Identifying patients who may develop acute kidney injury (AKI) remains challenging as clinical determinants explain only a portion of individual risk. Another factor that likely affects risk is intrinsic genetic variability. Therefore, we performed a systematic review of studies that related the development or prognosis of AKI to genetic variation.

Design: We searched MEDLINE, EMBASE, HuGEnet, SCOPUS and Web of Science for articles from 1950 to December 2007. Two independent researchers screened articles using predetermined criteria. Studies were assessed for methodological quality via an aggregate scoring system.

Results: The 16 included studies were of cohort or case-cohort design and investigated 35 polymorphisms in 21 genes in association with AKI. Fifteen gene-gene interactions were also investigated in four separate studies. Study populations were primarily premature infants or adults who were critically ill or post-cardiac bypass. Among the studies, five dif-

ferent definitions of AKI were used. Only one polymorphism, APO E e2/e3/e4, had more than one study showing a significant impact ($p < 0.05$) on AKI incidence, while of gene-gene interactions, this was true only with the IL-6 -174G/C and TNF-a -308G/A combination. The mean quality score of 5.8/10 (range 4-9) heterogeneity in the studies and the dearth of studies precluded additional meta-analysis of the results.

Conclusions: Current association studies are unable to provide definitive evidence linking genetic variation to AKI. Future success will require a narrow consensus definition of AKI, rigorous epidemiologic techniques and a shift from a priori hypothesis-driven to genome-wide association studies.

A Novel Virtual Reality Curriculum Improves Laparoscopic Skill in Novices.

Michael Joel Martinez and Andrew John Duffy. Department of Surgery, Yale University School of Medicine, New Haven, Connecticut.

Surgical skills training, which faces work hour restrictions and increasing numbers of procedural skills to master, requires an innovative approach to ensure success. We developed a novel basic laparoscopic skill, a virtual reality-based simulator curriculum on the LapSim (Surgical Science, Goteborg, Sweden), with a training module and a skills exam enabling trainees to develop a minimum skill level. We hypothesize that unskilled trainees' laparoscopic skills performance will improve when compared to controls. Also, those who are able to successfully complete our training curriculum and pass the exam will demonstrate higher skills levels compared to non-passers during the training period. We anticipate that skills will begin to degrade after 30 days without repetitive training. We expect that individual trainee performance will correlate with past experience with video games, sports, or musical instruments.

Thirty-two novice, pre-clinical medical students were randomized to various training schedules. All students trained on the curriculum with the goal of completing the practice drills and passing the skills exam. Students' laparoscopic skills were assessed at baseline and monthly intervals using two tasks from the Fundamentals of Laparoscopic Surgery (FLS) curriculum that are known to correlate with operative laparoscopic skill. Additional FLS testing was performed after a one-month layoff to evaluate short-term skill degradation. Objective skill FLS scores were compared between training and non-training groups and between passing and non-passing groups at the completion of the study. All participants' prior experiences with video games, sports, and musical instruments were correlated with study performance.

Training improved FLS performance for all participants. There was significantly greater skill development in passers vs. non-passers ($p < 0.05$). Skills did not degrade after a 30-day layoff but continued to improve for all participants even reaching a statistically significant improvement on one task. Performance was not correlated with past video game, sports, or musical instrument experience.

Trainees who successfully completed our curriculum demonstrated significantly higher laparoscopic skills. These skills should translate to improved operative performance. Skills were retained after the last training session and demonstrated improvement at 30 days. We demonstrated no performance correlation with prior video game, sports, or musical experience.

Social Determinants of Mixed Feeding Behavior Among HIV-Infected Mothers in Jos, Nigeria.

Sheela Smith-Rohrberg Maru. Yale University School of Medicine, New Haven, Connecticut.

Mixed feeding confers excess risk of mother-to-child transmission (MTCT) of Human Immunodeficiency Virus (HIV) compared with exclusive breastfeeding (EBF) and exclusive formula feeding (EFF). We undertook a quantitative and qualitative cross-sectional survey to identify the social determinants of mixed feeding among a subset of HIV-infected women enrolled in a MTCT prevention program in Jos, Nigeria. Of the 91 participants, 68 (75 per-

cent) exclusively formula fed, seven (8 percent) exclusively breastfed, and 16 (18 percent) practiced mixed feeding. Of the mixed feeding women, seven primarily formula fed and nine primarily breastfed. Women who primarily formula fed described family pressure as the reason for mixed feeding; whereas, women who primarily breastfed indicated insufficient breast milk. In a multivariate analysis, lack of partner support of the feeding decision predicted mixed feeding behavior (OR: 4.2; 95 percent CI: 1.2-14.9; $p = 0.03$). Disclosure of HIV status was significantly correlated ($p < 0.001$) with partner support. HIV prevention interventions aimed at reducing mixed feeding should encourage supportive partner relationships that facilitate disclosure of HIV status. Attention also should be made to the differing pressures faced by women attempting to exclusively breastfeed and exclusively formula feed.

Fibrocytes in Human Lung Fibrosis. Susan K. Mathai. Yale University School of Medicine, New Haven, Connecticut.

Idiopathic Pulmonary Fibrosis (IPF) is a rapidly progressing interstitial lung disease (ILD) with an unclear etiology and poorly understood pathogenesis. IPF has no known curative treatment and a grim prognosis. One emerging area of interest in the field of fibrosing diseases is the role that bone marrow-derived cells, specifically fibrocytes, play in lung repair and remodeling. Derived from circulating CD14+ progenitors in the peripheral blood, these cells are identified by CD45 and pro-Collagen I co-expression. Scant data exist regarding fibrocytes derived from the peripheral blood in patients with pulmonary fibrosis.

We hypothesized that (1) fibrocyte levels in the peripheral blood of patients with IPF would be greater than in patients with non-specific interstitial pneumonia (NSIP), the second most common type of ILD; (2) intrapulmonary fibrocyte levels would vary significantly between patients with IPF and non-IPF pathology; and (3) plasma from subjects with high fibrocyte levels would reveal a profile of immunomediators differing from that of patients with lower fibrocyte levels, regardless of disease state. Peripheral blood from patients with IPF ($n = 16$), NSIP ($n = 7$), and age-matched healthy controls ($n = 15$) was collected, their peripheral blood mononuclear cells (PBMCs) isolated by Ficoll separation, and their plasma stored for proteomic analysis. PBMCs and lung tissue digests from patients with fibrotic lung disease ($n = 9$) or normal controls ($n = 3$) were then co-stained for intracellular pro-Collagen I and CD45. Plasma underwent multi-analyte ELISA for a battery of immunologic targets. We found that patients with IPF had elevated fibrocytes as percentage of PBMCs (2.74 ± 2.12 percent) when compared to NSIP (0.88 ± 0.43 percent) and healthy controls (0.94 ± 0.84 percent), as measured by flow cytometry for CD45 and pro-Collagen I co-expression ($p < 0.05$ NSIP vs. IPF). Furthermore, within the IPF group, fibrocyte levels varied with disease severity ($p < 0.05$). Interestingly, while lung tissue from patients with active fibrosing pulmonary processes contained elevated fibrocyte levels (3.97 ± 2.7 percent) when compared with normal human lung tissue (1.04 ± 0.43 percent, $p = 0.11$), there was no difference between IPF and non-IPF pathology. Lastly, plasma from patients with higher fibrocytes as percentages of PBMCs revealed distinct immune mediator patterns. Specifically, patients with elevated fibrocytes had higher plasma levels of IL-18, IL-8, IL-10, Beta2-microglobulin, ICAM-1, and TIMP-1 ($p < 0.05$).

No previous study has compared fibrocyte levels in patients with IPF and NSIP. These data suggest there is a relationship between circulating fibrocytes and development of IPF. Moreover, patients with more severe IPF disease had higher levels of circulating fibrocytes, suggesting that they may be a biomarker of both disease state and severity. In addition, lungs of patients with both IPF and non-IPF fibrotic lung disease contained more fibrocytes than healthy lungs, suggesting a broader role for this cell type in the pathogenesis of ILD than previously hypothesized. Lastly, proteomic analysis suggests that elevated fibrocytes are associated with a distinct immunologic profile, but these results do not correlate with an expected dichotomy of profibrotic TH2 vs. TH1 immune profiles. These findings advance our understanding of fibrocytes as they relate to fibrotic lung disease and suggest novel avenues for future investigation.

Subcellular Localization of NEDD9 and HMB45 with Aqua Technology to Distinguish Spitz Nevi from Melanoma. Matthew C. McRae, Rossitza Lasova, Bonnie Gould-Rothberg, and David Rimm. Section of Plastic Surgery, Department of Surgery, Yale University School of Medicine, New Haven, Connecticut. (Sponsored by Deepak Narayan.)

Our hypothesis is that the expression level and subcellular localization of HMB45 and NEDD9 as demonstrated by the ln(nuclear/non-nuclear) Automated Quantitative Analysis (AQUA) score, defined as the subcellular AQUA ratio, will be consistently altered between benign nevi and melanoma and between Spitz nevi and Spitzoid melanoma. Our specific aims are to assess quantitative expression and subcellular localization of HMB45 and NEDD9 to aid in the diagnosis of benign Spitz nevi and malignant Spitzoid melanoma. This remains a vexing clinical problem with important implications for treatment and patient care. The quantitative expression and subcellular AQUA ratio will be assessed in the following samples: benign derived vs. malignant derived cell lines, human benign nevi, human primary melanoma, human metastatic melanoma, typical Spitz nevi, atypical Spitz nevi, and Spitzoid melanoma. AQUA was used to quantify protein expression levels in subcellular compartments using fluorescence-based immunohistochemistry. Tissue Microarrays (TMA) analysis was used for cell line, benign nevi, and malignant melanoma while whole section analysis was used for Spitz nevi and Spitzoid melanoma. NEDD9 subcellular AQUA ratio was significantly reduced in primary melanoma (mean = -0.645, std dev = 0.29) vs. benign nevi (mean = -0.429, std dev = 0.108) on YTMA98-2 ($p = 0.0086$), significantly reduced in melanoma metastases (mean = -0.482, std dev = 0.149) vs. benign nevi (mean = -0.342, std dev = 0.159) on YTMA66A ($p < 0.0001$), and significantly reduced in primary melanoma (mean = -0.435, std dev = 0.185) and melanoma metastases (mean = -0.42, std dev = 0.188) vs. benign nevi (mean = -0.319, std dev = 0.141) in SPORE84 array ($p = 0.0003$, Tukey/Kramer post-hoc significance $p < 0.05$). HMB45 subcellular AQUA ratio was significantly reduced in primary melanoma (mean = -0.463, std dev = 0.264) vs. benign nevi (mean = -0.159, std dev = 0.158) on YTMA 98-2 array ($p = 0.0001$). On whole section analysis, the HMB45 and NEDD9 subcellular AQUA ratio shared a similar distribution between Spitz nevi, atypical Spitz nevi, and Spitzoid melanoma. Subcellular localization using the subcellular AQUA ratio of HMB45 and NEDD9 defines benign nevi from melanoma on TMA but is not useful in discriminating between benign Spitz nevi and melanoma with Spitzoid features. The maximum HMB45 AQUA score in the tumor mask in a single 20X high-powered field of a whole tissue section was deemed promising on discovery analysis at differentiating between Spitz nevi and melanoma with Spitzoid features ($p = 0.007$, receiver operating characteristic area under curve 0.711) but requires validation on an independent cohort.

Balancing Safety and Availability: A Historical Perspective on the Pace of Drug Approval, 1950s-2009. Fabienne C. Meier-Abt and Bruno J. Strasser. Section of the History of Medicine, Yale University School of Medicine, New Haven, Connecticut.

Over the course of the past 50 years, drug approval processes have ranged from 42 days to more than 10 years. What are the consequences of slow or rapid drug approvals on drug safety and drug availability? How slow is too slow? How fast is too fast? These questions have engaged the public, the government, physicians and the pharmaceutical industry for decades. This essay adopts a historical approach to examine the search for the right balance between drug safety and drug availability in the changing political climates of the past 60 years.

Before 1962, the discovery of life-saving antibiotics fostered an emphasis on drug availability and the rapid marketing of drugs. The drug approval process was reframed after the thalidomide crisis in the early 1960s. The 1962 Kefauver-Harris Amendments ensured a new focus on drug safety rather than drug availability. Efficacy standards were introduced and safety standards raised and, as a result, drug approval and drug marketing times increased.

During the 1970s, the term "drug lag" was coined and rapidly endorsed by pharmaceutical companies, physicians, and conservative parties. The term referred to the unnecessary suffering of American patients as a result of the delayed market introduction of life-saving drugs in the United States. General consumer movements and issues with sodium valproate caused patients, too, to use the notion of "drug lag" as a political weapon to fight government regulations on the pharmaceutical industry.

Political pressure on the Food and Drug Administration rose with the Reagan administration's emphasis on economic deregulation and the public health crisis caused by the emergence of AIDS. The drug review process was revised to emphasize drug availability rather than drug safety. In the late 1980s and throughout the 1990s, several measures were introduced, intended to reduce drug approval and drug marketing times, especially for drugs targeting life-threatening diseases.

Finding the right balance between drug safety and drug availability has been a controversial task. As illustrated by the case of gefitinib, the current system depends heavily on post-marketing studies and trust in the pharmaceutical industry's ethical behavior. So far, however, the drug industry has not proven to deserve such trust, as exemplified by cases like rofecoxib. Hence, in 2009, the drug approval process awaits to be reframed again. A renewed focus on drug safety with more careful pre-approval studies and more thorough drug reviews seems warranted.

Yield of Diagnostic Tests in the Evaluation of Syncopal Episodes in Older Patients. Mallika L. Mendu, Gail McAvay, Rachel Lampert, Jonathan Stoehr, and Mary E. Tinetti. Department of Internal Medicine, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut.

Syncopal episodes are common among older adults; etiologies range from benign to life-threatening. We determined the frequency, yield, and costs of tests obtained to evaluate older persons with syncope. We also calculated the cost per test yield and determined whether the San Francisco Syncope Rule (SFSR) improved test yield.

Review of 2,106 consecutive patients 65 years and older admitted following a syncopal episode.

Electrocardiograms (99 percent), telemetry (95 percent), cardiac enzymes (95 percent), and head computed tomography (CT) (63 percent) were the most frequently obtained tests. Cardiac enzymes, CTs, echocardiograms, carotid ultrasounds, and electroencephalography all affected diagnosis or management in < 5 percent of cases and helped determine etiology of syncope < 2 percent of the time. Postural blood pressure, performed in only 38 percent of episodes, had the highest yield with respect to affecting diagnosis (18 to 26 percent) or management (25 to 30 percent) and determining etiology of the syncopal episode (15 to 21 percent). The cost per test affecting diagnosis or management was highest for electroencephalography ($32,973), CT ($24,881), and cardiac enzymes ($22,397) and lowest for postural blood pressure ($17-$20). The yields and costs for cardiac tests were better among patients meeting, than not meeting, SFSR. For example, the cost per cardiac enzymes affecting diagnosis or management was $10,331 in those meeting, vs. $111,518 in those not meeting, the SFSR.

Many unnecessary tests are obtained to evaluate syncope. Selecting tests based on history and examination and prioritizing less expensive and higher yield tests would ensure a more informed and cost-effective approach to evaluating older patients with syncope.

The Rise of Emergency Medicine in the Sixties: Paving a New Entrance to the House of Medicine. Anne K. Merritt. Section of the History of Medicine, Yale University School of Medicine, New Haven, Connecticut. (Sponsored by John H. Warner.)

This thesis investigates how emergency medicine evolved in the United States in the 1960s. Three case studies — Alexandria Hospital, Hartford Hospital, and Yale-New Haven Hospital — demonstrate the changes in emergency medicine at a small community hospital,

a mid-sized teaching hospital, and an urban academic institution, respectively. The government, the media, the American public, and the medical community brought emergency medical care to the forefront of national attention in the Sixties. In an era of population migration to the suburbs, the rise of group practices, and medical specialization, patients' relationships with their general practitioners dissolved. Emergency visits increased astronomically because patients started to use the emergency room for non-urgent health problems. Simultaneously, physicians and house staff resisted working in the emergency room. In response to rising patient loads, mounting criticism of emergency services, and staffing problems, hospital administrators devised strategies to improve the quality and efficiency of emergency care. The rise of emergency medicine in the Sixties was a result of advances in pre-hospital, trauma, and coronary care that distinguished a new clinical field and the emergence of full-time emergency physicians at community hospitals. Urban teaching hospitals, which established triage systems and ambulatory care facilities in order to improve emergency services, resisted the idea of emergency medicine and ultimately delayed its development as a specialty.

Seroprevalence of Helicobacter Pylori in Rural Ecuador. Sarah Allison Milgrom. Yale University School of Medicine, New Haven, Connecticut.

Helicobacter pylori infection causes chronic type B gastritis, peptic ulcer disease, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tumor. Infection with H. pylori is common in parts of the developing world. The Clínica Misional "Nuestra Señora de Guadalupe" serves indigenous people of the Ecuadorian Amazon. At the clinic, "gastritis" is a common diagnosis that is based solely on reported symptoms and is presumed to be due to H. pylori infection. Additionally, gastric cancer, a corollary of H. pylori infection, is the leading cause of cancer deaths in Ecuador and, thus, an important public health concern. To the best of our knowledge, the prevalence of H. pylori infection among the inhabitants of rural Ecuador has never been assessed. The primary aim of this study was to determine the seroprevalence of H. pylori in this population. We compared rates of seropositivity among patients with and without symptoms suggestive of gastritis and among patients who reported untreated and exclusively treated water consumption. Additionally, a sampling of children was tested to begin to assess the age of serological conversion. Using the Quidel QuickVue H. pylori gII test, we found near universal seropositivity among adults aged 18 to 65 years (117/120 = 98 percent) and among children aged 2 to 18 years (13/14 = 93 percent). Given the high prevalence of H. pylori and its complications in rural Ecuador, this population may benefit from intervention to eradicate the bacterium. However, there is a lack of evidence to inform management decisions. There is a need for studies with large numbers of patients and long-term follow-up to assess the costs and benefits of population-based treatment.

The Impact of a School Garden on Nutrition Knowledge, Attitudes, and Behaviors of Urban Youth. Erica Rose Menkel Mintzer. Yale University School of Medicine, New Haven, Connecticut.

Hypothesis: A garden-based high school curriculum and school lunch program positively impact the nutrition knowledge, attitudes, behaviors, and health outcomes of participating urban youth.

Specific aims: To characterize the objectives and implementation of the Common Ground High School's garden-based curriculum and school lunch program and to evaluate the effectiveness of the program in promoting healthy nutrition knowledge, attitudes, behaviors, and health outcomes among Common Ground students.

Methods: Mixed quantitative and qualitative methods were used to conduct the program evaluation. The Common Ground curriculum was characterized through in-depth staff interviews and review of relevant policies and procedures. Surveys on nutrition attitudes, knowledge, and behavior were administered in the fall and spring at Common Ground and two comparison schools. Student focus groups were conducted at the three schools. Demo-

graphic data and body mass index data were gathered at Common Ground and one of the comparison schools. Direct observations were conducted in the cafeterias of the three schools; students were served vegetables during three different typical lunch periods, and the number of students that tasted and ate the vegetables were counted.

Results: Common Ground students learn about health, nutrition, and the food system through coursework in the organic garden, the school lunch program, and informal interactions with teachers and staff. Students at comparison schools desire higher quality school food and more control over what is served. Students at Common Ground have more knowledge about the food system than students at comparison schools, but not more knowledge about basic nutrition. Students at Common Ground ate 6.6 and 9.0 servings per week of fruits and vegetables at school at the beginning and end of the school year, respectively, while students at Comparison School No. 2 ate 7.7 and 6.9 servings per week. In the cafeteria observations, students at comparison schools ate more of the familiar vegetables than students at Common Ground. Students at Common Ground ate more of the unfamiliar vegetables. Average BMI of students at Common Ground from freshmen to seniors is 27.4, 26.1, 23.4, and 26.3 kg/m2. At Comparison School No. 2, average BMI of freshmen to seniors is 26.5, 24.1, 26.6 and 29.7 kg/m2 (ANOVA shows $p = 0.0622$).

Conclusion: Common Ground's garden-based curriculum and school lunch program positively influences students' nutrition knowledge, attitudes, behavior, and health outcomes. Similar interventions should be implemented in other schools and school systems in order to improve population health.

Outcome of Treatment for Vaginal Recurrences of Endometrial Cancer. Tejaswini K. More. Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut. (Sponsored by Dr. Susan Higgins.)

The purpose of this study was to assess treatment outcomes for vaginal recurrences of endometrial cancer following total abdominal hysterectomy and bilateral salpingo-opherectomy (TAH-BSO). We hypothesized that poor survival after salvage treatment for disease recurrence is associated with the following factors: age, primary tumor stage, primary tumor grade, prolonged time to treatment initiation after diagnosis of recurrence, recurrence size greater than 2 cm, recurrence location in the lower third of the vaginal vault, and histopathologic features of lymphovascular space invasion, deep myometrial invasion, and endocervical involvement. We reviewed the records of all patients treated for endometrial adenocarcinoma at Yale-New Haven Hospital between January 1994 and December 2007. Twenty patients initially treated with TAH-BSO (± adjuvant therapy) developed recurrent disease involving the vagina and received definitive therapy. FIGO staging for initial disease ranged from IA - IIIC. Treatment of recurrent disease consisted of vaginal brachytherapy (VB) and pelvic external-beam radiotherapy (EBRT) for 14 patients, VB alone for two patients, pelvic EBRT alone for one patient, and a combination of chemotherapy and surgery for three patients. Median follow-up from diagnosis of recurrence was 2.2 years. The median time from initial treatment to disease recurrence was 24 months (range: 6-105 months). At last follow-up, 11 of 20 (55 percent) patients were alive and free of disease. Two-year and five-year cumulative local control rates were 79 and 61 percent, respectively. Two-year and five-year overall survival were 77 and 68 percent. Two-year and five-year disease-free survival rates were 74 and 57 percent, respectively. Clinical and pathologic factors associated with poor outcome included age at diagnosis, nuclear grade, stage and endocervical involvement of the primary tumor. We conclude that local failure following TAH-BSO (± adjuvant therapy) carries a poor prognosis. In our cohort, local control of isolated vaginal recurrences of endometrial carcinoma corresponds to trends in overall survival, suggesting that primary treatment for recurrence must be aggressive. Furthermore, we observed a significant number of local recurrences at greater than two years after initial treatment, emphasizing the need for long-term surveillance following treatment.

Psychiatric Illness in the Next-of-Kin of Intensive Care Unit Patients. Janelle Katie Moulder. Yale University School of Medicine, New Haven, Connecticut.

The prevalence of psychiatric symptoms in next-of-kin (NOK) of intensive care unit (ICU) patients has been reported at higher than 70 percent when screening is performed using the Hospital Anxiety and Depression Scale (HADS). The primary purpose of this study was to assess the ability of the HADS to predict psychiatric illness, diagnosed with the aide of a validated tool, the Structured Clinical Interview for DSM-IV (SCID). In addition, we asked NOK to rate aspects of the ICU experience to determine possible associations with psychiatric diagnosis. Thirty-four NOK were enrolled in this study from July 2006 to November 2006. Subjects were interviewed to gather demographic information, their perception of the ICU experience, and administer the SCID and the HADS. At least six months later, subjects were contacted by telephone to determine presence of psychiatric morbidity after the ICU experience. Fifty-six percent of all NOK experienced symptoms of either anxiety or depression during the ICU admission, and 24 percent had psychiatric illness. The HADS had 100 percent sensitivity and 58 percent specificity when used as a screening tool for psychiatric diagnosis. Those with any SCID diagnosis were more likely to be a spouse (50 percent vs. 9 percent, $p = 0.013$) or a primary caregiver (60 percent vs. 8 percent, $p = 0.003$). Most NOK identified the health care team as supportive, though a subgroup of NOK who slept in the ICU reported that they found the health care team less supportive. This small study suggests the HADS is able to predict psychiatric illness in NOK of ICU patients. The ability to implement this tool as part of clinical practice to better meet the needs of families in the ICU warrants further investigation.

Characterization of a Murine Gammaherpesvirus In Vitro Latency System. Kudakwashe Mutyambizi. Yale University School of Medicine, New Haven, Connecticut. (Sponsored by Michael Kashgarian, Department of Pathology, Yale University School of Medicine, and Stacey Efstathiou, Department of Pathology, University of Cambridge.)

The human gammaherpesviruses EBV and KSHV realize their oncogenic potential during latent infection. The species specificity of the human gammaherpesviruses has hindered the study of latency in animal models. Murine gammaherpesvirus MHV-68 (MHV-68) may be used as a representative gammaherpesvirus for the study of latency. The goal was to establish an *in vitro* model of MHV-68 latency using replication defective MHV-68. ORF50 has been identified as the major viral trans-activator essential for entry into the lytic replication cycle and necessary and sufficient for reactivation of MHV-68 virus from latency. ORF50 null mutants (Δ50) theoretically can be used to infect cells *in vitro* to facilitate an analysis of virus gene expression and episome maintenance during latency. In this project, Δ50 mutants containing the luciferase or green fluorescence protein (GFP) under ORF50 promoter control were used to infect a variety of cell types. 3T3 fibroblasts are a permissive cell line and were used for an initial characterization of the ability of Δ50 MHV-68 to establish latency. B lymphocytes and macrophages are the major reservoirs of persistence *in vivo*, thus the ability of Δ50 mutants to establish latency in NS0 B and RAW macrophage cell lines was explored. Latency was readily established and maintained in 3T3 and RAW cells. The low infectability of NS0 B- cells restricted the utility of this cell line in studies of latency. Examination of patterns of lytic and latent transcription in 3T3 and RAW cells coordinately infected with Δ50 MHV-68 revealed reactivation efficiencies of 40 to 60 percent. Following long-term passage Δ50 exhibited stable transcription of two latency related genes M2 and ORF73, with episomal maintenance of the viral genome, in the absence of contaminating lytic infection. The results demonstrate the utility of Δ50 mutants for studies of gammaherpesvirus latency *in vitro*.

HIV/AIDS Knowledge, Attitudes, and Sexual Practices of Medical and Nursing Students in Sierra Leone and Their Willingness to Treat HIV/AIDS Patients.

Titilope Oduyebo. Yale University School of Medicine, New Haven, Connecticut.

After a decade-long war (1991-2001), government agencies and non-governmental organizations (NGOs) are assisting Sierra Leoneans in reconstructing their country and aiding their reintegration into their communities. It has been shown that HIV transmission is on the rise due to the effects of the war. As more and more people are diagnosed with HIV/AIDS, most physicians and nurses in Sierra Leone will find it difficult to avoid patients with the disease. Many post-conflict development programs are addressing this rise in HIV transmission; however, no studies have been conducted to assess the HIV/AIDS related knowledge, attitudes, and practices of emerging health care workers and their willingness to treat HIV positive patients.

A survey designed to assess the HIV/AIDS knowledge, attitudes toward HIV/AIDS patients, sexual practices, and willingness to treat HIV/AIDS patients was distributed to medical and State Registered Nursing (SRN) students at COMAHS, Freetown. This survey was adapted from previous literature. This instrument was pilot tested on 15 students and revised in the early phase of the study. Data collected were entered into Microsoft Excel and subjected to statistical analysis using SAS version 9.0. Descriptive statistics, t-tests, and spearman correlation were used to examine the relationship between certain variables such as HIV/AIDS knowledge; attitudes to infected patients; fear of contagion; homophobic attitudes; professional and ethical obligation to patients; and interaction with HIV/AIDS patients to the outcome variable which was students' willingness to treat infected patients as future health care providers.

One hundred seventy medical students and 52 SRN students participated, giving a response rate of 76 percent for the medical students and 36 percent for the SRN students. The response rate for the SRNs was much lower because a significant amount of the students chose not to participate in the study due to their scheduled final examination during the time this study took place. The key findings were that students had good overall knowledge of HIV/AIDS evidence; 93.35 percent of the students are willing to care for HIV/AIDS as future health professionals. The factors associated with the willingness to treat HIV/AIDS patients were lack of fear of contagion, professional/ethical obligation to treat HIV/AIDS patients, and positive attitudes toward HIV/AIDS patients. Homophobic attitudes and knowing someone with HIV/AIDS did not affect the students' willingness to treat HIV/AIDS patients. In terms of their sexual behavior, the majority of the students (83 percent) have had sexual intercourse at least once in their lifetime. The average sexual debut age was 17, with 10.4 percent of the students sexually active before the age of 15 years. Age of sexual debut was significantly earlier for male than for female students ($p < 0.0001$). A few of the students who are sexually active have risky sexual behavior in terms of never using condoms or infrequent use of condoms (62.89 percent), multiple sexual partners (23.66 percent), and exchanging sex for gifts (8.11 percent). All students that had multiple sexual partners were male except one. In addition, there was a significant difference in exchange of gifts for sex based on gender ($p = 0.0071$), with all 18 students exchanging sex for gifts being male except one.

The findings of this study show that an overwhelming majority of the student sample are willing to treat HIV/AIDS patients and have positive attitudes toward patients with HIV/AIDS. Educators should be prepared to model supportive and tolerant attitudes and strict adherence to medical professionalism to help students continue to have positive attitudes toward HIV/AIDS patients as they progress through medical school. In terms of risk for HIV infection, some students are at high risk because of some of the risky practices they report. Further research should be performed to learn more about the students that exchange sex for gifts. These risky sexual behaviors by the students as described above necessitate education and prevention work to be carried out by the university (COMAHS) to encourage safe sexual practices.

Living Kidney Donor Informed Consent Practices Vary Between U.S. and Non-U.S. Centers. Ami Mahendra Parekh. Yale University School of Medicine, New Haven, Connecticut.

Living kidney donation rates are increasing internationally and in the United States. Major consensus statements on the care of living kidney donors recommend communicating all potential health and psychosocial risks to donors. We evaluated the degree of international variation in the process of informed consent of potential donors during their evaluation.

Transplant professionals attending the 2006 World Transplant Congress responded to a survey assessing their informed consent processes, donor evaluation, and risk communication to living donors. U.S.-based respondents were compared to non-U.S. respondents. There were 221 respondents from 177 transplant centers and 40 countries (48 percent U.S. respondents). Across U.S. and non-U.S. transplant centers, potential donors were most likely to receive written material about living donor risk by mail prior to evaluation, receive risk information in person during evaluation, have a psychosocial evaluation (usually lasting longer than 30 minutes), and sign an official donation consent form presented to them by a surgeon or a nephrologist. Although more than 75 percent of respondents stated that donors received information about medical risks such as hypertension, chronic kidney disease, and potential need for dialysis, there was less consistency regarding whether respondents conveyed an increased risk of these medical complications to donors. Additionally, the financial and psychosocial costs associated with being a living donor were inconsistently communicated to donors during the informed consent process. Compared to non-U.S. respondents, U.S. respondents were more likely to use written material and visual aids to convey risks to donors, have mandatory psychosocial evaluations, and provide access to donor support groups. U.S. transplant centers were also more likely to discuss the possibility of the donor needing dialysis or a transplant if his remaining kidney fails in the future and possible travel expenses and loss of work income due to donation recovery. Conversely, the U.S. respondents' centers were less likely to offer long-term follow-up and utilize nephrologists to obtain written donor consent for donation.

As dependence on living organ donation increases, the best practices for informed consent, donor evaluation, and uniform risk conveyance need to be established. This may be accomplished by using a model informed consent template to ensure that informed consent from donors is consistently obtained.

Trends in Pediatric Acute Pancreatitis: A 12-Year Analysis at Yale-New Haven Hospital. Alexander J. Park[a], Sahibzada U. Latif[b], Steven L. Werlin[c], Allen Hsiao[a], Dinesh S. Pashankar[a], Vineet Bhandari[a], Anil B. Nagar[d], and Sohail Z. Husain[a]. Departments of [a]Pediatrics, Yale University School of Medicine, New Haven, Connecticut; [b]Internal Medicine, Michigan State University, East Lansing, Michigan; [c]Pediatrics, Medical College of Wisconsin, Milwaukee, Wisconsin; [d]Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Acute pancreatitis is a painful inflammatory disorder known to occur in children. Recent reports, primarily based on adult data, suggest an increasing incidence. However, pediatric studies are limited. We posit that the frequency of disease also has increased among children in the last decade. This is most likely due to one or more trends in etiologies, referral patterns for tertiary pediatric care, and/or rising obesity in children. To assess this hypothesis, a retrospective chart review spanning the last 12 years was conducted at Yale-New Haven Children's Hospital (YNHCH). Presentation and management of pediatric pancreatitis also was assessed for the time period. International Classification of Diseases (ICD)-9 codes were used to electronically identify admissions for acute pancreatitis at YNHCH between 1994 and 2007. Charts were obtained and cases were subjected to inclusion criteria for acute pancreatitis. Five hundred ninety-four cases were identified by ICD-9 codes, of which 271 fulfilled inclusion criteria. Mean age was 13.1 ± 5.6 years (yr). Over the last decade (between 1995

and 2000 and 2001 and 2006), frequency of acute pancreatitis increased 53 percent (16 ± 3.35 cases/yr to 23.5 ± 5.5 cases/yr, $P < 0.02$). The most common etiologies for pancreatitis over time were idiopathic, medications, and biliary disease. These did not change in a statistically significant manner to account for the rising frequency of disease. Median body-mass-index (BMI) percentile increased from 50 to 58.9, but was not significant ($P = 0.85$). Frequency of disease was normalized by total annual pediatric Emergency Department visits to YNHCH over the study period to analyze the effect of referral bias. This reduced the increase in pancreatitis to 22 percent and rendered the trend non-significant ($P = 0.16$). This is the first report in the field to demonstrate that acute pancreatitis in children may be rising in part due to growing referrals to tertiary care centers. It is also the first to assess the role of BMI in pediatric pancreatitis from an epidemiologic perspective.

The Long-Term Neuropsychological Outcomes in Sagittal Craniosynotosis: Limited-Strip Craniectomy vs. Whole-Vault Cranioplasty. Anup Patel. Yale University School of Medicine, New Haven, Connecticut.

The "functional" morbidity in nonsyndromic craniosynostosis is not obvious. Because of this disconnect between cranial deformity and "functional" disability, cranial reconstructive surgery in patients with single-suture sagittal craniosynostosis has been regarded as a "cosmetic" intervention. However, it has been observed in a preliminary study that children with simple craniosynostosis often have a higher proportion of learning disabilities and cognitive problems compared to non-afflicted children. The influence of modern comprehensive surgical treatment, including the optimal age to perform surgery, has not been well documented.

This study examined long-term neuropsychological outcomes of children and adolescents with isolated sagittal craniosynostosis undergoing either limited-strip craniectomy or whole-vault cranioplasty. Furthermore, it assessed if a relationship between the age of surgery on children with isolated sagittal craniosynostosis and neuropsychological effects exists. It is hypothesized that those children with isolated sagittal craniosynostosis will have a lower incidence of neuropsychological abnormalities, albeit at a higher incidence than the general population, the earlier in age they undergo the more comprehensive surgical whole-vault cranioplasty. If this study can confirm this hypothesis, then whole-vault cranioplasty at an early age may reduce the long-term neuropsychological effects of children with isolated craniosynostosis.

Retrospective inspection of Yale-New Haven Hospital medical records from 1987 to 2002 identified 11 patients who underwent whole-vault cranioplasty and four patients who underwent limited-strip craniectomy. In terms of surgical age, eight patients underwent surgery at younger than 6 months and seven patients older than 6 months underwent surgery. The small sample size of patients in the limited strip-craniectomy group circumvented comparisons between the types of surgery. The study demonstrated that patients undergoing surgery prior to 6 months of age had improved general cognitive function, academic achievement, executive functioning, and behavior compared to patients undergoing surgery after 6 months of age. These preliminary findings suggest that the age of surgery impacts long-term neuropsychological outcomes, although further studies are necessary to explore the consequences of the type of surgery and specific-suture involvement in craniosynostosis.

Characterization of MicroRNA Expression Levels in Melanoma. Rajeshvari Mahesh Patel. Yale University School of Medicine, New Haven, Connecticut.

While it has been shown that alterations in microRNA (miRNA) expression profiles can serve as phenotypic signatures of particular cancers, there is little available data concerning melanoma. This study was designed to investigate the relative expression of miRNAs in normal adult melanocytes, newborn amelanotic foreskin melanocytes, and several subtypes of melanoma: acral, nodular, and mucosal. Our hypothesis is that up- and/or down-regulation of individual microRNAs will elucidate potential genetic mediators by which

melanoma develops, based on existing knowledge of their downstream molecular targets, and will provide insight into the diagnosis and unique treatment of melanoma subtypes.

We performed microarray-based miRNA profiling of adult and newborn melanocytes and melanoma cell lines of primary or metastatic origin. Newborn melanocytes appeared to have higher levels of expression of many miRNAs, consistent with the role miRNAs play in development and differentiation of tissues. Melanoma cell lines exhibited upregulation of the oncogenes mir-222, mir-21, and mir-20a, and downregulation of the known tumor suppressor miR-16, relative to benign controls. Furthermore, the acral lentiginous melanoma samples displayed underexpression of several miRNAs when compared with normal melanocytes and other subtypes. Investigation of these miRNAs may prove essential to understanding the unique clinicopathological characteristics of this subtype.

Capillary Blood Gas Measurement as a Novel Means of Assessing Flap Perfusion in Free Tissue Transfer. Aaron K. Remenschneider and Douglas A. Ross. Section of Otolaryngology, Department of Surgery, Yale University School of Medicine, New Haven, Connecticut. (Sponsored by Dr. Clarence Sasaki.)

Our objective was to demonstrate that in comparison to implantable O2 microelectrodes, capillary blood gas measurements represent a reliable, accessible, and easy method of identifying failing free flaps and to assess post-operative free-flap monitoring techniques nationwide, determining the openness of surgeons to new surveillance modalities.

Groin fasciocutaneous flaps were elevated in 10 rats, and following arterial or venous occlusion, oxygen microelectrode measurements (pO2 and flow) and capillary blood gas measurements (pO2, pCO2, pH, HCO3) were obtained at 0, 10, and 20 minutes. A nine-question, Internet-based survey on post-operative flap surveillance techniques was sent to the personal e-mail addresses of 238 microvascular surgeons from around the United States. Response data were collected and analyzed utilizing an online resource.

Measurements with capillary blood gas paralleled measurements with O2 microelectrodes. Average capillary blood gas pO2 fell from 42.72 mm Hg at 10 minutes and then to 28.67 mm Hg at 20 minutes. Average pH fell from 7.38 to 7.33 at 10 minutes and to 7.30 at 20 minutes. Results were statistically significant with both the paired Student's t test and the Wilcoxon signed rank test. Seventy-five percent of survey respondents indicated that clinical assessment was more important than available adjunctive tests in the decision to re-explore the vascular pedicle in a threatened free flap, and 56 percent listed pinprick with flap bleeding as an important marker of flap health in their practice. Ninety percent of respondents indicated they are open to new quantitative monitoring techniques.

While providing users the ability to simultaneously monitor accepted modalities of flap surveillance, pH and pO2, the capillary blood gas is a reliable and reproducible marker of flap tissue health. Given that no single monitoring modality enjoys a clear preference among microvascular surgeons and that more than half of these surgeons already utilize pinprick assessment of the flap, this study demonstrates that the capillary blood gas is well positioned for further study in humans.

Prevalence of Overweight Resident Physicians and Year of Training. Maya Roberts[a], Mark R. Zonfrilloa[a], James Dziura[b], Sunkyung Yu[b], David Spiro[c]. [a]Division of Emergency Medicine, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; [b]Yale Center for Clinical Investigation, New Haven, Connecticut; [c]Department of Emergency Medicine and Pediatrics, Oregon Health & Sciences University, Portland, Oregon. (Sponsored by Howard Pearson, Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.)

Post-graduate clinical training has numerous implications for the health of resident physicians. The primary goal of this study was to monitor the health of resident physicians

by year of training through measurement of body mass index (BMI), blood pressure (BP), and health-related behaviors.

We conducted a cross-sectional study of 375 resident physicians and longitudinal follow-up of 93 of the resident physicians at two training centers. Resident physicians were enrolled at the onset of each post-graduate year (PGY) of training in 2006, 2007, and 2008. BMI and BP were measured, and questionnaires on eating habits and physical activity were administered. Controls from the National Health and Nutrition Examination Survey (NHANES) were selected using 1:1 matching for age, gender, ethnicity, and years of education.

A greater percentage of resident physicians were overweight (BMI ≥25) at the beginning of PGY3 than at PGY1 (49 percent vs. 30 percent, OR 2.26, 95 percent CI 1.19-4.28, P = 0.01). Longitudinally enrolled resident physicians were more likely to be overweight at PGY3 than at PGY1 (OR 2.32, 95 percent CI 1.17-4.62, P = 0.02). The average diastolic BP of resident physicians was higher at PGY3 than at PGY1 (79.7 (SE 1.32) vs. 76.8 (SE 0.79), P = 0.04).

Eating habits and physical activities were not mediators of change in BMI. However, there were several significant trends. Overweight resident physicians were more likely to have high-risk eating habits than non-overweight resident physicians. Nearly half of overweight resident physicians (43 percent) described themselves as "normal weight." The mean BMI of resident physicians was lower than that of matched controls on entering residency, but the magnitude of this difference decreased significantly by program year (P for interaction = 0.02).

Post-graduate clinical training appears to be associated with an increased prevalence of overweight status among resident physicians.

Blue Cohosh: History, Science, Safety, and Midwife Prescribing of a Potentially Fetotoxic Herb. Aviva Jill Romm. Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut. (Sponsored by Errol Norwitz.)

Blue cohosh (*Caulopyhyllum thalictroides*) has been used traditionally and historically as an obstetric aid for labor induction to ensure a prompt delivery, relieve childbirth pain, and induce abortion. Officially listed in the U.S. Pharmacopoeia from 1882 to 1905 and in the National Formulary from 1916 to 1950 for labor induction, its use remains popular. Maternal ingestion has been implicated in acute nicotinic toxicity, neonatal heart failure, perinatal stroke, and multiorgan ischemia.

This study evaluated blue cohosh use patterns in midwives and assessed the relationship between maternal ingestion in pregnancy and adverse neonatal outcomes.

A systematic review of the literature was conducted in major computerized databases (MEDLINE, CAB Abstracts, CINAHL, BIOSIS, and Cochrane Library) using the subject headings "pregnancy AND blue cohosh;" "pregnancy and Caulophyllum thalictroides;" "lue cohosh;"and "Caulophyllum thalictroides." A formal structured survey also was devised and implemented to evaluate midwife use of this herb.

The literature review identified 10 published pharmacology papers from 1954 to 2008; two abstracts; one undergraduate paper; one teratogenicity study; four independent case reports; two general papers; one review of blue cohosh-associated risks; and six published letters. Of the 90 midwife respondents to the survey, blue cohosh was the most popular labor induction agent; the percentage of adverse effects was 22.

While the pharmacology of blue cohosh supports the adverse outcomes with which use of this herb has been associated, the case reports do not demonstrate causality. Similarly, while midwives report an increased incidence of adverse effects with use of this herb, confounding factors may be responsible. Nonetheless, the pharmacology of the herb and the ease with which it is available over-the-counter is cause for concern. Prospective and retrospective studies of use in pregnancy must be conducted to adequately determine safety. First trimester use and use as a partus preparator must be avoided; use for labor induction and augmentation should only occur with the guidance of a trained obstetric care provider, if at all.

How Interns Spend their Time: A Time-Motion Study at Yale-New Haven Hospital. Oliver Rothschild. Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut. (Sponsored by John Moriarty.)

The goal of this research is to evaluate the effect of placing a clerical assistant on an inpatient internal medicine house staff team and to identify segments of intern work that are perceived by interns as of particularly high or low value for patient care and education. Data was collected through a time-motion study, following six interns over six days, recording their activities, with whom they spent their time, and how valuable they found each activity to their patients and to their own education. Compared to interns on teams without a clerical assistant, interns on teams with a clerical assistant spent more time on educational activities (27.5 percent vs. 19.1 percent of their time) and less time on the phone (7.2 percent vs. 14.9 percent of their time). In addition, direct patient care was consistently rated as high value for patients (4.81 + 0.12, out of 5) and educational activities were rated as high value for education (3.83 + 0.60, out of 5). However, interns spent substantially more time on indirect patient care (251.67 + 48.75 minutes) relative to both educational activities (163.33 + 57.85 minutes) and patient care (50 + 21.91 minutes). In conclusion, our study found that interns spend a large proportion of their time on activities that are not directly related to patient care or education and that clerical assistants can assume some of the non-clinical activities interns currently assume. Assumption of these duties by a clerical assistant, however, does not necessarily increase direct patient care and education of interns, implying that other barriers need to be identified and addressed.

The Assessment of Cervical Foraminal Areas on Oblique Radiographs as Compared to Computed Tomography. Jennifer Marie Sabino. Yale University School of Medicine, New Haven, Connecticut.

Cervical oblique radiographs often are obtained to evaluate the patency of the intervertebral foramina. Previous work has demonstrated that computed tomography (CT), particularly oblique reconstructions of the spine, allows for the accurate measurement of foraminal dimensions. Although oblique radiographs are routinely ordered by practitioners for this reason, there are currently no studies that have directly compared these measurements to those derived from CT scans. The purpose of this study was to establish whether there is any correlation between the dimensions of cervical foramina assessed from oblique radiographs vs. those observed on CT scans.

Radiographs of four fresh-frozen cadaveric cervical spine specimens were obtained at an angle of 50 degrees. Using digital measurement tools, the foraminal height, width, and cross-sectional area were calculated at each level between C2-C3 and C7-T1. CT scans were subsequently performed so that these values could also be acquired from 50 degree oblique reconstructions.

Statistical analyses revealed excellent inter-observer reliabilities for radiographs and CT scans (ICC = 0.91 and 0.99 for height, 0.90 and 0.97 for width, and 0.84 and 0.92 for area). For the two imaging modalities, the Pearson correlation coefficients for height, width, and area were 0.439, 0.871, and 0.899, indicating a moderate correlation for height and strong correlations for width and area. The only significant differences ($p < 0.05$) between CT and radiograph measurements were for height at C6-C7 and C7-T1, for width at C5-6, and for area at C2-3. Based on these findings, we believe that oblique radiographs provide reasonably accurate estimates of intervertebral foraminal dimensions for the initial evaluation of the cervical spine.

The Role of Frizzled-1 and Frizzled-3 in Olfactory Sensory Neuronal Targeting. Mina G. Safain. Department of Neurosurgery, Yale University School of Medicine, New Haven, Connecticut.

While most areas of the brain do not exhibit profound neurogenesis or continuing synaptogenesis in the adult, there are notable exceptions, including the olfactory and hippocampal re-

gions of the nervous system. In the olfactory system, the olfactory sensory neurons continually turn over and extend their axons into the olfactory bulb in a highly precise manner. Preliminary data suggests the presence of Wnt and Frizzled (Fz) family members in the primary olfactory pathway. Recent evidence has suggested that these proteins could function as guidance cues, but they have not been studied in the olfactory system. Therefore this family of proteins, including Fz-1 and Fz-3, could have a role in olfactory sensory neuron targeting. This study proposed to test the hypothesis that the expression pattern and temporal regulation of Fz-1 and Fz-3 is consistent with a role in olfactory sensory neurons axon targeting. Mouse embryos at ages E10, 10.5, 11, and 13 (E0 is the day of conception) were removed, fixed, sectioned on a cryostat, and then thaw-mounted onto slides. Immunohistochemistry was performed on the sections and labeled with antibodies for either Fz-1 or Fz-3 and a variety of other antibodies that labeled mature and immature olfactory sensory neurons (GAP 43, NCAM, PSA-NCAM, OCAM, ß-Tubulin). Nuclear staining was accomplished using DRAQ-5. Stained sections were analyzed with a confocal microscope. Fz-1 and Fz-3 were present as early as embryonic day 10-10.5, and expression increased dramatically over the next three days of development. These receptors also co-localized with markers of both mature and immature olfactory sensory neurons. Fz-1 and Fz-3 are upregulated and expressed more heavily in olfactory sensory neurons beginning and during the period that is essential for proper glomerular targeting, suggesting a role for Fz-1 and Fz-3 in the intricate navigation of olfactory sensory neurons from the olfactory epithelium into the glomerular layer of the developing olfactory bulb.

Forehead Laser Doppler and Transcranial Doppler During Simulated Hypovolemia.

Kathleen Jessica Samuels. Yale University School of Medicine, New Haven, Connecticut.

We employed lower body negative pressure (LBNP), a rapidly titratable, safe, and reversible means of inducing simulated hypovolemia, for a comparison of transcranial Doppler (TCD) ultrasound of the middle cerebral artery and laser Doppler (LD) flowmetry of the forehead microvasculature.

With Institutional Review Board (IRB) approval, nine healthy volunteers (26.3 ± 2.7 years) were monitored continuously with EKG, noninvasive finger arterial blood pressure (BP), and TCD positioned at the transtemporal window. After a baseline (Base) period, subjects underwent rapid onset of LBNP to -70 mmHg over the course of one minute, followed by progressive declines of ~10 mmHg until lightheadedness or had a BP decline >20 percent of baseline BP. Changes in the peak (systolic) and trough (diastolic) values with each heart beat were analyzed at Base, at approximately 30 seconds prior to the onset of lightheadedness (Presympt) and at onset of symptoms (Sympt).

In the six subjects who subsequently became lightheaded, forehead LD flow decreased by 10.9 ± 11.7 percent at Presympt (p = NS for interphase difference), then decreased by an additional 20.4 ± 18.7 percent with the onset of lightheadedness (p = 0.035 for Presympt vs. Sympt). Peak TCD readings decreased by 29.3 ± 9.7 percent from Base to the time of the Presympt measurement (p = 0.001); they then increased by 4.1 ± 12.9 percent with the onset of Sympt (p = NS). In the two subjects who remained asymptomatic, LD did not change significantly in the Presympt and Sympt phases in which Sympt was the time when the study was terminated because the BP cutoff was reached. In these asymptomatic subjects, the TCD flow velocity declined progressively.

The findings suggest that monitoring of the microvasculature in the distribution of the carotid arteries provides a better indication of changes in perfusion associated with lightheadedness than measurement of velocity at the middle cerebral artery. The discordance between LD and TCD is consistent with autoregulatory mechanisms at the level of the forehead microvasculature that previously have been reported in the context of systemic administration of phenylephrine.

Tryptophan Depletion by Indoleamine 2,3-Dioxygenase (IDO) Contributes to Medial Immunoprivilege in Graft Arteriosclerosis. Amanda Mondoñedo Silverio. Yale University School of Medicine, New Haven, Connecticut.

Since blood vessels and their endothelial linings are major stimulators and targets of the graft rejection response, study of the differential immune properties of vascular cells is needed for the proper application of human vessels in the transplant setting. Experimental models of atherosclerosis and graft arteriosclerosis show leukocytes selectively infiltrating the intima and adventitia while sparing the media. We explored the role of vascular smooth muscle cells (VSMCs) in mediating the observed immunosuppression and attributed it to the expression of indoleamine 2,3-dioxygenase (IDO) by VSMCs. IDO, in response to interferon-gamma (IFN-γ) signaling, catalyzes the first and rate-limiting step in the oxidative catabolism of tryptophan, an essential amino acid, and generates kynurenine metabolites. We further investigated the role of IDO in vascular immune regulation using both *in vivo* and *in vitro* studies.

Segments of human coronary arteries from explanted hearts of cadaveric organ donors or cardiac transplant recipients were interposed into the infrarenal aortae of SCID/beige mice and harvested after five weeks for histologic analysis. RT-PCR reactions were prepared with pre-developed assay reagents for IDO, tryptophanyl-tRNA synthetase (WRS), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Co-culture experiments were performed for up to nine days with endothelial cells (ECs) or VSMCs with CFSE-labeled CD4+ T-cells and treating with IFN-γ for three days. T-cell proliferation was assessed by flow cytometry by CFSE dilution; interleukin-2 (IL-2) levels were measured in the supernatants by enzyme-linked immunosorbent assay (ELISA).

Vessel grafts showed that medial sparing by allogeneic T-cells is associated with IDO expression by VSMCs. Exposure to the T-cell-derived cytokine, IFN-γ, led to 100-fold greater expression of IDO mRNA in graft VSMCs than in ECs or CD4+ T-cells (2.00, 0.02, and undetectable IDO/GAPDH mRNA ratios, respectively). An immunoregulatory effect was shown when IFN-γ-treated VSMCs decreased CD4+ T-cell proliferation and IL-2 production (levels decreased by 98 percent and 90 percent, respectively), and addition of the IDO inhibitor, 1-methyl-tryptophan, led to a reversal of the inhibition. Inhibition was not seen with ECs or untreated VSMCs. CD4+ T-cell anergy was replicated by tryptophan depletion, but not by the addition of tryptophan metabolites kynurenine, 3-hydroxykynurenine, or 3-hydroxyanthranilic acid. Tryptophan supplementation rescued T-cell proliferation in a dose-dependent fashion.

We confirmed that vascular cells, namely VSMCs, could regulate adaptive immune responses by preferentially expressing IDO to inhibit CD4+ T-cell activation and clonal expansion. We also characterized IDO regulation of T-cells in the medial wall by showing that the depletion of tryptophan in the microenvironment inhibited CD4+ T-cell proliferation. Considering that the immune system relies on tryptophan regulation as a method to selectively modulate T-cell infiltration in graft vessel walls, the expression of IDO and the availability of tryptophan serve as potential therapeutic targets in the management of graft arteriosclerosis.

Chest X-Ray Clues to Osteoporosis: Criteria, Correlations, and Consistency. Natalie Renee Simmons. Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to determine whether radiologists could accurately assess osteopenia on chest plain films. Two chest radiologists evaluated lateral chest films from 100 patients (80 female and 20 male), ranging in age from 16 to 86 years, for osteopenia and its associated findings. Intra- and inter-observer agreement was determined using weighted kappa statistics, and accuracy was assessed by making comparisons to bone mineral density as measured by the non-invasive gold standard of dual-energy X-ray absorptiometry (DXA). Overall, radiologists were good at identifying signs of late, but not early, disease. Intra-ob-

server consistency was substantial for fish vertebrae (Kw1 = 0.638; Kw2 = 0.712), with moderate inter-observer agreement (Kw = 0.45). Similarly for wedged vertebrae, intra-observer consistency was substantial to moderate (Kw1 = 0.654; Kw2 = 0.533), with substantial inter-observer agreement (Kw = 0.622). These radiographic signs correlated with true disease as shown by high specificity values. Therefore, this study indicates that if osteopenia is suspected (i.e., there is a wedge or fish vertebra) or its associated features are seen on a CXR, it is crucial for radiologists to comment on it. The literature suggests that referring physicians do not pay attention to such findings in radiology reports. Radiologists could effect change in clinical treatment by not burying these findings in the report body, but instead putting it in the impression, along with a recommendation that the finding be followed up with DXA. Because effective interventions for women with osteoporosis exist, the results of this study will contribute to a major change in the practice of chest radiology and improve women's health by preventing the devastating disability associated with osteoporosis.

Longitudinal Evaluation of Quality of Life in Older Persons with Advanced Illness. Rachel Solomon, Paul Kirwin, and Terri Fried. Section of Geriatrics, Departments of Internal Medicine and Psychiatry, Yale University School of Medicine, New Haven, Connecticut; VA Connecticut Healthcare System.

Background: Efforts to understand and evaluate quality of life (QoL) among persons with chronic disease have resulted in the development of indices that measure QoL according to the severity of disease, symptoms, and functional impairments. By definition, inclusion of these domains presumes that QoL declines as illness progresses. However, this assumption may not reflect the subjective experience of QoL in older persons with advanced illness. There has been little empiric longitudinal study of QoL in this population.

Methods: At interviews performed at least every four months for up to two years (more frequently for individuals with significant changes in their health status), 185 community-dwelling individuals ≥60 years of age with advanced cancer, heart failure, or chronic obstructive pulmonary disease were asked, "How would you rate your overall quality of life?" Response choices included: worst possible, poor, fair, good, and best possible.

Results: We identified four different QoL trajectories that we defined as: improving (QoL rating in at least one interview was higher than that at the previous interview and either improved or remained the same at each of the subsequent interviews); worsening (QoL rating in at least one interview was lower than that at the previous interview and either declined further or remained the same at each of the subsequent interviews); no change (QoL ratings at each time point were the same); and variable (there were two or more changes in the direction of the trajectory over time; e.g., QoL improved then worsened or vice versa). Nearly one-half (49 percent) of participants reported variable QoL trajectories. Among participants who died during the study, 46 percent reported good or best possible quality of life at the last interview and 21 percent reported improvement in QoL from the second-to-last to final interview. Functional status, symptoms, self-rated health, social support, and religious identity were associated with QoL in bivariate analysis; in multivariable analysis, greater activities of daily living disability and depressed mood were significantly associated with a lower QoL, while higher self-rated health and feeling closer to one's religious community were significantly correlated with higher QoL ratings.

Conclusions: Declining QoL is not an inevitable consequence of advancing illness, but rather appears to be highly variable over time. Although QoL may decline with objective measures of worsening illness, a sense of closeness to a religious community and higher subjective ratings of health appear to preserve QoL despite worsening illness.

The Rate and Time Course of Complications in Catheter-Dependent Hemodialysis Patients. Shreya Sood. Yale University School of Medicine, New Haven, Connecticut.

Many patients with end-stage renal disease come to rely on catheters as their only means of hemodialysis when other options are no longer viable. These patients have a very

poor quality of life due to their chronic illness as well as many long-term complications related to the use of tunneled catheters. Many prior attempts have been made to understand these catheter-related problems. Yet, they continue to be a major cause of morbidity and mortality in chronic catheter-reliant patients. We hope to examine the rate as well as long-term time course of these complications such that in future, we may decrease their occurrence. We predict that over time, chronic catheter use decreases the mean indwell time for each catheterization and increases the incidence of complications. To study this, we conducted a retrospective study looking at all patients who had three or more tunneled catheter exchanges between July 2003 and July 2008. We collected information from Yale IDX database on the patient's age and gender, the type of catheter used, the indwell time of the catheter, the vessel used as access, the indication for catheter removal, whether the procedure was performed by a medical doctor (MD) or a physician's assistant (PA) and whether it was a de novo insertion or an over-the-wire exchange. We collected 764 data points on 191 patients (89 males and 102 females). They ranged from 8 to 87 years old with a median age of 56 years. Infection was the number one indication for catheter removal at 37 percent. The rate of infection was 3.34 per 1,000 catheter days. There was no difference in the rate of complications by the side of vessel accessed or by type of catheter. However, right-sided catheters had a longer indwell time of 117 + 159 days compared to left-sided catheters, 87 + 124 days ($p = 0.008$). There was no significant difference in the indwell duration of first catheter in comparison to all subsequent placements. There was also no difference in complications whether the catheter was exchanged over the wire or placed de novo. Nor were complication rates different among MD vs. PA conducted procedures. We conclude that the rates of infection at Yale are similar to other institutions and the vessels located on the right side of the neck are preferable to left-sided vessels to increase catheter longevity. Future research is needed to better assess how rates and incidences of complications change with long-standing catheter reliance.

Hemangiomas of Infancy: Mesenchymal Stem Cell Tumors of Perivascular Origin. Christopher Spock. Yale University School Of Medicine, New Haven, Connecticut.

Introduction: Hemangiomas of infancy (HOI) are the most common benign tumors of childhood. Initially thought to be composed entirely of endothelial cells, it has recently been shown that mesenchymal stem cells reside within these tumors. We propose that hemangiomas represent mesenchymal stem cell tumors of pericyte origin, as demonstrated by expression of pericytic markers (NG2, PDGFR-β, and DLK), neural crest origin markers (expression of nestin and sox10), expression of factors that play a role in the maintenance of stem cell pluripotency (Oct4, Sox2, Nanog, C-myc, and piRNAs), and a microRNA expression profile suggestive of mesenchymal stem cells.

Methods: Quantitative RT-PCR was performed on 19 hemangioma specimens (four proliferating, 10 plateau, five involuting), analyzing transcription factors (Oct4, Sox2, C-myc, and Nanog) known to regulate stem cell pluripotency. Transcription factors RB, IGF2, CTCF, BORIS, DLK, and CDX-2 were also examined. PiRNA analysis was performed on seven hemangioma specimens to investigate the role of these small RNA transcripts that interact with Piwi proteins expressed in germline and stem cells. MicroRNA microarray analysis was performed on nine hemangioma specimens. MicroRNA pathway analysis was performed using Ingenuity Pathway Analysis and MetaCore software. Freshly resected hemangioma specimens were cultured in embryonic stem cell media with and without recombinant human basic fibroblast growth factor (rhbFGF), recombinant human transforming growth factor β (rhTGF-β), and 17-β estradiol.

Results: All hemangiomas expressed factors RB, Oct-4, Sox-2, Nanog, C-myc, DLK, IGF-2, and CTCF at higher levels than endothelial cell controls. DLK, a gene that functions as a negative regulator of adipocyte differentiation, is increased in hemangiomas by more than 105 orders of magnitude compared to control endothelial cells. MiRNA-195, which is

known to target DLK, is also upregulated in hemangiomas. PiRNA analysis revealed that hemangiomas do not contain piRNA transcripts. A microRNA microarray analysis using adult and neonatal dermal endothelial cells as controls indicated that microRNAs associated with mesenchymal stem cells (miR-143, miR320a, miR320c, and let-7c) were expressed in nine samples studied. Hemangioma growth in culture was not observed in embryonic stem cell media with or without supplementation with bFGF and TGF-β. Growth was observed in standard culture media with 17-β estradiol supplementation.

Conclusion: Hemangioma specimens in all stages of growth express transcription factors and genes known to play a role in the maintenance of stem cell pluripotency at a level greater than control endothelial cells. Specifically, transcription factors Oct-4, Sox-2, Nanog, and C-myc are increased. Furthermore miR-143, miR320a, miR320c, and let-7c (all microRNAs identified in mesenchymal stem cells) are upregulated in hemangioma tissue in all stages of growth. DLK, a gene that functions as a negative regulator of adipocyte differentiation, is increased in hemangiomas compared to controls. The downregulation of this gene may lead to transformation of mesenchymal stem cells into adipose tissue. Future experiments are necessary to confirm this role.

The Cost-Effectiveness of Alternative HIV Intervention Portfolios in South Africa. Robert Stavert and Elisa Long. Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut. (Sponsored by David Paltiel.)

A dynamic compartmental model was instantiated with recent epidemiological data from South Africa to compare the efficacy and cost-effectiveness of different portfolios of interventions to prevent HIV infection over a 20-year time horizon. We hypothesized that portfolios that combined scaling up the delivery of highly active antiretroviral therapies (HAART), increasing availability of HIV screening and counseling, and establishing widespread circumcision campaigns would be the most effective and most cost-effective strategies. Portfolios that utilized widespread circumcision for adult men were found to be the most cost-effective, while portfolios that utilized a combination of interventions were found to be the most efficacious, in terms of quality adjusted life years (QALYs) gained. These findings highlight the urgency of scaling up access to life-saving antiretroviral treatments and providing concomitant investments in HIV prevention and testing programs in a generalized HIV epidemic setting such as South Africa.

Discussing Physician-Assisted Dying: A Qualitative Study of Doctors' Experiences in the United States and the Netherlands. Jennifer R. Voorhees. Section of Geriatrics, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut. (Sponsored by Margaret A. Drickamer.)

This qualitative study was undertaken to further understand the complex issue of discussing physician-assisted dying (PAD) within the context of doctor-patient interactions, to elucidate the emotions of the physicians during such discussions, to explore the effects on the doctor-patient relationship, and to determine factors that influence the discussions. Semi-structured, one-on-one interviews were conducted with 36 physicians in the Netherlands and the United States (including Oregon) by a single interviewer. Ongoing inductive qualitative analysis, aided by NVivo7 software, directed the data sampling and saturation. Multiple coders and a multidisciplinary team analyzed emerging themes. This research found that PAD discussions were a gateway to other end-of-life issues important to patients and intensified and strengthened doctor-patient relationships. Physicians who considered participating in PAD found the journey with patients intense but rewarding. Where PAD is legal, criteria in place were utilized by physicians to guide responsible communication, and discussions were more open and honest, with both patients and colleagues. In contrast,

where PAD is illegal, conversations were less explicit, and physicians dealt with requests in relative isolation. In conclusion, PAD can be both a challenging and rewarding discussion for physicians to have with patients. Discussion and consideration of PAD is an energy consuming yet enriching part of the doctor-patient relationship. Legalization is particularly helpful for providing structure and support for individual doctors who consider assisting patients.

Polymorphisms and Biologic Effects of Acidic Mammalian Chitinase in Asthma. Heather Wachtel, Chuan Hua He, and Jack A. Elias. Section of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

In this study, we hypothesize that human acidic mammalian chitinase (AMCase) binds and is regulated by the epidermal growth factor receptor (EGFR) and that AMCase interacts with Galectin-3 (Gal-3) to mediate anti-apoptotic functions. We further hypothesize that asthma-associated polymorphisms of AMCase alter chitinase activity and modulate anti-apoptotic effects. We investigated the interactions between AMCase, Gal-3, and EGFR by establishing binding and co-expression *in vitro*. Apoptotic effects were evaluated via Annexin V/Propidium Iodide staining. Molecular cloning was performed to generate single nucleotide polymorphisms (SNPs) of AMCase associated with asthma. Our data showed that co-expression of AMCase and EGFR induces chitinase activity; we found that AMCase and Gal-3 bind each other *in vitro* and that they co-localize in the cytoplasm of cells. Co-transfection of AMCase and Gal-3 demonstrates a greater anti-apoptotic effect than Gal-3 alone, while recombinant Gal-3 induces apoptosis, which is not blocked by incubation with recombinant AMCase. From these data, we conclude that AMCase is regulated by EGFR and that AMCase and Gal-3 physically interact. However, contrary to our hypothesis, the anti-apoptotic effects of AMCase are unlikely to be mediated by Gal-3. Further exploration of this pathway using SNP constructs generated in this study will shed light on the mechanism of AMCase in asthma.

Living Arrangements, Intergenerational Dynamics, and Psychological Well-Being of Elders: An Examination of Predictors of Elder Depression in Retired Persons in Yancheng, Jiangsu, China. Ying Wang. Yale University School of Medicine, New Haven, Connecticut.

This study explores the relationship between living arrangement and psychological well-being in retired elderly individuals living in Yancheng, Jiangsu (PR China). Data on mode of residence, socio-economic background, daily activities, and intergenerational dynamics were collected from 200 subjects, and their potential correlations with depression (assessed via the Geriatric Depression Scale Short Version) were analyzed. Univariate as well as logistic regression confirmed mode of residence as a significant predictor of depression in this group. The following depression odds ratios associated with each mode of residence were derived via logistic regression: 1) nuclear household, i.e., living with a spouse only, OR = 1.000 [reference category]; 2) multigenerational households in which a spouse is not present, OR = 4.341; 3) multigenerational households in which a spouse is present, OR = 0.781; and 4) living alone, OR = 3.018. Based on these ratios, we conclude that the traditional model of intergenerational co-residence is not, in itself, associated with less depression. Rather, it is the presence of a spouse in a household (whether single or multigenerational) that protects against elderly depression. Other predictors of depression identified in backward logistic regression included presence of a chronic illness and self-assessed wealth status. Additionally, a number of psychosocial variables were identified as independently correlated with depression but were subsequently selected out by multivariate analysis. These included: educational background, religious affiliation, membership in an organization, attitude toward aging, and family status. Based on this study, we believe that

efforts to promote mental well-being among today's Chinese elders should be directed toward psychosocial factors that are modifiable (education, building supportive social networks, etc.) rather than insisting on the traditional ideal of multigenerational living and dependence on filial piety.

Differential Induction of Interleukin-6 by Clinical Isolates of Respiratory Syncytial Virus. Rachel L. Wattier, Isaac Lazar, Richard A. Martinello, Carla Weibel, and Jeffrey S. Kahn. Division of Infectious Diseases, Department of Pediatrics, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut.

This study was conducted to determine whether genetic variation between naturally circulating respiratory syncytial virus (RSV) isolates results in different capacities to elicit innate immune responses in human pulmonary epithelial cells. We hypothesize that genetically distinct RSV isolates interact with the immune regulatory mechanisms in human pulmonary epithelial cells to elicit different patterns of cytokine expression. Human pulmonary epithelial cells (A549) were infected with 36 genetically distinct RSV clinical isolates. Induction of interleukin (IL)-1α, IL-6, and tumor necrosis factor (TNF)-α was measured by ELISA up to 48 hours post-infection. Cytokine mRNA expression and replication kinetics were measured by quantitative RT-PCR. Two genetically distinct but closely related isolates were selected for further investigation, based on differences between these isolates upon initial comparison of cytokine induction. These isolates were found to induce markedly different levels of IL-6 beginning at six hours post-infection and continuing up to 48 hours post-infection. Isolate NH/GB4/1125/01-02 induced up to 13-fold higher levels of IL-6 at 24 hours post-infection than did isolate NH/GB1/1067/01-02. These differences in IL-6 secretion were accompanied by significant differences in IL-6 mRNA expression. The two isolates had similar replication kinetics. Neither isolate induced IL-1α or TNF-α when A549 cells were infected with purified viral preparations. We conclude that RSV clinical isolates differ from one another in their capacity to induce IL-6. The different levels of IL-6 secretion are due in part to differences in transcriptional regulation. Different levels of IL-6 induction cannot be attributed to differences in replication kinetics. Phenotypic differences in the capacity to induce innate immune responses may account for the wide variation in clinical manifestations of RSV infection in children. Further investigation of these and other RSV isolates with phenotypic differences will identify genetic markers related to cytokine induction by RSV. This will enhance understanding of RSV virulence factors and may identify novel therapeutic targets for RSV infection.

The Relationship Between Economic Deprivation and Emerging Inhibitory Control in Young Children. Rachel S. Weston, David J. Bridgett, and Linda C. Mayes. Yale Child Study Center, Yale University School of Medicine, New Haven, Connecticut.

An extensive body of research has documented detrimental effects of growing up in poverty on global child cognitive development, particularly when economic deprivation occurs in early childhood. However, little is known about the impact of poverty on component neurocognitive capacities in children. The prefrontal cortex is a brain region responsible for executive control functions that has a prolonged period of postnatal development and, therefore, may be especially susceptible to environmental influences like poverty. Inhibitory control is an important executive function to investigate because it appears to be a significant predictor of language and math skills in preschool and later school years. In the current study, we hypothesized that children living in more economically disadvantaged families would have delayed development of their inhibitory control abilities and would have altered developmental trajectories with increasing developmental lag compared to children living in more economically advantaged families. The current study employed latent growth curve

modeling to model the developmental trajectories of inhibitory control for a cohort of 125 children followed longitudinally between ages 5 and 8. Commission errors from a picture AX Continuous Performance Task were used to measure inhibitory control. Consistent with developmental expectations, we found that as children get older, they make progressively fewer inhibitory control errors (age 5 mean = 19.86 vs. age 8 mean = 4.76). Significant inter-individual differences were also present in both slope and intercept factors. Adding child gender and income-to-need ratio at age 5 to the model as predictors, we found that both factors accounted for significant inter-individual differences, together explaining 12 percent of the variance in the intercept (i.e., 5-year-old inhibitory control ability). This predictor model provided an excellent fit for the data. At age 5, male children made more inhibitory control errors than female children. Also, children from more economically disadvantaged families made more inhibitory control errors than their peers from more advantaged families. An unexpected finding was that child gender and income-to-need at age 5 did not account for significant inter-individual differences in trajectory slope (i.e., no developmental lag was observed). These results suggest that the impact of economic deprivation on prefrontal cortex development and subsequent development of inhibitory control occurs early (before age 5), putting children on a particular trajectory based on this early exposure to poverty. Tailoring interventions (e.g., early education programs) to reinforce executive functions like inhibitory control below the age of 5 years could potentially maximally improve cognitive outcomes among low-income children.

Utility of Repeat Screening for Asymptomatic Bacteriuria in Pregnancy. Sara Whetstone, Stephen Thung, and Jessica Illuzzi. Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale University School of Medicine, New Haven, Connecticut.

Asymptomatic bacteriuria (ASB) during pregnancy is associated with an increased risk of developing pyelonephritis. The objectives of our study were to determine the incidence of ASB throughout the first two trimesters of pregnancy and to compare the cost effectiveness of performing repeat screening with a single screening strategy for ASB to prevent pyelonephritis. In this prospective cohort study, 206 pregnant women at an urban academic obstetric clinic provided urine for culture at monthly prenatal visits, and the incidence of ASB was calculated at four-week intervals in the first and second trimesters. Descriptive statistics were calculated and used as baseline estimates in the cost-effectiveness analysis. Decision and cost-effectiveness analyses were performed. In the decision analysis, three strategies were compared: (1) no screening; (2) screening for ASB once in the first trimester; and (3) screening for ASB once in the first trimester and once between 18 and 22 weeks gestational age (GA). On initial screening culture for ASB, 9.71 percent of women were positive. Among women with an initial negative culture, the incidence rate of ASB was 0 percent at less than 14 weeks GA, 1.1 percent between 14 and 18 weeks GA, 4.2 percent between 18 and 22 weeks GA, and 1.8 percent at greater than 22 weeks GA. The proportion of women identified with ASB on initial culture did not differ statistically from the proportion identified on repeat culture (McNemar's test, p-value > 0.05). In the decision analysis, a policy of routine screening in the first and second trimester (2 urine culture strategy) was the dominant strategy compared to no screening and a single culture strategy. The model was robust in the sensitivity analysis.

Venous Thromboembolism: A Case-Control Study of Patients in the Neuroscience Intensive Care Unit. Rachel H. Wolfson and Mark D. Siegel. Section of Pulmonary and Critical Care, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Venous Thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a significant source of morbidity and mortality in hospitalized pa-

tients. However, despite ample research into VTE in hospitalized subpopulations, critically ill patients with primary neurological disorders have been insufficiently studied. We hypothesized that there is a high incidence of VTE in the NICU despite a high thromboprophylaxis rate and that this population would carry a unique set of risk factors. Our goal was to identify those patients at higher risk for VTE who may then be served by more aggressive screening and thromboprophylaxis.

We performed a retrospective chart review and case-control study of patients admitted to the NICU of a major urban hospital for three or more days, between 2001 and 2005. The two groups were matched, 2:1 (two controls per case), based on year of hospital discharge and presence of surgical intervention.

The incidence of VTE in the NICU was 9.5 percent (125 of 1,318 patients), despite an overall thromboprophylaxis rate of 97.6 percent. Fifty-five percent of DVTs were in the upper and 45 percent in the lower extremity. Forty-eight patients had PE. Univariate analysis utilizing $p < 0.05$ as a statistical threshold revealed 12 factors associated with VTE. These factors were entered into a multivariable analysis logistic regression, which yielded five factors that remained independently with VTE: higher rates were associated with use of a central-venous catheter (OR: 2.5, CI: 1.4 – 4.6, $p = 0.003$), arteriovenous malformation (OR: 4.9, CI: 1.2 – 20.1, $p = 0.026$), prior VTE (OR: 5.6, 1.4 – 22.4, $p = 0.014$), and mechanical ventilation (OR: 2.1, CI: 1.1 – 4.2, $p = 0.036$). VTE prophylaxis was protective (OR: 0.8, CI: 0.0 – 0.9, $p = 0.043$). In conclusion, VTE remains common among NICU patients despite a high rate of prophylaxis. Several factors appear to be associated with VTE in this population. Future studies are needed to validate the association between these factors and VTE and to determine if more aggressive surveillance and prophylaxis can decrease the frequency of VTE and its complications.

AMP-Activated Protein Kinase Activation Preconditions the Heart Against Ischemic Injury. Tracy M. Wright, Agnes S. Kim, and Lawrence H. Young. Section of Cardiovascular Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

AMP-activated protein kinase (AMPK) is a well-established regulator of cellular energy status and metabolic function and is a vital molecule during the acute response to ischemic stress in the heart. However, its role in preconditioning against ischemic injury is still not clearly defined. Using a novel and specific AMPK activator, A-769662, we wanted to determine if pharmacologic, pre-ischemic activation of AMPK is sufficient to protect the heart against subsequent ischemia-reperfusion injury. Using two mouse models of ischemia, the Langendorff perfused heart and *in vivo* coronary occlusion, we investigated whether A-769662 treatment would activate the AMPK pathway and if pre-ischemic AMPK activation was cardioprotective. In these models, wild type C57BL/6 and transgenic AMPK kinase dead (KD) mice hearts were subjected to ischemia for 25 minutes (perfused heart) or 20 minutes (*in vivo*), followed by reperfusion. A-769662 or vehicle control was administered in the perfusion buffer (100uM, perfused heart) or by intra-peritoneal injection (6mg/kg, *in vivo*), prior to ischemia. A-769662 treatment resulted in AMPK activation in the perfused heart and in the intact heart *in vivo* in the absence of ischemia, and decreased myocardial injury when administered prior to ischemia in both models. These cardioprotective effects were abolished in the AMPK deficient AMPK KD hearts. In the wild type perfused heart, we found evidence that pre-ischemic A-769662 treatment leads to increased end-ischemia adenosine triphosphate (ATP) content, increased end-ischemia phosphorylation of eukaryotic elongation factor 2 (eEF2) at threonine 56, and increased endothelial nitric oxide synthase (eNOS) phosphorylation at serine 1177 residue. These findings show that A-769662 treatment leads to myocardial AMPK activation and preconditions the heart against ischemia in an AMPK-dependent manner, possibly through an AMPK-eEF2 or AMPK-eNOS signaling pathway.