

Yale University School of Medicine Thesis Abstracts — 2006

Long-Term Mortality for Older Diabetics Hospitalized with Acute Myocardial Infarction. Marwah Abdalla^a, Barbara Gulanski^a, Yun Wang^a, Edward Havranek^b, Frederick Masoudi^b, Harlan Krumholz^a, JoAnne Micale Foody^a. ^aYale University School of Medicine, New Haven, Connecticut, and ^bUniversity of Colorado Health Sciences, Denver, Colorado.

Diabetics have higher mortality after myocardial infarction (MI), yet little is known regarding the impact of quality of care on long-term survival in older post-MI diabetics. Using data from the Cooperative Cardiovascular Project (CCP), a national cohort of 234,769 Medicare patients aged 65 or older hospitalized with confirmed AMI between 1994-95, we assessed differences in 10-year mortality outcomes between diabetics and non-diabetics using Cox proportional regression. To account for quality of care, a composite measure among ideal candidates was constructed and entered into the final model, adjusting for use of aspirin and beta-blocker on admission/discharge, angiotensin-converting enzyme inhibitors at discharge, reperfusion within six hours of admission, and smoking counseling at discharge. We also assessed the relationship between insulin use, sulfonylureas/biguanides and statin therapy, and long-term mortality within the diabetic cohort.

The final study sample included 203,658 cases: 32 percent were diabetics. Compared to non-diabetics, diabetics were younger (75 vs. 76, $p < 0.001$), female (53 percent vs. 47 percent, $p < 0.001$), had more comorbidities, and were unlikely to receive evidence-based care (59 percent vs. 64 percent, $p < 0.001$). The unadjusted HR for mortality among diabetics vs. non-diabetics was 1.38 (95 percent CI: 1.37-1.40). After adjusting for demographics, past medical history, procedures during hospitalization, medications on admission/discharge, and quality of care, the HR was 1.29 (95 percent CI: 1.27-1.31). Among diabetics, those on insulin or oral hypoglycemic therapy during the initial hospitalization for AMI had the highest risk of mortality during the last seven years, after adjustment for demographics, clinical characteristics, and quality of care (HR insulin=1.30, 95 percent CI: 1.25-1.35; HR oral hypoglycemics=1.11, 95 percent CI: 1.08-1.15), whereas those on statin therapy were not at increased risk (HR statin=0.95, 95 percent CI: 0.90-1.02).

As compared to non-diabetics, older diabetics had a 29 percent increase in mortality even after adjusting for demographics, clinical variables during hospitalization, and quality of care (HR=1.29, 95 percent CI: 1.27-1.31). Additionally, within the diabetic cohort, the risk of long-term mortality was highest among those on insulin or oral hypoglycemic therapy during initial hospitalization for AMI. Our study demonstrates that neither patient characteristics nor quality of care fully account for the poor outcomes among diabetics suggesting that metabolic risk factors associated with diabetes ultimately require therapies beyond those currently recommended for post-MI patients.

Medicine in the Margins: Access, Resistance and Health Care Utilization Among the Tuareg of Niger. Teeb Al-Samarrai (Sponsored by Naomi Rogers). Section of the History of Medicine, Associate Professor, Yale University School of Medicine, New Haven, Connecticut.

This thesis explores the historical, cultural, and social reasons for the wariness that the nomadic Tuareg of Niger have toward Western medicine and medical practitioners. I give a historical account of their interactions with and resistance to the French colonial admin-

istration and the postcolonial state of Niger and how this resistance to Western medicine and health clinics was an embodied form of political and social resistance to governmentality and state attempts at sedentarization. I provide a historical example of when health care delivery was successful and embraced rather than resisted, as well as the ways in which the Tuareg have not only integrated Western medicines into their lives, but the ways in which these often scarce medicines are distributed to the community as a whole.

I performed a systematic review of the medical, public health, and social science literature by examining published and unpublished documents and doctoral dissertations on the health of the Tuareg and history of Niger. I also conducted interviews with a physician, journalists, anthropologists, and humanitarian aid workers who have worked with the Tuareg in Niger.

Despite the resistance and physical remoteness, there are also success stories of how trust can be achieved and health care successfully delivered to the Tuareg. This research demonstrates that even with enormous cultural, social, and political resistance and under circumstances of poor infrastructure and limited resources, Western medicine is not only desired but can be delivered to remote populations. In conclusion, I discuss the differential impact that sedentarization and recent famines have had on the way of life of the Tuareg and their access to health care.

Surgical Implant Generation Network Intramedullary Nailing of Femur and Tibia Fractures in Rural Haiti. Natasha M. Archer and Trace Kershaw (Sponsored by Maria Small). Department of Epidemiology & Public Health, Yale University School of Medicine, New Haven, Connecticut. (Sponsored by Christian Blanc, Department of Surgery, Hôpital Albert Schweitzer).

Trauma is the most common cause of mortality and disability among working-aged adults in resource-poor countries. While injury prevention is crucial, epidemiologists and clinicians also must work to decrease mortality and disability that results from injury, through cost-effective improvements in the entire system of trauma treatment. This review sought to determine if performing internal fixation using the Surgical Implant Generation Network (SIGN) intramedullary nail to treat femur and tibia fractures is feasible in rural Haiti and which variables improve post-operative recovery, defined as weight bearing (WB) and range of motion (ROM).

Sixty fractures, treated using the SIGN nail, were compared to 46 fractures treated prior to its advent. There was no significant difference between the groups based on OR time ($p = 0.56$) and LOS ($p = 0.47$). Within the SIGN group, a correlation was observed between weight bearing and age ($p = 0.007$), delays to surgery ($p = 0.001$), and polytrauma ($p = 0.017$). Age ($p = 0.079$) and delays to surgery ($p = 0.010$) were also found to influence knee range of motion.

The low production cost of the SIGN nail and its design simplicity offer a potential solution to the multiple trauma fractures that frequently lead to disability in settings like Haiti. Its utility, in settings like Haiti, must be further studied. In addition, it is also essential that we continue to make efforts to improve post-trauma transport.

Shoot the Abortionist Twice: The Crisis in Abortion Provision in the United States. Dara Beth Arons. Department of History of Medicine, Yale University School of Medicine, New Haven, Connecticut.

The purpose of the paper is to examine where and how abortion training takes place throughout medical education in the context of a current shortage of abortion providers in the United States. The study was conducted using Internet search engines Scopus, Academic Search, History of Science and Technology, and OVID, with keyword searches for “abortion,” “medical education,” “residency training,” and “family medicine.” Personal interviews also were conducted with leading abortion educators and researchers. The paper addresses the training of potential abortion providers, during medical school and residency education in obstetrics

and gynecology and in family medicine. Through an examination of where abortion providers practice in the United States, how medical professionals gain exposure to abortion throughout their education, and how the medical community addresses the matter, this paper demonstrates how the omission of exposure to this prevalent procedure throughout medical education contributes to the shortage of abortion providers in this country today. For all women in the United States to have equal access to full reproductive health care, more physicians must be trained in abortion care. Moreover, as the sole primary care providers in much of the country, family physicians are best equipped to resolve the shortage.

C-Mpl Expression in Osteoclast Progenitors: A Novel Role for Thrombopoietin in Regulating Osteoclast Development. Calvin L. Barnes, Yougen Xi, Kimberley M. Wilson, Mark C. Horowitz, and Melissa A. Kacena. Section of Bone Biology, Department of Orthopaedic Surgery and Rehabilitation, Yale University School of Medicine, New Haven, Connecticut.

A new paradigm has evolved in which multiple regulatory interactions between the skeletal and hematopoietic systems have been identified. Previous studies have demonstrated that megakaryocytes (MK) play a dual role in skeletal homeostasis by stimulating osteoblast proliferation and simultaneously inhibiting osteoclast (OC) development. Here we identify a novel regulatory pathway in which the main MK growth factor, thrombopoietin (TPO), directly regulates osteoclastogenesis. To study the role of TPO in OC development, spleen or bone marrow (BM) cells (2×10^6 cells/ml) or BM macrophages (BMM, 1×10^5 cells/ml) from C57BL/6 mice, as a source of OC precursors, were cultured with M-CSF (30 ng/ml) and RANKL (50 ng/ml) to induce OC formation. TPO (0.1-1000 ng/ml) and/or primary MK (0-0.5 percent), derived from C57BL/6 fetal livers, were titrated into these cultures and OC were identified as tartrate resistant acid phosphatase positive (TRAP+) giant cells with >3 nuclei. There was a significant, up to 15-fold, reduction in OC formed when MK were added to all OC generating cultures, $p < 0.001$. Moreover, if OC generating cultures did not contain MK or MK progenitors, TPO treatment significantly enhanced OC formation up to six-fold, $p < 0.01$. This data demonstrates that MK are responsible for the inhibition of OC formation and that in cultures containing MK or MK progenitors such as BM or spleen cells, that TPO acts indirectly to inhibit OC formation by stimulating megakaryopoiesis, whereas in the absence of MK or MK progenitors, TPO directly enhances OC formation. This conclusion is further supported by Real-Time PCR data that demonstrates OC progenitors express c-mpl, the TPO receptor, albeit at low levels when compared to expression of c-mpl on MK. Finally, we have begun to dissect the c-mpl signaling pathway in OC progenitors. We have found that TPO induces tyrosine phosphorylation of several specific cellular proteins in the JAK/STAT pathway. Thus, TPO acts in a somewhat paradoxical manner by inhibiting OC formation through the stimulation of MK, while simultaneously playing a direct role in enhancing osteoclastogenesis.

The Ventilatory Response to Normoxic Hypercapnia in Male Pet-1 Knockout Mice and the Influence of Female Sex Hormones. Simon R.A. Best and Matthew R. Hodges (Sponsored by George B. Richerson). Department of Neurology, Yale University School of Medicine, New Haven, Connecticut.

Purpose: To determine if the deficiency in the hypercapnic ventilatory response as a result of 70 percent loss of serotonergic neurons in male Pet-1 knockout mice and the sparing of the female Pet-1 knockout mice can be accounted for and corrected by supplementation with estrogen and progesterone.

Methods: Using whole-body flow-through plethysmography, five male Pet-1 $-/-$ mice and five wild type mice were exposed to room air, 3 percent, 5 percent, 7 percent, and 10 percent CO₂ and V_E measured. All mice were then treated with oral 17 β -estradiol (2500 nM) for 48 hours followed by a SC injection of progesterone (2 mg/kg). One hour after injection, all plethysmography studies were repeated.

Results: Before treatment, Pet-1 knockout mice showed a trend toward decreased V_E at room air, 3 percent, and 7 percent CO₂, with statistical significance at 5 percent CO₂ (p

<0.05), and an identical V_E only at 10 percent CO_2 . Absolute changes in V_E after treatment were insignificant; the differences in V_E between genotypes achieved significance at control, 3 percent, and 5 percent CO_2 ($p < 0.05$) while now V_E at 7 percent and 10 percent CO_2 exposures were identical ($p < 0.05$).

Conclusion: The partial recovery of the male Pet-1 knockout phenotype provides evidence that the remaining serotonergic neurons can recover some chemoreceptor function under the influence of female sex hormones, which in turn may partially explain the female Pet-1 knockout phenotype.

Factors Surrounding and Influencing the Primary Disclosure in Sexual Abuse of Children. Kira O'Neil Bona (Sponsored by Dr. John M. Leventhal). Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

This study aimed to investigate the context within which children initially disclose their sexual abuse. The study sought to identify triggers that prompted the initial disclosure event and to investigate the relationship between the choice of initial confidante and the child's age and likelihood of disclosing during formal interview.

Data were obtained in a prospective fashion from 60 alleged child sexual abuse victims referred to the Yale Child Sexual Abuse Clinic (CSAC). Inclusion criteria required that a child must have disclosed to a confidante prior to referral to the Clinic; 57 of 60 children met this criterion and were included. Victim and perpetrator demographics, details of the initial disclosure event, and any identified triggers were obtained in a systematic fashion as part of the standard clinical evaluation by CSAC social workers. An analysis was conducted to investigate the relationship between the child's age and choice of confidante and the child's choice of confidante and likelihood of disclosing in a formal interview.

Of 57 children, 23 percent were abused by immediate family members and 39 percent by extended family members; 49 percent of cases involved penetrative abuse; and 51 percent of perpetrators were aged 18 or younger. The three most common triggers for disclosure included: questioning by an adult (26.3 percent), witnessed abuse (12.3 percent), and safety of being away from a perpetrator (10.5 percent). The three most common initial confidantes included parent-figures (42 percent), DCF workers or police (15 percent), and child peers (12 percent). The majority of children (81 percent) disclosed during a formal interview with a clinic social worker. There was a statistically significant relationship between victim's age and choice of confidante: 60 percent of children aged 2-7 initially disclosed to a parent figure, in comparison to only 28 percent of children aged 8-15 ($p=0.034$). Additionally, 21 percent of older children first disclosed to a child peer or sibling, while no younger children did so. We found no relationship between a child's initial choice of confidante and likelihood of disclosing during formal interview ($p=0.06$). No relationship existed between a child's age and likelihood of disclosing during formal interview ($p=0.43$); older children, however, were more likely to provide detailed disclosures during formal interview than younger children ($p=0.054$).

In support of our first hypothesis, our data showed a statistically significant relationship between victim's age and choice of confidante. Of equal interest, the results did not support our hypothesis that there would exist a relationship between a child's initial choice of confidante and likelihood of disclosing during the formal interview, nor our hypothesis that educational programs or discussions would result in spontaneous disclosures. Of central importance to the understanding of children's disclosures, our sample most frequently disclosed to a parent-figure while at home and often while engaging in one-on-one activities with the trusted adult confidante to whom they disclosed.

The Association Between Elevated Hippocampal Glutamate Levels and Cognitive Deficits in Epilepsy. Michele S. Buragas (Sponsored by Idil Cavus). Departments of Neurosurgery and Psychiatry, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to investigate the association between extracellular basal hippocampal glutamate levels and cognitive function in epileptic patients. We used the

zero-flow microdialysis method to measure the extracellular concentrations of glutamate in the epileptogenic and non-epileptogenic hippocampus of 23 awake epileptic patients during the interictal period. All patients underwent extensive neuropsychological testing to assess cognitive functioning prior to probe implantation. Basal glutamate levels in the epileptogenic hippocampus were significantly higher than the non-epileptogenic hippocampus (mean, 11.96 micromolar (μM) vs. 2.92 μM , respectively). Elevated basal glutamate levels in the epileptogenic hippocampus correlated with decreased scores on the Verbal Selective Reminding Test (V-SRT) ($R^2 = 0.36$, $p = 0.0244$). When controlling for MRI-detected hippocampal atrophy within epileptogenic regions, elevated basal glutamate levels within atrophic hippocampus correlated with decreased cognitive functioning measured by both the V-SRT ($R^2 = 0.7764$, $p = 0.0204$) and Performance Intelligence Quotient (PIQ) ($R^2 = 0.7324$, $p = 0.0297$), but not within non-atrophic hippocampus (V-SRT: $R^2 = 0.1013$, $p = 0.4424$; PIQ: $R^2 = 0.2303$, $p = 0.2288$). These data suggest that elevated basal glutamate levels in the epileptogenic hippocampus may be implicated in the pathogenesis of hippocampal atrophy and may contribute to impaired cognitive functioning involving verbal memory and visual-spatial skills in patients with temporal lobe epilepsy.

Trends in Usage of CT in the Early Detection and Diagnosis of Adnexal Torsion. Juliana Capatosto (Sponsored by Christopher Moore). Section of Emergency Medicine, Department of Surgery, Yale University School of Medicine, New Haven, Connecticut.

Ovarian torsion (OT) is frequently considered in the differential diagnosis of women presenting to the ED with pelvic pain but is a relatively uncommon occurrence. While ultrasound is considered the test of choice for OT, CT may be used as an initial imaging study with undifferentiated pelvic pain. The aim of this study was to determine the frequency of CT used in the diagnostic evaluation of women with proven OT. We hypothesized that all CTs of the pelvis in women with proven OT would be abnormal. This was a retrospective chart review from a 500-bed urban teaching hospital. Patients admitted between 1985 and 2005 and discharged with ICD-9 code of ovarian or adnexal torsion were included in the study. Those patients with no surgical evidence of OT after chart review were excluded.

Data were stratified into four five-year periods for analysis of imaging trends. One hundred seventy-eight cases of surgically proven torsion over a 20-year period were reviewed. The average age of the subjects was calculated as 32.2 years, with a range from two weeks of age to 84 years (24.7 percent of patients were under age 18). One hundred thirty-six patients received ultrasounds, and 58 patients received CT scans. The percent of patients who received CTs from 1985 until 2005 increased from 12.5 percent to 34.2 percent. The percentage of patients who received ultrasounds from 1985 to 2005 increased from 37.5 percent to 58.9 percent.

We conclude that CT scanning has increased in frequency as a diagnostic tool in the workup of ovarian torsion over the past 20 years. In this study of 178 patients and 58 CT scans, there were no normal pelvic CT scans in patients with surgically proven adnexal torsion. This suggests a possible role for CT in excluding the diagnosis of adnexal torsion.

Occipital White Matter Volumes Predict Visual Motor Outcome in Preterm Infants With Retinopathy Of Prematurity (ROP). Renu Chundru, Betty Vohr, Shelli Kesler, and Laura R. Ment. Section of Neurology, Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

Although very low birth weight preterm (VLBW) infants with grade 3,4 retinopathy of prematurity (ROP) are at high risk for unfavorable visual outcomes, the middle school vision motor integration (VMI) skills and cognitive outcome scores of these children remain largely unknown. Data for 323 very VLBW survivors of the Multicenter Randomized Indomethacin IVH Prevention Trial (BW 600 – 1250 g) were analyzed to test the hypothesis that grades 3, 4 ROP would be an important predictor of cognitive and VMI skills. Three

subgroups were evaluated: ROP negative (N = 163), ROP grades 1,2 (N = 137) and ROP grades 3,4 (N = 23) were evaluated prospectively at 12 years of age with a neurocognitive battery. High-resolution volumetric MRI scans were quantified for 40 of the study subjects, and occipital brain volumes were correlated with Beery VMI scores. Children with ROP 3-4 had increased vision impairment and lower test scores. Whole brain volumes were significantly less for children with any grade of ROP ($p = 0.02$), occipital white matter volumes tended to be less for the same study subjects ($p = 0.08$), and both total occipital brain volumes and occipital white matter volumes were significantly correlated with Beery VMI scores ($r = 0.610$, $p = 0.009$ and $r = 0.652$, $p = 0.005$, respectively). Prematurely-born children with a history of grade 3-4 ROP continue to have increased vision impairment, special needs and lower performance on cognitive, language, and visual motor integration scores at age 12. Both whole occipital brain volumes and occipital white matter volumes were predictive of VMI scores for children with ROP. (supp by NS 27116)

The Effects of Benzo- α -Pyrene on the Insulin-like Growth Factor-I Gene. Brittiny A. Epperson and Ahmed M. Fadiel. Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to look at the genotoxic and cytotoxic effects of benzo- α -pyrene (BaP), a chemical mutagen that is present in cigarette smoke, on the insulin-like growth factor-I (IGF-I) gene. Women who smoke during pregnancy are more likely to have a growth-restricted baby. We hypothesized that BaP exerts its effects through genotoxic and cytotoxic avenues. The cytotoxicity is manifested by chromosomal abnormalities and a decrease in the rate of cell division. The genotoxicity is manifested by changes in certain genes known to be important in mammalian fetal development such as IGF-I. IGF-I is implicated in intrauterine growth restriction (IUGR), a problem that greatly increases the risk of perinatal morbidity and mortality. To further understand the mechanism by which BaP influences the normal growth and development of human placental cells, human placental trophoblast cells from an established immortalized cell line were utilized. Cells were cultured in appropriate media, starved (using starvation "Serum Free Medium"), and treated with two doses of BaP, 1 μ M (dose 1), and 5 μ M (dose 2). Chromosomes were prepared for cytogenetic analysis and visualized using light microscopy after Giemsa staining. Chromosomal aberrations were identified, and the rate of cell division was determined through the analysis of the mitotic index for treated cells compared to a control group. To further understand the influence of BaP on the IGF-I gene expression level, RNA was extracted from control and treated cells, from which cDNA was synthesized and used for further analysis using polymerized chain reaction (PCR). The PCR results were used to better understand the genotoxicity of BaP, while chromosomal aberration analysis was used to determine the cytotoxic effects of BaP on human placental cells. Our results indicate that many chromosomal abnormalities were present in the treated groups compared to the control group. In addition, there was a significant decrease in the mitotic index of the BaP-treated cells (MI = .3 percent) vs. the control group (MI = .93 percent), p value .0447. Through the PCR assay, we speculate that there is a dose-related response to BaP of the IGF-I RNA expression level, with low levels in the treated groups compared to the control group. We conclude from these results that BaP influences placental cells at both the gene and chromosome level. It also affects the cell cycle of human placental cells. It is known that smoking is deleterious for fetal development. We believe that the current study brings us closer to understanding the mechanism by which smoking can lead to fetal growth restriction.

A Quantitative Analysis of Computed Tomography Scanner Utilization in an Academic Medical Center. Amichai J. Erdfarb, Howard P. Forman, and Irena Tocino. Department of Radiology, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study is to quantify computed tomography (CT) scanner utilization and productivity in an academic hospital setting and determine the primary causes of idle time.

Two CT scanners were observed for 202 scanner hours. Scanner time was divided into two primary components: “active” and “idle.” Active time was further divided into preparation, scan, and take-down times. Independent variables recorded include inpatient vs. outpatient, IV contrast (IVC) vs. non-IVC, and scanner type. Primary contributors to idle time were identified in six main categories: preventative maintenance (PM), technical failure, upgrades, calibration, understaffing, and poor flow management.

Two hundred seventy-five CT scans and 10 CT guided procedures performed on 235 patients were observed. Total active time was 62:09:00 (30.75 percent). Average hourly weekday utilization was 20:56 min/hour (34.89 percent). Scanner utilization peaked from 4 to 5 p.m. at 34:35/hr (57.65 percent) and reached a minimum value of 3:10/hr (5.27 percent) between 11 p.m. and midnight. Total weekday idle time was 115:59:30, categorized as follows: poor flow management – 90:45:18 (78.24 percent); understaffing – 10:54:17 (9.40 percent); technical failure – 10:12:40 (8.80 percent); calibration – 2:15:00 (1.94 percent); PM – 1:01:15 (.88 percent); and upgrades – 0:51:00 (.73 percent). Average total exam time was 12:38 (n = 218, SD 7:16), compared to a standard appointment block of 30 minutes. Average component times were preparation – 4:58 (n = 218, SD 3:53); scan – 5:08 (n = 224, SD 3:33); and take-down – 2:36 (n = 225, SD 1:47). Contrast exams took longer than non-contrast exams with average total exam times of 17:05 (n = 104, SD 7:21) and 8:34 (n = 114, SD 4:09), respectively. Scanner type and in/outpatient status of the examinee did not significantly affect total study times, all four of these groups having average total exam times of 12 to 13 minutes.

There is considerable under-utilization associated with the present operation of the CT scanners, primarily resulting from poor patient flow management. Implementing new scheduling processes, modifying appointment block lengths, and more effectively managing inpatient flow and scanner idle time has the potential to significantly increase patient throughput.

Drug Users’ Beliefs on Mandatory Newborn HIV Testing in the State of Connecticut. Odicie O. Fielder, John Hodges, and Frederick Altice. Section of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

We examined health beliefs among drug users about mandatory HIV testing of newborns and voluntary vs. mandatory testing of pregnant women. We also examined to what extent negative experiences and stigmatization affect attitudes toward HIV testing.

Baseline structured interviews of active drug users from 1997 to 2001 were examined. Multivariate data analysis was performed using SAS statistical software. Subsequently, five distinct focus groups were conducted in September 2003. Focus groups were transcribed, coded, and analyzed using Microsoft Word 2000.

Of 610 drug users interviewed, nearly all (89 percent) had been previously HIV tested. Nearly all (91 percent) subjects believed pregnant women should be tested for HIV. More subjects who had prior HIV testing believed all pregnant women should be HIV tested (92.9 percent vs. 82.6 percent, $p = .008$). Though 86 percent of subjects agreed with testing of all newborns, only 57 percent of all subjects believed that this should be mandatory. Among women, however, more injectors than non-injectors would avoid prenatal care if HIV testing was required during pregnancy (16.2 percent vs. 6.1 percent, $p < .01$). Of the 499 subjects reporting a usual site for care, 31.8 percent believed that “certain types of people” received better treatment than others. Not using drugs, being of a certain race/ethnicity, and having private insurance were associated with receiving better care. Perceived discrimination by the health care system also was cited as a barrier to acceptance of testing strategies. In the focus groups, arguments against mandatory testing of pregnant women included the loss of choice, right not to know HIV status, and the belief that mandatory testing was both a means of provoking rebellion and promoting discrimination. Concern for the baby’s health was the primary reason for supporting mandatory newborn testing.

The current practice of mandatory newborn and voluntary prenatal screening for HIV in Connecticut appears to have been acceptable to a population of stigmatized drug users

with or at risk for HIV. Despite acceptance, perceived discrimination by the health care system persists and may result in adverse outcomes for drug using men and women.

Onset and Exacerbation of Obsessive-Compulsive Disorder in Pregnancy and the Postpartum Period. Mariel A. Focseneanu, C. Neill Epperson. Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut.

The overarching goal of this study was two-fold: to determine the prevalence of perinatal onset or worsening of OCD symptoms in women participating in a university-based research program and whether there is a continuity between perinatal onset or worsening of OCD and premenstrual exacerbation of such symptoms.

Women ages 18 to 69 years old who were enrolled in the Yale OCD Research Program between 1990 and 1995 were interviewed by phone or in person regarding demographics, onset and course of OCD, types of primary OCD symptoms, treatment history, comorbid diagnoses, including substance use and abuse, and the impact of pregnancy and menstruation on OCD onset and symptoms. Those who had at least one pregnancy were placed into the Preg group and those who had never been pregnant into the NPreg group. The Preg group was further subdivided; those who reported onset of OCD during pregnancy or the puerperium were assigned to the Puerperal Related (PR) group, while those who denied onset of OCD related to pregnancy were assigned to the Non-Puerperal (NP) group. For our secondary aim addressing premenstrual worsening, those women who were in the PR group were combined with women with pre-existing OCD that worsened during pregnancy or the postnatal period.

All data were summarized using descriptive statistics (means, SDs, frequencies). Continuous measures were compared between groups using a Student's t-test, and categorical variables were assessed using the chi-square test. All analyses were considered statistically significant at $P < 0.05$ and performed using SAS, version 9.1.

Of the Preg group, 24 (30.8 percent) fell into the PR subgroup; 11 (14.1 percent) reported onset during pregnancy, one (1.3 percent) had onset after a miscarriage, and 12 (15.4 percent) had onset during the postpartum period. Out of 132 total pregnancies, 29 (22.0 percent) involved an improvement in OCD symptoms, 45 (34.1 percent) involved an exacerbation of symptoms, and 58 (43.9 percent) did not change symptom severity in women with pre-existing illness. Although worsening of symptoms prior to menses was reported by the same proportion of women in the Preg group as in the NPreg group, women in the PR group and those with perinatal exacerbation were more likely to report premenstrual worsening of OCD symptoms compared to all others.

Findings from this study provide additional evidence that pregnancy and childbirth are frequently associated with the onset of OCD or worsening of symptoms in those with pre-existing disorder. In addition, there appears to be continuity between OCD onset and/or exacerbation across the reproductive life cycle, at least with menstruation and pregnancy. These data cannot address the impact of menopause on OCD symptoms. Our findings are consistent with those from other groups, but all need to be confirmed in prospective studies.

Comparison of MRI and Symptom Outcomes of Uterine Artery Embolization for Uterine Leiomyomata Using Tris-Acryl Gelatin Microspheres, Poly-Vinyl Alcohol Spheres and Poly-Vinyl Alcohol Particles. Jorge A. Gálvez, Shirley M. McCarthy, Jeffrey Pollak, Jeffrey Weinreb, Daniel Zelterman, Robert White, and Michael G. Tal. Section of Vascular and Interventional Radiology, Departments of Diagnostic Radiology and Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut.

Purpose: To compare the recurrence rate of symptoms and MRI enhancement of uterine fibroids in patients treated with uterine artery embolization (UAE) among three embolic agents: polyvinyl alcohol (PVA) particles, spherical polyvinyl alcohol (SPVA) particles, and tris-acryl gelatin microspheres (GM).

Materials and Methods: Women treated with UAE for fibroids with PVA, SPVA, or GM were contacted by telephone/mail to complete a modified Uterine Fibroid Symptom Quality of Life (UFS-QOL) survey. Baseline and post-UAE gadolinium-enhanced magnetic resonance imaging (MRI) studies were evaluated for residual or persistent enhancement of any uterine fibroids after UAE. Data was analyzed using 2-tail Fisher's exact test to correlate symptoms and enhancement and determine the likelihood of recurrence of enhancement and symptoms following UAE among three embolic agents.

Results: A total of 101 women underwent UAE with one of the three embolic agents and had complete pre- and post-embolization MRI follow-up. In this group, 24 of 59 (41 percent) women in the PVA group, 18 of 24 (75 percent) women in the SPVA group, and four of 18 (22 percent) women in the GM group showed residual enhancement in some or all fibroids. Statistically significant differences in recurrence of residual enhancement on follow-up MR imaging were found between SPVA and PVA ($p = .0072$), as well as SPVA and GM ($p = .0015$), but not between PVA and GM ($p = .1756$). No statistically significant correlation between residual enhancement and symptom recurrence was found based on the survey responses.

Conclusion: Patients embolized with SPVA have a higher risk of having residual enhancement on follow-up MR imaging than those embolized with PVA or GM.

Increase in Peripheral Arterial Tone Predicts Myocardial Ischemia Induced by Mental Stress. Brendon Graeber, Matthew M. Burg, Aseem Vashist, Christine Earley, Joyce Liu, and Robert Soufer. Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Mental stress ischemia (MSI) is associated with poor prognosis for coronary artery disease (CAD) and is amenable to treatment, yet no easily administered test exists to diagnose it. Given the known increase in systemic vascular tone in response to stress, we studied the ability of peripheral arterial tonometry (PAT), a noninvasive functional measure of arterial tone, to predict those vulnerable to MSI. Seventy-seven patients with chronic stable CAD were subjected to mental stress with concomitant assessment of myocardial perfusion and pulse wave amplitude. Nuclear perfusion imaging was used to document MSI, and PAT was used to measure pulse wave and microarterial tone. A ratio of PAT measurements during stress to those before stress was used to characterize vascular responses. Serum catecholamines and endothelin-1 (ET-1) were simultaneously measured. Subjects who experienced MSI had a lower average PAT ratio than those who did not ($.76 \pm .04$ vs. $.91 \pm .05$, $P = .03$). A receiver operating characteristics curve for PAT ratio predicting MSI had an area under the curve of .613 (standard error, .065, one-sided $P = .04$). Maxima of sensitivity and specificity were observed at a threshold of .78 to define an abnormal PAT ratio. Cross-tabulation of groups above and below this threshold with groups of subjects with and without MSI showed a significant predictive relationship between PAT ratio and MSI ($P = .03$). Subjects at or below this threshold ($\leq .78$) displayed a significant increase in norepinephrine levels during mental stress (235 pg/ml at baseline, 259 pg/ml during mental stress, $P = .007$). Subjects above this threshold ($> .78$) displayed a significant decline in their ET-1 levels 24 hours after mental stress (1.15 pg/ml after mental stress, .93 pg/ml 24 hours later, $P = .01$), while those at or below threshold had a continued increase. PAT ratio is a complex functional measure of peripheral arterial tone that we have shown significantly predicts the occurrence of MSI. It may have clinical value as an easily administered screening test for MSI.

Telling Time: Doctors' Memoirs from the Early AIDS Epidemic. Jennifer Greenwold. Yale University School of Medicine, New Haven, Connecticut.

This thesis investigates physicians' personal memoirs from the early days of the Acquired Immunodeficiency Syndrome (AIDS) epidemic. It proposes that AIDS doctors wrote to explore the personal, professional, and social crises of AIDS. Their memoirs reveal that during the AIDS epidemic, healing often took place in the personal connection between

doctor and patient — that is, during the AIDS epidemic, doctors, unable to cure, cared for their patients by listening to them, empathizing with them, and engaging them not from a stance of clinical detachment but rather as friends and witnesses to their suffering.

This study considers why these doctors were compelled to tell their stories of AIDS care. In order to find out, six physician-authors — Rafael Campo, Jerome Groopman, Kate Scannell, Peter Selwyn, Abraham Verghese, and Abigail Zuger — were interviewed. They were asked why they wrote, how they decided what to write about, and how having written such a book has affected their doctoring. Their responses are considered alongside analysis of their memoirs. All six felt that writing allowed them to process for themselves and present to the medical and lay publics a model of care which posits devotion, compassion, and companionship at the center of a doctor's work.

Race/Ethnicity as a Moderator in Child and Adolescent Depression and Anxiety Trials. Natalie Guerrier^a, John March, M.D., M.P.H.^b, Andres Martin, M.D., M.P.H.^a ^aChild Study Center, Yale University School of Medicine, New Haven, Connecticut, and ^bDepartment of Child and Adolescent Psychiatry, Duke University School of Medicine, Durham, North Carolina.

The inclusion of racial/ethnic minorities in treatment outcomes trials for children and adolescents with depression and anxiety is essential, particularly given the assumption, required by the National Institutes of Health (NIH), that racial diversity is important to the generalizability of clinical trial outcomes. A search for randomized clinical trials on the treatment of child and adolescent depression and anxiety was conducted using the Medline and Psychinfo databases. These were then reviewed to determine whether race or ethnicity were 1) factored into recruitment strategies; 2) represented in the trial sample; and 3) included in moderator analyses to determine the extent to which they may influence trial outcomes. Thirty-seven original and 13 follow-up trials were identified (total N = 3330). None identified strategies for targeted recruitment of racial/ethnic minorities. Six did not report race. All minority groups except for Native Americans are underrepresented, as compared to 2000 U.S. Census figures; however, only one study reported Native Americans as participants. Overall, 67 percent of the sample was Caucasian, 26 percent minority, and 6 percent unreported. There was no trend in minority representation by year. Most studies reviewed do report the ethnic breakdown of their sample populations, although methods vary. Six studies, three original and three follow-up, explored the ethnicity as a moderator. Without an increased presence of minorities in clinical trials, it is unclear that the results of these studies can reliably generalize to a diverse population. The importance of studies in minority samples becomes apparent, as does the need for a greater emphasis on recruitment.

Factors Associated with Lack of Knowledge of Glaucoma Risk Factors at Three New Haven Clinic Sites. Jane A. Gwira and M. Bruce Shields. Department of Ophthalmology, Yale University School of Medicine, New Haven, Connecticut.

Purpose: To evaluate variables associated with lack of knowledge regarding glaucoma risk factors.

Methods: A survey was administered to 397 participants in July 2004 at two primary care clinics and an eye care center. The survey had social variables and knowledge of risk factors associated with glaucoma. The variables were then correlated with lack of knowledge of glaucoma using the Chi squared test and logistic regression analysis.

Results: When controlling for confounding variables in multivariate analysis, lack of knowledge for glaucoma risk factors was associated with not having a family history of glaucoma (OR 3.7, $p = .0003$), being an ethnic minority (OR 2.3, $p = .012$), and being at a primary care center (OR 2.2, $p = .02$). Furthermore, at primary care centers, variables associated with lack of knowledge of glaucoma were not having a family history of glaucoma (OR 3.6, $p = .0003$), being an ethnic minority (OR 2.9, $p = .0042$), and having no perceived risk of developing glaucoma (OR 2.0, $p = .045$). Among minorities, lack of awareness of

glaucoma is associated with having no family history of glaucoma (OR 5.08, $p = .0001$), being at a primary care center (OR 3.89, $p = .0054$), and being of Hispanic ethnicity (OR = 2.5, $p = .012$).

Conclusion: In this analysis, we identify various factors that may predispose patients to having no knowledge of risk factors associated with glaucoma. Our results suggest that attention to educating minority patients who visit primary care clinics may improve knowledge of glaucoma among those less likely to know much about glaucoma. Knowledge may increase if patients who do not have regular eye care are targeted for education about glaucoma and other potentially serious eye diseases.

Uncovering the Role of Stress In Craniosynostosis. Justin B. Heller. Yale University School of Medicine, New Haven, Connecticut.

Current theory on normal cranial suture fusion entrusts the dura with the regulatory role. Studies suggest the dura responds to stress with changes in gene expression. Noggin (bone morphogenetic protein inhibitor) expression is decreased in normal (rat and murine) cranial suture fusion. However, its role in craniosynostosis and response to stress has not been studied. In our study, we investigated: 1) sutural fusion changes and 2) expression changes of noggin and Runx2 in response to mechanical stress.

Posterior-frontal (fusing) and sagittal (patent) rat cranial sutures were held static, oscillated, or distracted for 10 days in an organ culture microdistraction device beginning at five days of age (10 days prior to onset of posterior frontal suture fusion)($n=15$). Fusion scoring was given with 0 for patent, 1 fusing or partial fusion and 2 complete fusion. Percent fusion equaled the score received for bony closure. Expression of noggin, Runx2, and AP was also localized by immunohistochemistry for all groups.

Both the posterior frontal and sagittal suture demonstrated a statistically significant ($p < .05$) increase in fusion percentage with oscillation relative to the static control from 39 percent to 73 percent for the posterior frontal (fusing suture) and from 0 percent to 56 percent for the sagittal (patent suture) respectively. Immunohistochemistry of our static control demonstrated that noggin was not expressed in the fusing posterior frontal suture, but expressed in the normally patent sagittal suture. Conversely, Runx2 was expressed in the PF suture, but not in the sagittal suture. However, when a mechanical stress was applied either via oscillation or distraction, both the posterior frontal and sagittal sutures expressed Runx2 but not noggin as in the static fusing suture.

The application of oscillatory stress to cranial sutures results in fusion of both the posterior frontal and the normally patent sagittal suture. However, distractile stress did not cause fusion. This later finding is a likely result of the existence of a range of acceptable stresses. Thus, the stress applied to the suture in distraction did not result in bony bridging because there was too much separation between the two calvarial halves. Both stressed groups however, did demonstrate the same gene expression relative to control: significantly increased expression of the bone differentiation markers Runx2 and the late marker AP with nearly no expression of noggin. Thus, mechanical stress influenced the cells involved in sutural fusion and stimulated them to undergo osteogenic differentiation. Stress may therefore play a role in craniosynostosis.

The Effects of Tort Reform on Medical Malpractice Litigation. Jeffrey D. Hoschander and Morris Traube. Yale University School of Medicine, New Haven, Connecticut.

The medical liability environment during the first few years of the 21st century frequently has been referred to as the third medical malpractice “crisis.” This period has been characterized by perceived increases in malpractice insurance costs and defensive medicine, as well as concerns about resulting decreases in access to health care. Since the 1970s, states have implemented a variety of tort reform measures intended to ameliorate medical malpractice liability and combat the perceived harms. The effectiveness of these initiatives has been

the subject of vigorous debate. This investigation sought to demonstrate that specific tort reform measures have had distinct effects on the volume and costs of medical malpractice litigation in recent years.

We conducted a survey of the tort reform initiatives adopted in each state. Three major classes of tort reform were subjected to analysis, including statutory limitations on damages, collateral source rule reform, and modification of joint and several liability. The study period was defined as 1994-2004. Data on the number and value of medical malpractice payments made on behalf of physicians was collected for the years 2000-04. For each class, we compared the data from states with the reform in continuous effect throughout the study period to the data from states without that same reform.

Statistical analysis demonstrated that only statutory limitations on damages were apparently effective in reducing medical malpractice payment costs. The average annual value of payments in states with limitations on damages, \$1,032,344 per 100,000 people, was nearly 40 percent lower than the \$1,663,896 in states without any damages limitations ($p = .027$; 95 percent CI: \$76,061, \$1,187,043). None of the reforms under study were demonstrated as having been effective in reducing the average annual number of medical malpractice payments.

This study thus demonstrated that in contrast to two other prominent types of liability reform, statutory limitations on damages effectively reduce the annual costs of medical malpractice payments. Although medical malpractice payments are not the sole component of medical liability costs, the reduction in the former should result in an amelioration of the medical liability environment.

Staging, Prognosis, and Treatment of Merkel Cell Carcinoma: A Population-Based Study. Douglas M. Housman, Benjamin D. Smith, and Lynn D. Wilson. Department of Therapeutic Radiology, Yale University, School of Medicine, New Haven, Connecticut.

Merkel cell carcinoma (MCC) is a rare form of skin cancer, often described as the most aggressive cutaneous malignancy. Its high propensity for dermal-lymphatic invasion, local recurrence, and rapid lymphatic and distant metastasis poses a significant treatment challenge to clinicians. Combining its highly aggressive nature with its low incidence, Merkel cell carcinoma is a particularly difficult cancer to study. Two major staging criteria exist for Merkel cell carcinoma.

The purpose of this study is to validate and compare the Memorial Sloan Kettering Cancer Center (MSKCC) staging criteria with the American Joint Committee on Cancer (AJCC) Tumor, Node, Metastasis (TNM) staging criteria for Merkel cell carcinoma (MCC) utilizing the Surveillance, Epidemiology, and End Results (SEER) database. The role of radiation therapy (RT) is also evaluated.

One thousand five hundred fifty-six cases of MCC from the SEER database (1988-2002) were identified and evaluated. Tumor size, lymph node status, and metastases were staged, according to the MSKCC and AJCC TNM staging criteria respectively ($n = 561$). The primary outcome was overall survival. Covariates included: age at diagnosis, site of primary tumor, receipt of radiation therapy, and MSKCC or AJCC stage, respectively. Kaplan-Meier survival analyses and Cox proportional hazards regressions were analyzed using SAS 9.1.

The median age was 75 years (range: 22-98) with 39 percent of patients being female. The median follow-up was 2.2 years with a range of 0.4-14.3 in the staged populations. Under the MSKCC staging criteria: five-year overall survival was 59 percent for stage I ($n=224$), 45 percent for stage II ($n=114$), 33 percent for stage III ($n=140$), and 28 percent for stage IV ($n=83$). When compared with stage I, the adjusted mortality HR was 1.44 (95 percent CI 1.03-2.00) for stage II, 2.14 (95 percent CI 1.57-2.93) for stage III, and 2.61 (95 percent CI 1.85-3.67) for stage IV. Under AJCC TNM staging criteria: five-year overall survival was 60 percent for stage I ($n=223$), 47 percent for stage II ($n=107$), 31 percent for

stage III (n=148), and 28 percent for stage IV (n=83). When compared with stage I, the adjusted mortality HR was 1.41 (95 percent CI 0.99-1.99) for stage II, 2.13 (95 percent CI 1.57-2.89) for stage III, and 2.62 (95 percent CI 1.86-3.69) for stage IV. Among 478 patients with local or regional disease, 49 percent received radiation. After adjusting for MSKCC stage and age, radiation was not associated with survival, mortality HR 0.83 (95 percent CI 0.63-1.09). The interaction of radiation with stage was not significant (P=0.69). Similarly, in the AJCC TNM staged population, radiation was not associated with survival, mortality HR 0.83 (95 percent CI 0.63-1.09), with no interaction of radiation with stage (P=0.42).

The MSKCC staging criteria appropriately and significantly risk stratified MCC within this SEER population. Alternately, the AJCC staging criteria did not significantly risk stratify MCC within this SEER population. The MSKCC criteria appears to better risk stratify MCC than the AJCC staging criteria, within this SEER population. Radiation does not appear to confer a survival advantage among SEER patients with local or regional disease.

Cataract Formation After Retinal Procedures. Ryan I. Huffman and Ron A. Adelman. Department of Ophthalmology, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study is to examine the risk of cataract development in patients who have undergone pars plana vitrectomy, scleral buckle, or both. This is a retrospective study of phakic patients who underwent pars plana vitrectomy, scleral buckle, or both at Yale University Eye Center from 1998 to 2005. A mild post-operative cataract, defined as a change in severity of 1+, developed in 32 of 53 (60 percent) eyes following vitrectomy, two of 19 (11 percent) post scleral buckle, and 14 of 16 (88 percent) after both. A moderate post-operative cataract, defined as a change in severity of 2+, developed in 14 of 53 (26 percent) eyes post vitrectomy, one of 19 (5 percent) post scleral buckle, and 11 of 16 (69 percent) after both procedures. In eyes that underwent vitrectomy, a lens change of at least 2+ occurred in 8 percent of eyes at three months, 15 percent at six months, 21 percent at 12 months, and 26 percent at 36 months. In eyes status post scleral buckle surgery, one eye (5 percent) experienced a 2+ change at 36 months. In eyes that underwent both vitrectomy and scleral buckle, a lens change of at least 2+ occurred in 44 percent of eyes at three months, 50 percent at six months, 63 percent at 12 months, and 69 percent at 36 months. Cataract extraction surgery was performed in 15 percent of eyes post vitrectomy, 0 percent post scleral buckling, and 50 percent after both. The most common type of cataract to develop was nuclear sclerotic, which accounted for 61 percent of cataracts after vitrectomy, 50 percent after scleral buckling, and 50 percent after combined vitrectomy and scleral buckling. Scleral buckling surgery is associated with a low risk of cataract formation. Pars plana vitrectomy and combined vitrectomy and buckle have a higher risk of cataract development.

Differential Responsiveness of Early and Late Passage Endothelial Cells to Shear Stress. Peter J. Juran, Fabio A. Kudo, Bohdan Warycha, Hidenori Asada, Jared Frattini, Bauer E. Sumpio, and Alan Dardik. Section of Vascular Surgery, Department of Surgery, Yale University School of Medicine, New Haven, Connecticut.

Atherosclerosis and neointimal hyperplasia colocalize with areas of disturbed blood flow. Since the incidence of vascular disease increases with age, the effects of orbital shear stress on endothelial cell proliferation, Akt activation, and functional activity were analyzed using a senescence model. Early (p3-7) and late (p28-32) passage bovine aortic endothelial cells were exposed to orbital shear stress (210 rpm) or static conditions (0-5 days). Cell proliferation was directly counted and confirmed with PCNA reactivity. Phosphorylated and total Akt were assessed with Western blotting. Endothelial cell-induced smooth muscle cell migration was assessed with a Boyden chamber. Unlike early passage cells, late passage endothelial cells demonstrated no significant increase in orbital shear stress stimulated pro-

liferation ($p=0.42$). Unlike late passage cells, early passage endothelial cells showed a significant increase in Akt phosphorylation in response to shear stress ($n=6$, $p=0.01$). Shear stress-exposed early passage cells also showed significant increases in smooth muscle cell chemotaxis ($n=3$, $p=0.03$). Late passage endothelial cells demonstrate reduced proliferation, Akt phosphorylation, and secretion of smooth muscle cell chemoattractants in response to orbital shear stress compared to early passage cells. These results suggest that late passage endothelial cells respond to shear stress differently than early passage cells and confirm the utility of the *in vitro* senescence model.

The Effects of Novel Serms on Endothelial and Epithelial Tumor Cell Estrogen Receptor Activation. Palvos Zacharias Kaimakliotis. Yale University School of Medicine, New Haven, Connecticut.

Premenopausal women are relatively protected against the development of coronary heart disease, when compared with age-matched men. This difference dissolves after menopause and is accepted to be hormonally mediated. Despite recent clinical controversies in the use of hormone replacement therapy in postmenopausal women, there have been numerous *in vitro* and *in vivo* studies that demonstrate favorable effects of estrogen on the endothelium. The Bender laboratory has shown that 17β -estradiol (E_2) rapidly induces nitric oxide (NO) release from human endothelial cells (EC) *in vitro*. This occurs through a c-Src/phosphatidylinositol 3-kinase (PI3-kinase)/Akt pathway, in a rapid fashion in the absence of modulated gene expression. In addressing how these membrane growth factor receptor-type responses to a steroid hormone could occur, the Bender laboratory also demonstrated that ECs have more than one form for $ER\alpha$. The classical $ER\alpha$, a 66kDa protein, is predominantly cytosolic and nuclear and comprises a minority of the ERs in most ECs. ER46, a 46kDa protein, is a product of an alternative transcript splice form and represents a majority of the ERs in most ECs. ER46 has a predilection for membrane targeting and more efficiently transduces the favorable EC activation responses to E_2 (described above). Given the controversy surrounding the effects of hormone replacement therapy in postmenopausal women, the design and use of selective estrogen receptor modulators (SERMs) has recently gained great attention — encouraging hope that some of these compounds will have beneficial effects on vascular and bone cells, without the detrimental side/toxic effects.

The hypothesis is that, of a selected panel of potential SERMs, there will be a hierarchy of proliferative responses of breast cancer cells and a hierarchy of efficacy and toxicity with regard to rapid induction of endothelial nitric oxide synthase (eNOS) activation through EC membrane ER46. A compound that is found to be highly efficient at inducing eNOS activation and minimally pro-proliferative may be a tremendously useful prophylactic and therapeutic agent in humans.

The Epidemiology and Clinical Presentation of Leprosy in the Pediatric Population of Paraguay. J. Kattan, E.F. Velazquez, and M. Reyes-Mugica. Department of Pathology, Yale University School of Medicine, New Haven, Connecticut.

Background: Several aspects concerning the biology and epidemiology of leprosy remain unknown. It has been recognized that the study of children with leprosy could provide important insight into unanswered questions, particularly if disease manifestations are carefully observed.

Methods: A retrospective chart review of 308 cases of children aged 0-14 was conducted at the Ministry of Health Leprosy Department in Asuncion, Paraguay. Data regarding age, gender, leprosy classification, transmission, detection, clinical presentation, presence and class of reaction, and disability were abstracted.

Results: The study group ranged from 2 to 14 years of age. The incidence rate and the risk of having leprosy were shown to increase with age. The gender ratio of males to females was 1:1. A positive contact history was documented in 86.4 percent of cases, with

intrafamilial contact type accounting for 98.9 percent of known cases. The average time to diagnosis was 1.1 years. Paucibacillary leprosy was more common than multibacillary leprosy in this study population. While 16.9 percent of children experienced some type of nerve involvement, 1.9 percent of all children presented with hypersensitivity reactions, with Type 2 erythema nodosum leprosum reaction being the most common.

Conclusions: The minimum incubation period could be two years. Children may be less likely to develop severe forms of leprosy. Males and females may be equally susceptible to contracting the disease from a biological perspective. Close and prolonged contact appears to be necessary for transmission. Nerve involvement and hypersensitivity reactions are relatively uncommon in children.

Dysregulation of Sodium Channels in a Rat Model of Absence Epilepsy. Davender S. Khera, Josh P. Klein, Hrachya Nersesyan, Eyal Kimchi, Stephen Waxman, and Hal Blumenfeld. Department of Neurology and Department of Neurobiology, Yale University School of Medicine, New Haven, Connecticut.

Absence epilepsy is a generalized form of epilepsy in which spike-wave discharges (SWDs) involve both hemispheres of the brain and thereby alter consciousness. Recent evidence by Meeren et al. (2002) in the WAG/Rij rat model of absence epilepsy points to a cortical focus of SWDs before rapid generalization of the SWDs. This focus is in the peri-oral area of the somatosensory cortex, and it was found to consistently lead SWDs in other cortical and subcortical areas. With this recent finding, it seems plausible that a defect lies in this focal region of the cortex, leading to SWD in the WAG/Rij model. It is likely that an alteration of one or more ion channels leads to seizure generation in this rat model, as ion channels are what produce the hyperexcitability of seizures.

In this study, our laboratory performed three consecutive days of scalp EEG recordings on WAG/Rij animals at different ages and compared this to control rat EEGs. As has been found before, we saw an increase in time spent in SWDs as the WAG/Rij animals aged. After completing EEG recordings, the animals were sacrificed and quantitative PCR and immunocytochemistry was performed on six regions of the cortex. In comparison to control animals, WAG/Rij rats had an increase in sodium channel subunits $Na_v1.1$ and $Na_v1.6$ in the region corresponding to the seizure focus identified by Meeren et al. In addition, as WAG/Rij rats aged, the amount of $Na_v1.1$ and $Na_v1.6$ also steadily increased in the peri-oral region of the somatosensory cortex. These findings suggest that specific sodium channelopathies may initiate SWD generation in this rodent model.

The results of our study have many implications. Perhaps many, if not all, forms of human absence epilepsy are rooted in ion channelopathies which could be limited to specific regions of the brain. If this is so, and if the specific channelopathies are identified, it is also possible that very targeted therapies could be devised — either medically or surgically — to treat both “benign” and refractory absence epilepsies.

Future studies are needed to determine whether the sodium channel dysregulation found in this rodent model is the cause or effect of SWDs and whether other channelopathies or dysregulation of channels exists. Our lab is currently looking at what effects ethosuximide, an anti-absence drug, has on sodium channel composition in the cortex of the WAG/Rij rat.

Attentional Performance of Children with Primary Brain Tumors after Conformal Radiation Therapy. Erin N. Kiehna, Raymond K. Mulhern, Chenghong Li, Xiaoping Xiong, and Thomas E. Merchant. Divisions of Radiation Oncology, Behavioral Medicine and Department of Biostatistics, St. Jude Children’s Research Hospital, Memphis, Tennessee. (Sponsored by Michael Westerveld, Department of Neurosurgery, Yale University School of Medicine, New Haven, Connecticut.)

To assess the impact of conformal radiation therapy (CRT) and demographic and clinical variables on four measures of attention in pediatric and young adult patients with localized primary brain tumors, we prospectively evaluated 120 patients (aged 2.0 to 24.4

years, median age of 9.2 years) with primary brain tumors. Evaluations were completed using the computerized Conners' continuous performance test (CCPT). We analyzed errors of omission (inattentiveness), errors of commission (impulsivity), reaction time, and an overall index of performance before CRT, weekly during CRT, and serially up to 60 months after the start of CRT. Before CRT, patients exhibited mild inattentiveness. During CRT, impulsivity decreased significantly ($P = 0.002$). After CRT, inattentiveness increased significantly ($P = 0.03$), and global attention disorders were associated with craniopharyngioma ($P < 0.0001$), supratentorial tumors ($P = 0.008$), optic pathway and diencephalic tumors ($P = 0.012$), and subtotal resection of the tumor ($P = 0.010$).

In conclusion, brain tumors and their treatment impair sustained attention and reaction time. A decline in impulsivity and relative stability of the other CCPT scores over the course of CRT demonstrated the absence of early radiation-related cognitive sequelae. Local tumor effects, initial surgical intervention, and focal irradiation of central structures contribute to long-lasting attentional problems in pediatric and young adult patients.

Cyclooxygenase-2 Expression in Post-Mastectomy Chest Wall Relapse. Janet H. Kim^a, Veerle Bossuyt^b, Teresa Ponn^c, Donald Lannin^d, Bruce G. Haffty^e. Departments of ^aTherapeutic Radiology, ^bPathology, and ^cSurgery, Yale University School of Medicine, New Haven, Connecticut, and ^dDepartment of Radiation Oncology, Robert Wood Johnson Medical School, New Brunswick, New Jersey.

The purpose of this study was to assess the prognostic significance and clinical correlations of cyclooxygenase-2 expression (COX) in a cohort of patients treated with radiation (RT) for post-mastectomy chest wall relapse (PMCW). Between 1975 and 1999, 113 patients were treated for isolated PMCW. All patients were treated with biopsy and/or excision of the CWR followed by RT. Median follow-up was 10 years. All clinical data, including demographics, pathology, staging, receptor status, HER-2/neu status, and adjuvant therapy, were entered into a computerized database. Paraffin-embedded CWR specimens were retrieved from 42 patients, of whom 38 were evaluated, created into a tissue microarray, stained by immunohistochemical methods for COX, and graded 0 to 3+. A score of 2 to 3+ was considered positive. Overall survival from original diagnosis for the entire cohort was 44 percent at 10 years. Survival rate after chest wall recurrence was 28 percent at 10 years. The distant metastasis-free survival rate after CWR was 40 percent at 10 years. Local-regional control of disease was achieved in 79 percent of patients at 10 years after CWR. COX was considered positive in 13 of 38 cases. COX was inversely correlated with ER ($p = .045$) and PR ($p = .028$) and positively correlated with HER-2/neu ($p = .003$). COX also was associated with a shorter time to PMCW. The distant metastasis-free rate for COX negative patients was 70 percent at 10 years, compared with 31 percent at 10 years for COX-2 positive patients ($p = .029$). COX positive had a poorer local-regional progression-free rate of 19 percent at 10 years, compared with 81 percent at 10 years for COX negative ($p = .003$). Outcome following RT for PMCW is relatively poor. Positive COX correlated with other markers of poor outcome, including a shorter time to local relapse, negative ER/PR and positive Her-2/neu status. Positive COX correlated with higher distant metastasis and lower local-regional control of disease. If confirmed with larger studies, these data have implications with respect to the concurrent use of COX-2 inhibitors and radiation for PMCW.

White Matter Connectivity in Children with Reading Disability in Comparison to Nonimpaired Readers. Kendra Klang, Cheryl Lacadie, John Holahan, Karen Marchione, Xenios Papademetris, Marcel Jackowski, Rob Fulbright, and Todd Constable. (Sponsored by Sally Shaywitz, Bennett Shaywitz). Section of Pediatric Neurology, Department of Pediatrics, Yale-New Haven Hospital, New Haven, Connecticut.

Dyslexia is a common condition among both children and adults in the United States. Its prevalence is estimated to be between 5 percent and 17 percent of school-aged children.

This chronic condition is characterized by an unanticipated difficulty in reading in children with otherwise average or above average intelligence, education, and incentive. Although adults with a specific reading disability have demonstrated diminished diffusion anisotropy, this relationship between reading ability and white matter connectivity is relatively unexplored in children. In this study, diffusion tensor magnetic resonance imaging was utilized to compare the white matter connectivity in three groups of children with diverse reading ability: dysfluent and inaccurate ($n = 42$), dysfluent and accurate ($n = 69$), and nonimpaired ($n = 23$) children. Analysis of variance statistical analysis was performed to detect any significant group differences in anisotropic indices between the three groups of readers. In contrast to past studies, our study did not reveal any statistically significant differences in fractional anisotropy, fiber coherence index, or mean diffusivity between dysfluent and inaccurate, dysfluent but accurate, and non-impaired readers.

An Anatomy-Based Health Education Curriculum Taught By Medical Students May Improve High School Students' Health Knowledge. Jason Anthony Knight. Yale University School of Medicine, New Haven, Connecticut.

To date, few high school-based interventions have been shown to have lasting effects on adolescents' health behaviors. The need for health interventions targeting adolescents is underscored by data showing that several health behaviors with significant short- and long-term adverse effects begin in early adolescence and become progressively more prevalent toward late adolescence. This project tested the efficacy of a novel anatomy-based health education curriculum at increasing health knowledge. The course was taught by first-year Yale medical students. The curriculum placed emphasis on nutrition, physical activity, and infectious disease. Forty juniors from Career High School visited Yale's anatomy lab once every two weeks for 10 hour-long sessions. In addition to visits to the anatomy lab, students completed two class projects: One covered nutrition and the other focused on exercise. Four additional sessions at Career High School were dedicated to the class projects. Pre- and post-test analysis showed an improvement in health knowledge, with a 13 percentage point improvement on a standardized health knowledge survey. The students' performance was compared to a control cohort of 31 students who were not exposed to the curriculum. Students exposed to the curriculum had a 19 percentage point advantage compared to control students who had not been exposed. Curriculum efficacy as demonstrated by this small cohort validates further testing with larger cohorts and more vigorous controls as well as separate testing to measure changes in health behavior attributable to curriculum exposure.

The Effects of Novel Design Strategies on the Risks and Benefits of Phase I Oncology Trials. Shlomo A. Koyfman and Cary P. Gross. Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Considerable ethical debate surrounding the risks and benefits of Phase I oncology trials is based on older response and toxicity data that does not account for recent changes in the types of agents and trial design. This study aims not only to update these data but also investigate the affect of novel trial designs on various clinical outcomes.

We performed a review of the literature using the Medline database. Part I included nearly all Phase I trials published in 2002. Part II identified Phase I studies of cytotoxic agents alone, published from 2002 through 2004.

Two hundred twenty-one Phase I oncology studies, consisting of 6,008 patients, were studied in Part I, while 149 studies, comprising 4,532 patients, were analyzed in Part II. Overall, the response rate for Phase I oncology trials in 2002 was 19 percent, the mortality rate was 1.1 percent, and the rates of severe hematologic and non-hematologic toxicities were 19 percent and 22 percent, respectively. "Classic" Phase I trials of single agent cytotoxic drugs accounted for only 18 percent of trials, while more than half (55 percent) included at least one FDA-approved therapy. The response and toxicity rates varied with the

class of agent (e.g. cytotoxic, biologic, and vaccine), and the combinations of agents (e.g. approved and investigational) studied.

Only 34 percent of studies utilized aggressive dose escalation schemes; 22 percent permitted intra-patient dose escalation; and only 28 percent enrolled fewer than three patients to any dose level before proceeding to the next higher dose level. Studies that allowed intra-patient dose escalation or used fewer than three patients per dose were not associated with rates of response or toxicity that differed from trials using a more “traditional” design, nor did they increase the percentage of patients who received the recommended Phase II dose. However, aggressive dose escalations were associated with increased rates of both hematologic (17 percent vs. 10 percent) and non-hematologic (17 percent vs. 13 percent) toxicity for participating patients without increasing response rates. None of these novel design strategies were associated with a smaller patient requirement.

Phase I oncology trials represent a spectrum of different classes of agents and design strategies that are often associated with distinct clinical outcomes. Accounting for this variety is critical when evaluating their risk-benefit profiles and ethics. While some innovations in trial design do not appear to be any more helpful or harmful than standard methods in Phase I trials of single agent cytotoxic drugs, using aggressive dose escalations may be more hazardous for patients. These findings highlight the need for continued effort toward improving trial design and its impact on our patients.

Suppression of DGAT2 Expression Improves Hepatic Steatosis and Prevents Fat-Induced Insulin Resistance. Ameya Kulkarni, Cheol S. Choi., David Savage, Katsutaro Morino, Varman T. Samuel, Sheene Kim, Amy Wang, John G. Geisler, Sanjay Bhanot, Brett Monia, Xing-Xian Yu, Susanne Neschen, Anthony J. Romanelli, and Gerald I. Shulman. Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

It is well known that metabolites from the accumulation of fat in tissue results in fatty liver, obesity, and insulin resistance. Because triglyceride (TG) synthesis is essential for this process, inhibition of the final step of TG synthesis has been considered a new therapeutic target for hepatosteatosis and insulin resistance. In this study, we investigated the metabolic impact of acyl CoA: diacylglycerol acyltransferase 1 (DGAT1) and 2 (DGAT2) suppression. We used antisense oligonucleotides (ASOs) to reduce the expression of these enzymes in liver and fat in Sprague Dawley rats fed a 27 percent safflower oil high fat diet (HFD) for four weeks. Rats were injected with one of the following: saline, control ASO, DGAT1 ASO, or DGAT2 ASO subcutaneously twice a week for four weeks. DGAT1 and DGAT2 ASO treatment reduced DGAT1 and DGAT2 mRNA levels in liver by 95 percent and 57 percent respectively, but only DGAT2 ASO treatment significantly reduced TG content when compared to the saline group. We determined the effects of ASO treatment on insulin action *in vivo* during a 135 min hyperinsulinemic (4mU/kg/min)-euglycemic clamp. Glucose turnover and uptake were assessed using [3-3H]glucose infusion and [1-14C]2-deoxyglucose injection during clamps. DGAT2 ASO-treated rats were protected from HFD induced insulin resistance as demonstrated by an 80 percent increase in glucose infusion rate (24.0 ± 0.9 vs. 13.4 ± 1.1 mg/kg/min, $p < .001$). This was accounted for by significant suppression of hepatic glucose production (82 ± 6 vs. 53 ± 11 percent $p < .05$) and a 54 percent increase in insulin-stimulated whole body glucose uptake (25.3 ± 1.1 vs. 16.3 ± 0.7 mg/kg/min, $p < 0.001$) when compared to the control ASO group. Insulin-stimulated glucose uptake in skeletal muscle and suppression of plasma-free fatty acid levels during the clamp also significantly were increased in DGAT2 ASO-treated rats when compared to controls (2DG uptake: 329 ± 31 vs. 263 ± 28 nmol/g/min, $p = .03$, suppression of FFA: 64 ± 4 vs. 48 ± 5 percent, $p = .015$). Of note, the DGAT2 ASO group showed less weight gain than controls, despite the same food consumption over the treatment period. The ratio of weight gain vs. food consumption, or efficiency of weight gain, was significantly lower in the DGAT2 group when compared to other groups, suggesting an increase in energy expenditure in the DGAT2 ASO group.

In summary, this study demonstrates that the reduction of DGAT2 using an ASO protects against insulin resistance in liver and peripheral tissue.

Mother Knows Best: Maternal Experience and Choice of Infant Sleep Position.

Meghan Lane, Amy Margolis, Denis Rybin, and Eve Colson. Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

Purpose: The purpose of this project was to examine the associations between maternal child-rearing experience, choice of infant sleeping position, and the source, nature, and trust of advice received about infant sleeping position in a high-risk, primarily African-American population.

Background: The number of deaths attributed to Sudden Infant Death Syndrome (SIDS) has decreased since the initiation of the Back to Sleep campaign in 1994. Although this change has benefited all ethnic groups, African-American infants are still twice as likely to succumb to SIDS as Caucasian infants.

Design/Methods: We conducted 668 face-to-face standardized interviews with mothers of infants in Connecticut, Georgia, and Texas. Mothers were included in the interviews if they were the primary caregivers for an infant younger than 8 months. Mothers with children aged 10 years or older and mothers of younger children were compared with regard to the following variables: sleep position with current infant, advice received about sleep position, sources of advice, and trust in advice received. Univariate analysis was used to compare the two groups of mothers. Odds ratios and 95 percent confidence interval were calculated to determine relationship between sleep position and maternal characteristics such as age, race, and education.

Results: Mothers of older children differed from mothers with younger children in two ways. Women with children aged 10 or older were less likely to receive sleep position advice from their families than were women with younger children (12/87 or 14 percent vs. 249/581 or 43 percent, $p < .0001$). Of the multiparous women, mothers with older children were more likely than women with younger children to have placed a previous child in the prone position for sleep (55/87 or 63 percent vs. 100/282 or 36 percent, $p < .0001$). Having placed a previous child in the prone position has been found in other studies to be associated with an increased risk of placing the current infant in the prone position, and our data duplicate this finding. However, the mothers of older children in this sample were not found to use the prone position with the current infant more than mothers of younger children.

Conclusions: Mothers with children born before or near the initiation of the Back to Sleep campaign have different sources of advice about sleep position than women with younger children. They are also more likely to have placed a previous child in the prone position for sleep and so may constitute a group whose children are at increased risk of SIDS.

Child Abuse and Bone Fractures in Young Children: Local Trends Over Three Decades.

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The purpose of this study was to determine the patterns of fractures in children younger than 3 years of age that are distinctive of abuse and to examine changes in the frequency of abusive fractures in young children evaluated at a major pediatric hospital over three time periods: 1979-1983 (early), 1991-1994 (middle), and 1999-2002 (late).

All children 0 to 36 months of age who were treated for bone fractures at a major medical center from January 1999 to December 2002 were selected. Medical records were abstracted for sociodemographic and clinical characteristics, and radiographs were examined.

Using specific criteria, each case was rated by two clinicians and two pediatric radiologists on a seven-point scale ranging from definite abuse to definite accident. Cases were rated independently by each reviewer; when disagreements occurred, a consensus rating was reached. Cases rated as definite, likely, or questionable abuse were considered abuse. Demographics of the abused children were compared to those with either accidental fractures or fractures of unknown etiology using chi-square statistics. The proportion of children rated as abuse in the late sample was compared to the proportions previously identified in the early and middle time periods using adjusted odds ratios controlling for race and physician type (clinic vs. private).

Several fracture types were highly associated with abuse: 100 percent of rib fractures, 29.2 percent of femur fractures, 19.5 percent of humerus fractures, and 12.8 percent of tibia/fibula fractures were rated as abuse. Abused children were more likely than those with accidental or unknown fractures to present with vague or missing histories to explain the fracture (60.0 percent vs. 11.6 percent), and were more likely to be younger than 12 months of age (68.0 percent vs. 26.6 percent), insured by Medicaid or to be self-pay patients (68.0 percent vs. 41.1 percent), and of minority race (56.0 percent vs. 29.9 percent).

For the late time period, 10.8 percent of 232 cases were classified as abuse; in the middle group, 10.0 percent of 240 cases; and in the early group, 22.5 percent of 200 cases. Children in the early group had two and a half times the odds of an abusive fracture when compared with the late group (adjusted OR 2.58, 95 percent CI = 1.43, 4.65). The odds of abuse did not differ significantly between the middle and late groups (adjusted OR 0.86, 95 percent CI = 0.46, 1.63).

Fractures of the ribs, femur, humerus, and tibia/fibula were most highly associated with abuse. Abused children were more likely to present with vague or missing histories to explain the fracture and were more likely to be younger than 12 months of age, of minority race, and either self-pay patients or insured by Medicaid. The rate of fractures due to abuse has decreased dramatically over the past three decades at one major pediatric center.

Differentiation of Appendiceal Carcinoids By Marker Gene Expression. Igor Latich, Yale University School of Medicine, New Haven, Connecticut.

Objective: To utilize differential gene expression of candidate markers to discriminate benign appendiceal carcinomas (APCs) from malignant and mixed cell APCs.

Background Data: Considerable controversy exists in regard to the appropriate surgical management of APCs since standard clinical and immunohistochemical methods cannot reliably determine whether an APC is indolent or aggressive. We have identified five differentially expressed genes: nucleosome assembly protein 1-like 1 (NAP1L1); melanoma antigen D2 (MAGE-D2); metastasis-associated protein 1 (MTA1); NAcH Leucine-rich-repeat Protein 1 (NALP1) and Chromogranin A (CgA) that define gut neuroendocrine enterochromaffin (EC) cell behavior. We hypothesized that APC malignancy, also derived from EC cells, could be defined by using quantitative reverse transcriptase-polymerase chain reaction and immunohistochemical approaches that evaluate potential marker genes.

Methods: Total RNA was isolated using TRIzol reagent from 42 appendiceal samples, including APCs identified at exploration for appendicitis (no evidence of metastasis; n = 16), appendicitis specimens (n = 11), malignant appendiceal tumors (> 1.5cm, evidence of metastatic invasion; n = 7) and mixed (goblet) cell appendiceal (GBC) adenocarcinoids (n = 3), normal appendiceal tissue (n = 5), and five colorectal cancers. Gene expression (CgA, NAP1L1, MAGE-D2, MTA1 and NALP1) was examined by Q-RT PCR (Applied Biosystems) and quantified against GAPDH.

Results: CgA message was elevated (> 1000-fold, $p < .05$) in all tumor types. NAP1L1 was elevated (> 10-fold, $p < .03$) in both malignant and GBC adenocarcinoids compared to normal and incidental lesions ($p < .006$). MAGE-D2 and MTA1 message were significantly elevated (> 10-fold, $p < .01$) in the malignant and GBC adenocarcinoid tumors but not in

the appendicitis-associated carcinoids or normal mucosa. The apoptotic marker, NALP1, was over-expressed (> 50 -fold, $p < 0.05$) in the appendicitis-associated and malignant APCs but was significantly decreased (> 10 -fold, $p < 0.05$) in GBC adenocarcinoids. Elevated CgA levels indicative of a carcinoid tumor were identified in one acute appendicitis sample with no histological evidence of a tumor.

Conclusions: These data demonstrate that malignant APCs and GBC adenocarcinoids have elevated expression of NAP1L1 (mitotic regulation), MAGE-D2 (adhesion), and MTA1 (estrogen antagonism) compared to APCs identified at appendicitis. This, and the differences in NALP1 (apoptosis) gene expression (decreased in GBC adenocarcinoids), provides a series of molecular signatures that differentiate carcinoids of the appendix. CgA identified all appendiceal tumors as well as covert lesions, which may be more prevalent than previously recognized. The molecular delineation of malignant appendiceal tumor potential provides a scientific basis to define the appropriate surgical management as opposed to morphological assessment alone.

Timing and Predictors of Postpartum Return to Smoking in Women Who Quit Smoking During Pregnancy. Alyssa R. Letourneau and Eve R. Colson, M.D. Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

This study prospectively examined the timing and predictors of returning to smoking after pregnancy in a group of women who quit smoking cigarettes during pregnancy. We interviewed women during the postpartum hospital stay and at their infants' two-week and two-month health supervision visits. Urine cotinine levels were measured at each interview. Fifty-three women were interviewed during the postpartum stay, 37 women at the two-week and 36 women at the two-month visits. At the two-week visit, 40.5 percent had returned to smoking, and at the two-month visit, 47.2 percent had returned to smoking. Factors associated with a return to smoking at two weeks included a lower level of education (high school graduate/GED vs. some college education; 13/37 vs. 2/37, $p = .02$), the presence of someone else in the household who smoked (14/37 vs. 1/37, $p = .001$), formula-feeding their infant at the time of interview (14/37 vs. 1/37, $p = .003$), having discussed smoking with a doctor or nurse during pregnancy (12/37 vs. 3/27, $p = .009$), and being African-American vs. Caucasian or Hispanic (10/37 vs. 5/37, $p = .008$). Predictors of a return to smoking at two months included the presence of someone else in the household who smoked (17/36 vs. 0/36, $p < .001$) and smoking at least one cigarette during pregnancy after initially quitting (12/36 vs. 5/36, $p = .02$). Women who quit smoking cigarettes during pregnancy are likely to resume in the days immediately after delivery. The presence of household smokers and formula feeding are the strongest predictors of resuming smoking within two weeks.

Fourteen Years of Silence: An Exploration of Intimate Partner Violence in the Jewish Community. Rachel Rose Light (Sponsored by Linda Degutis), Section of Emergency Medicine, Department of Surgery, Yale University School of Medicine, New Haven, Connecticut.

With the background that Jewish women stay in abusive marriages twice as long as their non-Jewish American counterparts, we attempt to understand the religious and cultural factors that may inhibit Jewish women from leaving violent relationships and examine scriptural and rabbinic texts as to Jewish beliefs regarding spousal violence. A variety of academic sources and primary scriptural texts were analyzed for religious and cultural attitudes toward Jewish intimate partner violence. Eight Jewish victims of spousal abuse, five rabbis, and 17 community support workers were interviewed. Jewish women face a variety of unique issues with regard to how domestic violence is experienced. Issues of communal shame, fear of anti-Semitism, learned accommodation, community disapproval, divorce law, and other cultural and religious factors act as barriers to leaving. Biblical, Talmudic,

and rabbinic texts, however, speak clearly against marital violence and support a community effort toward victim support. There are thus conflicts between actual Jewish religious doctrine and the interpretation of Jewish values among Jewish community members. There are social and cultural barriers to Jewish women leaving their abusive relationships, but an analysis of religious doctrine offers a source of strength for women to leave. The onus is on the Jewish community to effect change by breaking the silence and renouncing abuse.

Ethnic Differences in Intramyocellular Lipid Levels and Insulin Resistance in Obese Children and Adolescents. David Liska, Ram Weiss, Sara E. Taksali, James Dziura, and Sonia Caprio. Department of Pediatrics, General Clinical Research Center, Yale University School of Medicine, New Haven, Connecticut.

The prevalence of insulin resistance and type 2 diabetes mellitus (T2DM) in obese children and adolescents is growing at an alarming rate, especially in ethnic minorities. It is not clear whether young people of different ethnic backgrounds vary in their metabolic response to excessive adiposity. Differences in lipid partitioning in the abdominal fat compartments have been observed among different ethnic groups. The aim of this study was to evaluate whether there are ethnic differences in intramyocellular lipid (IMCL) levels that are related to differences in insulin sensitivity. Eighty-two obese children and adolescents underwent 1) ^1H nuclear magnetic resonance (NMR) spectroscopy to non-invasively quantify IMCL levels in their soleus muscle, 2) an oral glucose tolerance test and (in a subset of subjects) a euglycemic-hyperinsulinemic clamp to assess insulin sensitivity, 3) a dual-energy X-ray absorptiometry (DEXA) scan to measure total percent body fat, and 4) magnetic resonance imaging to measure abdominal fat distribution. IMCL levels in Hispanic children and adolescents (1.50 ± 0.64 percent) were significantly greater than in their Caucasian (1.19 ± 0.40 percent) and African-American (1.09 ± 0.49 percent) peers. Visceral fat was significantly lower in African Americans ($42.7 \pm 18.8\text{cm}^2$) and were similar in Caucasians ($70.9 \pm 27.5\text{cm}^2$) and Hispanics ($77.3 \pm 41.9\text{cm}^2$). The three groups were not different with respect to insulin sensitivity. For the entire cohort, IMCL levels were inversely related to insulin sensitivity. There was a significant correlation between visceral fat and insulin resistance in Hispanics and Caucasians, but not in African Americans. In conclusion, these data suggest that there are significant ethnic differences in lipid partitioning in both the muscle and abdominal compartment. These findings may explain ethnic differences in insulin sensitivity and further the understanding of the pathogenesis of insulin resistance and T2DM.

Mega-Doses of L-Ascorbic Acid Alter the Antineoplastic Effects of Ionizing Radiation in Emt6 Cells *In Vitro*. Karina Ann Lund (Sponsored by Dr. Sara Rockwell). Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut.

Despite the common usage of high-dose vitamin C among breast cancer patients, the published medical literature is not in agreement as to how mega-dose vitamin C may interact with conventional therapy to affect clinical outcomes. The purpose of this study was to investigate the interaction of mega-dose vitamin C with radiation therapy and with doxorubicin in the treatment of breast cancer. Cultures of EMT6 mouse mammary tumor cells were treated concurrently with varying doses of vitamin C and either radiation or doxorubicin. A clonogenic assay was then performed to determine the surviving fraction of the cells. The surviving fractions of cells in cultures receiving different doses of vitamin C were compared among themselves, as well as with controls, and dose response curves were generated. Results show that ascorbic acid administered in concentrations of 1 mM or 10 mM four hours before x-irradiation protected the cells from radiation-induced cytotoxicity. The dose-modifying factors for 1 mM and 10 mM ascorbic acid as compared to controls were 1.23 and 1.37, respectively. These results support the hypothesis that mega dose vi-

tamin C, when taken concurrently with radiation therapy, protects cancer cells from the cytotoxic effects of ionizing radiation. No evidence was found to suggest that mega-dose vitamin C alters the antineoplastic effects of doxorubicin.

Dynamic Intervertebral Foramen Narrowing During Whiplash: A Biomechanical Study of Intervertebral Foraminal Narrowing During Simulated Automotive Head-forward and Head-turned Rear Impacts. Travis G. Maak, Paul C. Ivancic, Yasuhiro Tominaga, and Manohar M. Panjabi. Biomechanics Research Laboratory, Department of Orthopaedics and Rehabilitation, Yale University School of Medicine, New Haven, Connecticut.

The objective of this study was to quantify foraminal width, height, and area narrowing during head-forward and head-turned rear impacts and evaluate the potential for nerve root and ganglion impingement.

Muscle weakness and paresthesias, documented in whiplash patients, have been associated with neural compression within the cervical intervertebral foramen. Rotated head posture at the time of rear impact has been correlated with increased frequency and severity of chronic radicular symptoms, as compared to facing forward. No studies have quantified dynamic changes in foramen dimensions during head-forward or head-turned rear impacts.

Six whole cervical spine specimens with muscle force replication and surrogate head underwent simulated whiplash at 3.5, 5, 6.5, and 8 g, following non-injurious baseline 2 g acceleration. Continuous dynamic foraminal width, height, and area narrowing were recorded, and the peaks were determined during each impact and statistically compared to baseline narrowing. During head-forward rear impacts, significant increases ($P < 0.05$) in average peak foraminal width narrowing above baseline were observed at C5-C6, beginning with 3.5 g impact. No significant increases in average peak foraminal height narrowing were observed, while average peak foraminal areas were significantly narrower than baseline at C4-C5 at 3.5, 5, and 6.5 g. During head-turned rear impacts, significant increases ($P < 0.05$) in average peak foraminal width narrowing above baseline of up to 1.8 mm in the left C5-C6 foramen at 8 g were observed. Average peak dynamic foraminal height was significantly narrower than baseline at right C2-C3 foramen at 5 g and 6.5 g, while no significant increases in foraminal area were observed. Extrapolation of the present head-forward rear impact results indicated that the greatest potential for ganglia compression injury was at the lower cervical spine, C5-C6 and C6-C7. The present head-turned rear impact results indicated that the greatest potential ganglia compression injury exists at C5-C6 and C6-C7. Greater potential for ganglia compression injury exists at C3-C4 and C4-C5, due to head-turned rear impact, as compared to head-forward rear impact. Acute ganglia compression may produce a sensitized neural response to repeat compression, leading to chronic radiculopathy, following head-forward and head-turned rear impacts. Dynamic ganglion or nerve root compression may also lead to chronic radiculopathy.

Treating the Children of Bolivia Infected with Chagas Disease — A Cost-Benefit Analysis. Gregory A. Magee, Faustino Torrico, and Ravi Durvasula. Department of Internal Medicine, Veterans Affairs Medical Center, University of New Mexico, Albuquerque, New Mexico. (Sponsored by Michael Cappello, Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut).

The purpose of this study was to perform a cost-benefit analysis of an intervention to treat all the children in Bolivia (younger than 15 years of age) infected with Chagas disease. This research was carried out in La Paz, Bolivia, where the author lived for a year, collecting data in collaboration with the National Chagas Control Program, Bolivian Ministry of Health. Operational costs were based on current prices for laboratory testing and pharmaceuticals, average hourly wages for health care workers, and the number of children who would be treated. The benefit of the program was estimated as the sum of direct and indirect

costs associated with chronic cardiac disease caused by Chagas infection. Direct costs were calculated as the minimum amount needed for adequate medical treatment summed over the patients' life spans. Indirect costs were measured in Disability-Adjusted Life Years (DALYs) multiplied by average yearly salary to more fully account for the true burden of disease. Implementation cost was estimated to be approximately \$35 million. This intervention would prevent over 279,000 DALYs and alleviate \$123 million in direct and \$632 million in indirect costs. Clearly, such a program would be extremely cost-effective. Thus, with an initial investment of less than \$135 per infected child, approximately \$2,900 worth of future costs would be prevented, in addition to improvements in quality of life not captured by DALYs. A sensitivity analysis showed that even while assuming a high variability of the data, the cost and benefit of this intervention were significantly different (p -value < 0.001).

Health Status and Health Needs of Women and Girls Trafficked to Mumbai, India, for Sex Work. Ayonija Maheshwari and Jay G. Silverman. Department of Society, Human Development, and Health, Harvard School of Public Health, Boston, Massachusetts. (Sponsored by Kaveh Khoshnood, Yale School of Public Health, New Haven, Connecticut.)

Sex trafficking, recognized by the United Nations as a major human rights violation, disproportionately affects women and girls in Asia. To date, little research has investigated the health status and health needs specifically among sex-trafficked women and girls (STWG). This report will assess general and reproductive health concerns, including HIV prevalence among STWG recently rescued from brothels in Mumbai, India, and identify associations with age at trafficking and time spent in brothels. We hypothesize that among somatic complaints, reproductive health needs predominate and are largely unmet, with a positive association of HIV infection with young age at trafficking and longer duration in brothels.

One hundred ninety-five medical records of STWG rescued from various Mumbai brothels by a non-governmental organization (NGO) were retrospectively reviewed for demographics, trafficking experiences, and HIV status. All subjects indicated they had been tricked and/or forced into commercial sex work. Once rescued, they received a detailed health checkup by an NGO affiliated health care professional and were tested for HIV. Participants ranged in age from 9 to 30 years (mean age = 18.8 years, $sd = 3.3$ years). Age at trafficking varied from 8 to 29 years (mean age = 17 years, $sd = 3.4$ years). Twenty-nine percent of rescued STWG were married, 62 percent were illiterate, and an additional 20 percent indicated an education of grade six or less. Approximately half (51 percent) originated from India, 27 percent from Nepal, and 3 percent from Bangladesh. Of those indicating their length of time at the brothel, 22 percent had been there one month or less, 45 percent had been there for between two months to one year, and the remaining 33 percent had been at the brothel for a year or more. On average, women and girls provided services to 6.9 clients/day ($sd = 3.1$) averaging 8.9 hours ($sd = 2.9$) of work per day. Reproductive health concerns were the predominant health issues in this sample, accounting for 42.5 percent of all concerns; 29.2 percent of STWG were found to have urinary tract infections based on self-reported symptoms, while 11.8 percent complained of abnormal vaginal discharge. Over one quarter (25.2 percent) were found to be HIV positive. Women trafficked at younger ages were more likely to be found to have HIV ($p = 0.003$). Brothel duration was significantly associated with positive HIV status; a 3 percent increased risk of HIV was found for each additional month of brothel duration (OR = 1.03, CI = 1.01-1.06, $p < 0.05$).

There exists sparse knowledge on the health and health needs of STWG. These findings indicate large, unmet health needs and a high prevalence of HIV infection among sex trafficking victims; further, this risk appears to be exacerbated by young age at trafficking and increased brothel duration. Findings will be discussed in the context of related health needs of STWG with recommendations on the development of appropriate health management programs for this population.

Large, Single Institution Review of Prognostic Factors in Oligodendroglioma. Heather McKee. Yale University School of Medicine, New Haven, Connecticut.

Studies have demonstrated an association between loss of heterozygosity on chromosome 1p and chromosome 19q in oligodendrogliomas with both chemosensitivity and prolonged survival. This represents the first time genetic mutations have been utilized to guide clinical decision making. Studies also have found these genetic mutations to be associated with magnetic resonance imaging (MRI) features, including indistinct tumor borders on T1-weighted imaging, susceptibility effect, and mixed signal intensity. However, no study has yet demonstrated an association between imaging features and survival. We seek to confirm the clinical utility of known prognostic factors such as age and tumor grade while investigating the potential importance of imaging characteristics in predicting survival.

We conducted a large, single-institution retrospective chart review of patients with tissue diagnoses of oligodendroglioma. Pathology reports, allelic status studies, MR imaging, and survival information were reviewed. Survival curves, two-sided chi-square tests, and generalized linear models failed to reveal an association between survival and gender, age, tumor grade, allelic status, or imaging characteristics. We found no association between imaging characteristics and allelic status. The failure to confirm even well-accepted prognostic factors suggests limitations in the study, largely attributable to small sample size. This limitation was due to availability of necessary information, rarity of the tumor, and only recent availability of genetic testing. Further studies with larger populations need to be conducted to fully determine the prognostic utility of MRI features.

Hypoxic Regulation of VEGF and PAI-1 Expression by HIF-1 α and HIF-2 α in First Trimester Trophoblasts. Eliza Meade, Yuehong Ma, and Seth Guller. Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale University School of Medicine, New Haven, Connecticut.

Preeclampsia results from incomplete trophoblast invasion of the spiral arteries during early pregnancy. Vascular endothelial growth factor (VEGF) and plasminogen activator inhibitor-1 (PAI-1) are critical factors involved in angiogenesis, invasion, and hemostasis at the maternal-fetal interface. Both factors are transcriptionally regulated by hypoxia inducible factor (HIF), a heterodimeric complex consisting of HIF-1 β and either HIF-1 α or -2 α , whose specificity or redundancy in gene regulation is cell-type specific. This study uses siRNA technology to dissect the mechanisms of hypoxia-mediated regulation of PAI-1 and VEGF expression in first trimester trophoblasts. Immortalized first trimester human extravillous trophoblasts (HTR8/SVneo cells) were maintained in serum-free and serum-containing media for 4h (n=3-4), 8h (n=6), 24h (n=5), and 48h (n=5) under normoxic (21 percent O₂) and hypoxic (1 to 2 percent O₂) conditions to determine a time of maximum induction of both VEGF and PAI-1. Subsequently, cells were maintained for 48h in the presence or absence of siRNA for HIF-1 α , HIF-2 α , HIF-1 α + -2 α , a non-targeting (NT) sequence or Cyclophilin B (CB). Media were then removed, cells lysed, and Western blotting used to assess HIF- α knockdown. VEGF and PAI-1 levels in the media were quantified by ELISA and results expressed as pg or ng/ μ g protein. Results from three to eight independent experiments were analyzed using unpaired t-tests. Under hypoxic conditions, treatment of cells with HIF-1 α , HIF-2 α , or HIF-1 α + -2 α siRNA resulted in >90 percent HIF- α protein knockdown as determined by Western blotting. 48h of hypoxic treatment caused a statistically significant increase in PAI-1 levels (p<0.01) and VEGF levels (p<0.001) compared to normoxic controls. Under hypoxic conditions, PAI-1 levels were 4.75 \pm 0.46 ng/ μ g protein, and VEGF levels were 7.27 \pm 1.08 pg/ μ g protein. Treatment with siRNA to HIF-1 α , HIF-2 α , and HIF-1 α + -2 α significantly reduced PAI-1 levels to 3.3 \pm 0.35 (p<0.02), 3.1 \pm 0.38 (p<0.03), and 2.4 \pm 0.19 (p<0.003), respectively. No significant difference in PAI-1 reduction was noted between the three HIF siRNA conditions. Under hypoxic conditions, levels of VEGF in cells treated with siRNA to HIF-1 α (5.79 \pm 0.55), HIF-2 α (5.50 \pm 1.24), and

HIF-1 α + -2 α (4.24 ± 0.93) were reduced, compared to the hypoxic control (7.27 ± 1.08), yet these effects did not reach statistical significance. However, when compared with the levels observed in cells treated with NT siRNA ($9.90 \pm .98$), all HIF siRNA treatments promoted a significant reduction in VEGF expression ($p < 0.003$, $p < 0.02$, and $p < 0.003$ for HIF-1 α , HIF-2 α and HIF-1 α + -2 α , respectively). In conclusion, these results indicate that hypoxia-mediated changes in PAI-1 and VEGF expression in trophoblasts are regulated similarly by both HIF-1 α and HIF-2 α . This provides important insight into the molecular mechanisms regulating hemostasis and trophoblast invasion, as well as their potential dysfunction in pregnancies complicated by preeclampsia.

A Proposed Method for Noninvasive Assessment of Endothelial Damage.

Kirsten A. Menn, Robert B. Schonberger, William L. Worden, Kaveh Shahmohammadi, Tyler J. Silverman, Robert Stout, Kirk Shelley, and David G. Silverman. Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut.

Transdermal microvascular studies of endothelial cell function typically have used iontophoresis to facilitate acetylcholine absorption, but iontophoresis introduces an important confounding stimulus that can alter the behavior of the microvasculature. This study examines a non-iontophoretic technique for transdermal microvascular studies using acetylcholine and nitroglycerin and demonstrates a relatively impaired vasodilatory response to these substances in a population with known microvascular pathology.

Ten subjects without known vascular disease or diabetes were recruited for laser Doppler flowmetry (LDF) monitoring. Topical acetylcholine chloride, nitroglycerin, and placebo were applied to subjects' foreheads directly below LDF probes. Readings increased by averages of 406 percent (245 percent to 566 percent) and 36 percent (26 percent to 46 percent), respectively, at the acetylcholine and placebo sites ($p = 0.005$ by Wilcoxon Signed Rank Test (WSRT)); and they increased by 365 percent (179 percent to 550 percent) at the nitroglycerin site ($p = 0.005$ by WSRT vs. placebo; $p = 0.6$ vs. acetylcholine).

Ten diabetic subjects also were monitored. Mean percent increases in blood flow were 156 percent (91 percent to 221 percent) and 116 percent (79 percent to 153 percent), respectively, at the acetylcholine and nitroglycerin sites, vs. 21 percent (CI 4-37 percent) at the placebo site ($p = 0.005$ by WSRT for placebo vs. each active site). Diabetics' responses at both active sites were significantly impaired relative to healthy subjects ($p < 0.001$ and $p = 0.009$, respectively, by Mann-Whitney U Test).

Topical acetylcholine and nitroglycerin induced significant local vasodilatory responses without requiring iontophoresis in both healthy and diabetic subjects. Diminished responses were noted in diabetic patients. This technique may constitute a minimally invasive way to interrogate the microvasculature, including its responses in various disorders and the microcirculatory changes induced by therapeutic interventions.

The Impact of High Density Lipoprotein Cholesterol on Five-Year Mortality Outcomes in Older Adults.

Lisa M. Millman, Yun Wang, and Joanne M. Foody. Department Of Internal Medicine, Yale University School Of Medicine, New Haven, Connecticut.

The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) guidelines have defined a high-density lipoprotein cholesterol (HDL-C) of < 50 mg/dL in women and < 40 mg/dL in men as a risk factor for cardiovascular disease. Our research aim was to examine the relationship between untreated HDL-C levels below this recommended level on five-year cardiovascular, stroke, and all-cause mortality in adults over 71 years of age.

The Established Populations for Epidemiologic Studies of the Elderly (EPES) is a prospective cohort study of community dwelling adults over 65 years of age in East Boston,

Massachusetts; Iowa and Washington counties, Iowa; New Haven, Connecticut; and Durham, North Carolina. The National Institutes of Aging (NIA) started EPESE to study health, social, psychological, and economic aspects of older adults' lives through extensive annual interviews. The EPESE dataset is further enriched by serum measures, including low-density lipoprotein cholesterol (LDL-C), HDL-C, total cholesterol, triglycerides, glucose, BUN, and creatinine, which were obtained at the sixth annual follow-up interview.

Our primary outcome was all-cause mortality, with secondary mortality outcomes of acute myocardial infarction (AMI), coronary artery disease (CAD) not AMI, and congestive heart failure (CHF). The mean age of our cohort was 78.7 years, with the majority being female (63.86 percent), white (88.15 percent), and married (52.80 percent). Just over half (52.07 percent) of our cohort met the criteria for low HDL-C as defined by ATP III. Chi square and Fisher exact tests were used to compare demographics (age, gender, race, marital status, and education), clinical variables (history of MI, cancer, diabetes, angina, smoking, and alcohol use), and functional variables (activities of daily living, gross mobility, and cognitive status) at baseline and five-year follow-up. Cox proportional hazard models were created, using a step-wise approach to assess the impact of low HDL-C on mortality.

Low HDL-C was not significantly associated with crude all-cause ($P = .413$), AMI ($P = .473$), CHF ($P = .259$), and stroke ($P = .345$) mortality. HDL-C was significantly associated with unadjusted CAD ($P = .033$) mortality. However, after adjustment for demographics, clinical, and functional variables, as well as the other blood values all outlined above, HDL-C was not associated with five-year all-cause, AMI, CAD, CHF, or stroke mortality with adjusted hazard ratios of (HR=1.03, 95 percent CI 0.90-1.18), (HR=1.09, 95 percent CI 0.70-1.71), (HR=1.33, 95 percent CI 0.91-1.92), (HR=1.07, 95 percent CI 0.63-1.81), and (HR=0.80, 95 percent CI 0.51-1.27), respectively.

In older community dwelling adults enrolled in EPESE, low HDL-C levels as stratified by current recommended guidelines (<50 mg/dL in women and <40 mg/dL in men) were not associated with increased risk of five-year cardiovascular, stroke, or all-cause mortality. HDL-C alone may have minimal effect on future longevity in older adults due to competing risk and co-morbid conditions. Further studies are required to determine whether the movement toward more aggressive lipid profile interventions specifically to raise HDL-C in older adults would prove beneficial in this growing segment of our population.

Quality of Life in Macular Degeneration Between Photodynamic Therapy and Pegaptanib Treatment Groups. Sara M. Nayeem and Ron Adelman, M.D., M.P.H. Department of Ophthalmology and Visual Science, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to examine quality of life (QOL) in age-related macular degeneration (AMD), particularly across photodynamic therapy (PDT) and pegaptanib sodium injection treatment groups.

Patients with AMD were either mailed or administered in person a modified version of the Visual Function Questionnaire (VFQ-25). Subgroup analysis of the VFQ-25 was performed per NEI-prescribed algorithms, and additional analyses regarding questions on treatment side effects were also performed. A two-tailed student t-test and mean were calculated for each treatment group, and correlations between visual acuity and subgroup outcomes were calculated. Correlations between the subgroup and treatment-related subgroup outcomes also were calculated to determine which QOL deficits might occur together. Multiple linear regression models were used to estimate the association between the overall QOL score and scaled visual acuity, age, gender, and treatment history.

Thirty patients were interviewed in person, and 41 patients returned the questionnaire by mail. Of those, 37 had been treated with PDT (10 also had received intravitreal triamcinolone acetate (IVTA) injections); 16 had been treated with pegaptanib; seven had been treated with both pegaptanib and PDT (two also received IVTA); and 25 had not received any of these treatments. The mean age was 79 years. Patients' lowest subgroup scores

were in perception of general vision (43.2) and in driving (50.8). The ocular pain subgroup yielded a mean score of 82.9 for the PDT group and 87.5 for the pegaptanib group ($p = .59$). The average vision worsening score for the first two weeks following treatment was 87.5 for the PDT group and 77.8 for the pegaptanib group ($p = .29$). The average mental health score for concerns related to treatments was 78.2 for the PDT group and 73.6 for the pegaptanib group ($p = .61$), while the average independence score related to treatment appointments was 86.1 for the PDT group and 87.5 for the pegaptanib group ($p = .92$). Strong positive correlations ($> .45$) were seen between general health and ocular pain, between treatment-related mental health and both overall QOL score and treatment-related vision worsening, and between numerous measures of visual function. The best predictor of overall QOL score was the near activities score. Age was moderately or weakly negatively correlated with multiple measures. Stepwise multiple linear regression analysis demonstrated that the square of SVA provided the most explanatory power for the overall QOL score, implying a non-linear relationship between visual acuity and QOL. None of the treatment modalities added explanatory power to the model when added to the square of SVA.

In conclusion, QOL, stress regarding treatment, and ocular pain did not differ between PDT and pegaptanib treatment groups. Decreasing visual acuity was associated most strongly with decreases in ability to perform near and distance activities, overall QOL, driving, and independence. Scales denoting worry and frustration about treatment did not demonstrate a strong relationship to visual function, implying patient concern about treatment across the visual acuity spectrum. A nonlinear relationship was seen between QOL and visual acuity.

The Prevalence of Undiagnosed Hypertension in Ambulatory Emergency Department Patients and Lack of Adequate Referral. Andrew Nerlinger and Karen Jubanyik. Section of Emergency Medicine, Department of Surgery, Yale University School of Medicine, New Haven, Connecticut.

OBJECTIVES: According to a WHO estimate, one in every eight deaths worldwide is due to high blood pressure (BP). The Emergency Department (ED) provides an opportunity to identify individuals with undiagnosed hypertension (HTN) and refer them for BP recheck. The study objectives were to quantify the population in need of referral for BP recheck and to determine the frequency of referral from the ED.

METHODS: A retrospective, structured chart review of all patients older than 18 seen in an urban adult ED over five days, excluding major trauma and pregnant patients was performed. Patients with any systolic BP (SBP) greater than 140 or diastolic BP (DBP) greater than 90 had the following collected: demographics, all BPs, history of HTN, use of BP medication, and disposition. Patients with elevated BP, no prior diagnosis of HTN or BP medication use, and who were discharged met criteria for referral. For patients in need of referral, HTN-specific discharge instructions or physician plans were noted.

RESULTS: Of 967 patients who met inclusion criteria, 339 (35.1 percent; 95 percent CI: 35 to 46 percent) had at least one elevated BP, with a mean maximum BP of 152.4/89.7. Of those, 45.4 percent were male and the mean age was 52.3 years. One hundred thirty patients, or 13.4 percent (95 percent CI: 11 to 16 percent) had severe elevation (JNC-7 stage 2 level): SBP greater than 160 or DBP greater than 100; 85.4 percent would have been identified as having elevated BP by initial measurement. One hundred thirty-seven patients (14.1 percent; 95 percent CI: 12 to 16 percent) required referral for a repeat BP measurement, and 39 (4 percent of all included patients) had a SBP greater than 160 or DBP greater than 100. Of the 137 patients in need of referral, two patients (1.5 percent, 95 percent CI: 0 to 3.5 percent) received computer-generated discharge instructions, and three (2.2 percent, 95 percent CI: 0 to 3.9 percent) had a documented plan for referral. No significant correlation existed between need for referral and age, sex, or maximum or triage BP.

CONCLUSIONS: One in seven patients discharged from the adult ED has elevated BP with no prior diagnosis of HTN and should be referred for BP recheck. Few of these pa-

tients were identified as needing referral or received appropriate discharge instructions. Eighty-five percent of patients in need of referral would have been identified by initial BP, which suggests that a screening and referral protocol could be initiated at triage.

The Physiological Effects of Hockey Protective Equipment on High Intensity Intermittent Exercise. Benjamin Noonan. Yale University School of Medicine, New Haven, Connecticut.

Ice hockey is a contact sport played in a cold environment, which leads to assumptions that players are not exposed to a thermal challenge. The purpose of this study was to test the hypothesis that the wearing of protective equipment during an exercise protocol designed to simulate a hockey game would induce a thermal challenge and lead to decrements in performance.

In order to test this hypothesis and qualify the physiological responses, subjects performed a standardized protocol performed on a stationary cycle ergometer in an environmental chamber set at typical (12°C) ice hockey ambient conditions. The simulation was performed twice; once while wearing cotton undergarments only (NP), and once while wearing cotton undergarments and the typical protective equipment worn during a hockey game (P). Work intensity during each trial was held constant and evaluated by examining mean power output (W), which was similar under both P and NP conditions (348.2 W vs. 352.08 W, $p < .05$) P vs. NP, respectively. Body (37.18°C vs. 36.58°C) and skin temperatures (34.12°C vs. 28.85°C) were elevated in P vs. NP, respectively ($p < .05$). Core temperatures (37.50°C vs. 37.41°C) displayed a trend toward being higher in P vs. NP particularly during the third period of simulation ($p = 0.053$). Sweat loss as a percent of body mass was greater in P vs. NP (2.57 percent vs. 1.18 percent, respectively $p < .05$), which led to an increase in plasma osmolality (287 vs. 283 mosmol/kg H₂O, respectively $p < .05$) working heart rate (83.7 percent vs. 78.8 percent of maximum heart rate), resting heart rate (63.4 percent and 55.9 percent of maximum heart rate), and urine specific gravity (1.026 vs. 1.017) for P vs. NP, respectively (each $p < .05$). The drop-off in power from pre- to post-simulated game was examined in both conditions by the use of five repeated maximal six second sprints interspersed with 24 seconds of recovery. The drop-off in both peak (12.0 percent vs. 0.2 percent) and mean power (14.5 percent vs. 2.7 percent) was greater in P vs. NP ($p < .05$). Plasma lactate concentration was higher following the simulated game in P vs. NP (9.64 vs. 5.96 mmol/L, $p < .05$) as was plasma norepinephrine (2274.0 vs. 1366.9 pg/ml, $p < .05$). The rating of perceived exertion increased by 30 percent to 53 percent in the P condition ($p < .05$), even though power outputs were equivalent.

The elevated body temperature and increased water loss appeared to increase glycolytic flux, which, when coupled with the consequences of thermal stress, reduced power output and led to the perception of elevated work intensities during the simulated game.

Intracranial Aneurysm as a Paradigm for the Genetic Analysis of Complex Human Traits. Ali K. Ozturk, Brian V. Nahed, Kaya Bilguvar, Mohamad Bydon, Fatih Bayrakli, Bulent Guclu, and Murat Gunel. Department of Neurosurgery, Yale University School of Medicine, New Haven, Connecticut.

The genetic analysis of complex human traits is hampered by its multifactorial nature, since potentially many genes are imparting a relatively small effect on the disease trait. This makes it considerably more difficult to identify these genes as compared to single-gene diseases, whereby the disease trait is attributable to only one locus, due mostly to the difficulties of carrying out robust linkage analyses.

Several strategies have been employed in order to overcome the obstacles of complex human traits, including the candidate gene, non-parametric, and parametric linkage approaches. Of these, the latter two enjoy the benefit of being genome-wide, while also carrying the potential of missing genes that impart slight effect on the disease trait, a weakness that the candidate gene approach may overcome to some degree.

Our approach to unraveling the complex genetics of intracranial aneurysms (IA) has been a blend of the parametric linkage approach, followed by a smaller-scale candidate gene approach in which genes within a linked interval are sequentially analyzed based on relevance. We are able to conduct the parametric linkage approach by identifying rare, outlier families — whereby the disease trait is ostensibly being passed on in an identifiable, Mendelian fashion — enabling us to set the parameters required to perform parametric linkage analysis.

Using this method on four of our largest families, we have achieved linkage to chromosomes 1p34-36, 11q24-25, and 14q23-31, exceeding the statistical threshold of significance. Importantly, the latter two loci also have been identified in a non-parametric linkage study in Japanese sib-pairs. Analysis of genes that lie in these regions is ongoing.

Uterine Arterial Embolization: Classification of Leiomyomas to Determine Predictors of Response. Trushar J. Patel, Sharon D'Heureux, and Michael J. Tal. Section of Interventional Radiology, Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study is to determine features of uterine leiomyoma on Magnetic Resonance Imaging (MRI) that identify predictors of response to Uterine Arterial Embolization (UAE).

MRI images were obtained before and after UAE in 35 women. These images were analyzed for uterine and fibroid size changes, along with fibroid border characteristics and location, for a total of 73 fibroids. Fibroids were classified as either smooth or lobulated, based on border appearance on MR imaging, to determine any differences in mean fibroid volume reduction post-embolization. The mean decrease in fibroid volume from pre-embolization to post-embolization was 48.1 percent \pm 28.6 percent (SD) ($p < .001$). No statistical difference was detected in the mean volume reduction between lobulated and smooth fibroids, 40.6 percent \pm 23.1 percent (SD) and 50.9 percent \pm 30.2 percent (SD), respectively, with a confidence interval [-25.1, 4.6, SEM 7.5, Df 71], single factor ANOVA ($F[1, 71] = 1.88$, $F_{crit} = 3.98$, $p = .17$). However, some difference was detected in the failure rate of lobulated vs. smooth fibroids to embolization, 5.0 percent and 9.4 percent, respectively, ANOVA ($F[1, 71] = .37$, $F_{crit} = 3.98$, $p > .1$), albeit at low statistical power. Also, no difference was detected in mean fibroid volume reduction between intramural, submucosal, and subserosal fibroids.

Thus, we introduced a novel characteristic by which to classify uterine fibroids based upon border appearance on MR imaging.

Effect of Soy Isoflavone and Soy Lecithin on Endothelial Function in Healthy Postmenopausal Women. Meg Pearson, Valentine Njike, Marian Evans, Martha Huxley, and David L. Katz. Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to assess the effects of soy isoflavone protein concentrate and soy lecithin on endothelial function measured as flow mediated dilation (FMD) of the brachial artery in healthy postmenopausal women. In this randomized, double-blind, placebo-controlled crossover trial, 25 subjects (mean age 61 years; BMI 25.46 kg/m²) were recruited from the general population of southwestern Connecticut. Subjects underwent endothelial function testing using high frequency ultrasound at baseline and following four weeks of each randomly assigned treatment with intervening four-week washout periods. Treatment assignment included: soy isoflavone protein (SP, 25 g/day) or soy lecithin (SL, 20 g/day) alone with placebo for the alternative treatment; both active treatments; or double placebo. Main outcome measures were endothelial function, assessed as flow mediated dilation (FMD) of the brachial artery, and serum lipids.

Twenty-two women completed the trial. Baseline FMD (pre-treatment FMD) was 8.60 \pm 7.20. No statistically significant ($p > 0.05$) difference was seen in FMD between treatment

assignments. A trend was suggested, however, with FMD highest after treatment with both soy protein and lecithin (7.50 + 9.85), followed by soy protein and placebo lecithin (5.51 + 10.11), placebo protein and soy lecithin (5.35 + 6.13), and lowest after double placebo (4.53 + 7.84). Soy isoflavone protein and soy lecithin significantly ($p < 0.05$) increased HDL/LDL relative to baseline value (soy isoflavone protein and soy lecithin, 0.64 ± 0.19 ; soy isoflavone protein and placebo lecithin, 0.58 ± 0.17 ; placebo protein and soy lecithin, 0.65 ± 0.18 ; baseline, 0.49 ± 0.15).

In this sample of healthy postmenopausal women, soy isoflavone protein and soy lecithin significantly improved the lipid profile. A favorable influence on endothelial function by soy isoflavone and soy lecithin was suggested but could not be confirmed statistically, possibly due to small sample size, timing of testing, dose, or delivery vehicle. Although soy protein consumption is generally recommended as part of a heart-healthy diet, its favorable effects on cardiovascular disease risk factors such as endothelial function and lipids have not been consistently demonstrated in clinical trials, and further investigation into its effects on specific cardiovascular outcomes is necessary before a substantial cardio-protective role for soy protein can be asserted.

Prevalence and Predictors of Chronic Liver Disease in an Urban HIV Population. Sunanda M. Pejavar, Timothy J. Henrich, Naudia Lauder, Nicole Forbes, Krystn Wagner, Jose Salvana, Sharon Weissman, Pamela E. Jackson, Amanda Durante, and Andre N. Sofair. Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Chronic liver disease (CLD) is a leading cause of morbidity and mortality in HIV-infected individuals. The purposes of this study were to determine the prevalence and etiologies of CLD in an urban HIV-infected population and to identify CLD risk factors. We conducted a retrospective chart review of 799 HIV-infected patients seen at four New Haven health centers from 2002 to 2003. We applied the New Haven County Liver Study definition to identify patients with CLD. Sixty-five percent were male, 44 percent were African-American, and 23 percent were of Hispanic ethnicity. The mean age was 45 years. Thirty percent had a history of alcohol abuse. Thirty-five percent reported injection drug use as their HIV risk factor. Heterosexual contact and men having sex with men (MSM) were reported in 31 percent and 16 percent of cases. Fifty percent of patients had a diagnosis of AIDS. Sixty percent of patients had CLD. Over 50 percent of cases of CLD were attributed to chronic hepatitis C (HCV), either alone or with coexisting alcoholic liver disease. Alcoholic liver disease alone, hepatitis B virus (HBV), HAART-induced liver disease, and non-alcoholic liver disease (NAFLD) accounted for smaller percentages. Eighty-four percent of patients were on HAART, but only 3.6 percent of patients with positive HCV or HBV serologies were on treatment for CLD. Seventy-five percent of patients received pneumococcal and influenza vaccines, but only half of eligible patients received hepatitis A and B vaccines. In multivariate analysis, alcohol abuse and positive HCV status were associated with CLD. CLD is prevalent in our population. Preventive care and treatment for CLD are being overlooked in many people. Vaccines, treatment for viral hepatitis, and strategies for reducing drug and alcohol abuse are priorities.

Blood Pressure Changes During Weightlifting. Huy Phun, Kaveh Shahmohammad, Tyler J. Silverman, Robert Schonberger, William Worden, Robert G. Stout, John Elfteriades, and David G. Silverman. Department of Anesthesia, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to determine the degree to which noninvasive measurement of blood pressure (BP) taken after discontinuation of weightlifting underestimates the peak systolic BP attained during lifting. Abrupt changes in BP during such acute resistive challenges may be missed by intermittent BP measurements.

In this study, 11 healthy volunteers aged 21 to 32 underwent noninvasive monitoring while performing leg thrusts to 100 percent of their body weight. With the subject in lifting position, baseline measurements of heart rate (HR) and BP (via automated BP cuff over a brachial artery) were obtained; ultrasonic transducers were placed over both brachial arteries. The automated cuff was removed, and manual BP cuffs were placed over both brachial arteries and inflated to 50 and 100 mmHg above the baseline systolic BP. Once loss of ultrasound signal was confirmed, subjects began lifting until fatigued. If there was breakthrough by ultrasonic signal, the cuff was inflated an additional 100 mmHg; the subject continued lifting until breakthrough was again detected. The peak cuff inflation pressure at which breakthrough occurred was recorded. Immediately after fatigue, an automated BP was obtained. The peak changes during lifting were compared to those of the post-lifting measurement. Data were expressed as mean \pm SD; interphase differences were assessed with paired t-test.

Systolic BP increased from a baseline mean of 117 ± 11 mmHg to 272 ± 26 mmHg during lifting ($p < .001$) and returned to 133 ± 11 mmHg after lifting ($p < .001$). HR was 67 ± 7 beats/min at baseline and increased to 121 ± 9 beats/min during lifting ($p < .001$). The data indicate that during resistive challenges such as weightlifting, there are marked changes in BP that rapidly abate once the challenge is discontinued. This may have important implications during exercise, e.g. weight lifting and in acute care settings. Monitoring the pulse distal to an occlusive cuff constitutes a simple, noninvasive method to document the changes.

A Human Rights Approach to HIV Testing. Rahul Rajkumar (Sponsored by Kaveh Khoshnood and Robert Burt). Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut; Yale Law School, New Haven, Connecticut.

This paper describes the ethical, legal and public health implications of routine HIV testing — that is, testing such that individuals receive a routine offer of an HIV test whenever they come into contact with the health care system. In recent months, the broad international consensus in favor of voluntary testing has yielded to a debate over whether both our efforts to curb the spread of HIV and individual patients themselves would be better off if testing were initiated by health care providers. This paper argues in favor of routine provider-initiated testing. Specifically, I argue that the benefits of routine provider-initiated HIV testing both for individual patient as well as for the public health weigh heavily in favor of shifting to routine testing, provided that certain conditions are met. Routine testing must be coupled with a promise of antiretroviral treatment for those who test positive and meet the clinical criteria for treatment. Moreover, routine testing also must be coupled with a guarantee of confidentiality as well as a rigorous standard for informed consent. I argue that, if these conditions are met, it is possible to design a fair, equitable, and non-coercive testing regime that protects the human rights principles of autonomy, confidentiality, and volunteerism.

This paper first describes the history of HIV testing policy both in the United States and internationally. It outlines the arguments in favor of routine provider-initiated testing and responds to the objections to routine testing that have been raised in the literature. Finally, it describes a proposal for an ethical routine testing regime that is consistent with both human rights principles as well as U.S. and international statutes and case law on testing. This paper also proposes model legislation that addresses the issues of counseling, confidentiality, and informed consent in context of routine-offer HIV testing.

The Role of Ectopic Lymphoid Tissue in Allograft Rejection. Michael Reel^a, Isam Nasr^a, Nancy H. Ruddle^b, and Fadi Lakkis^a. ^aDepartment of Medicine and Section of Immunobiology; and ^bDepartment of Epidemiology and Public Health and Section of Immunobiology, Yale University School of Medicine, New Haven, Connecticut.

The location of the immunologic response to an allograft is not known with certainty. However, organized collections of T cells, B cells, and antigen presenting cells have been

found in peripheral tissue, in close proximity to organs undergoing rejection. It is hypothesized that this tertiary lymphoid tissue may be a location in which activation of lymphocytes can occur, leading to rejection of an allograft. We report here that in a splenectomized aly/aly mouse, which is devoid of secondary lymphoid organs and will normally fail to reject an allograft, the presence of tertiary lymphoid organs is associated with graft rejection. We additionally find that tertiary lymphoid organs can act as lymph nodes and can support effector and memory allograft rejection responses. It is demonstrated that ectopic lymphoid tissue in aly/aly mice will support the multiplication and transformation of transferred naïve CD4 and CD8 T cells into cells that display phenotypic markers characteristic of effector and memory lymphocytes. These results demonstrate that ectopic lymphoid tissue is associated with the loss of immunologic ignorance and is sufficient to enable graft rejection. This suggests that allograft rejection may take place within ectopic lymphoid tissue and that techniques to interfere with the development of this tissue might offer a therapeutic approach to preserving organ allografts.

Post-Operative Concurrent Chemoradiation with Mitomycin-C for Advanced Head and Neck Cancer. Amar N. Rewari, Lynn D. Wilson, Yung H. Son, John K. Joe, Douglas A. Ross, Rose J. Papac, Clarence T. Sasaki, James J. Fischer, and Bruce G. Haffty. Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut.

Purpose: Recent prospective randomized trials have shown concurrent chemoradiation improves local-regional control in post-operative patients with squamous cell carcinomas of the head and neck (SCCHN) using cis-platinum-based regimens. This report pools data from three randomized trials performed at Yale that employed mitomycin-C (MC), selecting those patients treated postoperatively, to evaluate the long-term benefit of MC in the postoperative setting and compare these results with other recently published randomized trials.

Methods and Materials: Between 1980 and 1999, 331 SCCHN patients from the three prospective trials were enrolled. Of those patients, 205 were post-operative, of which 103 were randomized to receive mitomycin-C and radiation, while 102 received radiation alone or radiation with porfirimycin in the third trial. Patients were treated with daily radiotherapy to a total median dose of 60 Gy over 47 days. Patients who were randomized to MC received 15 milligrams per square meter (mg/M²) of mitomycin-C on days five and 47 (or last day).

Results: The five-year rate of local-regional control was higher in the MC arms (85.3 percent vs. 69.9 percent, $p = .008$). There was no statistically significant difference in overall survival or distant metastasis. Patients had a lower percentage of high risk factors in both arms of the study, compared to patients of the large prospective trials, including positive margins, two or more positive lymph nodes, or oropharynx primary. The gains in local-regional control realized with MC were similar to the improvements in the recently published randomized trials using cis-platinum.

Conclusions: These results confirm significant gains in local-regional control using concurrent chemoradiotherapy in the postoperative setting for patients with SCCHN. The lack of consensus over a benefit in overall survival and distant metastasis emphasizes the need for further prospective trials in the postoperative management of SCCHN.

Periodontal Disease and Preterm Delivery: Results of a Pilot Patient Education and Intervention Feasibility Study. Brenda M. Ritson, Susan Richman, and Shera Sims. Yale University School of Medicine, New Haven, Connecticut.

Background: In the United States, there are over 470,000 babies born preterm each year. Despite the extant body of literature outlining risk factors and possible interventions, the preterm birth rate has remained unchanged over the last 30 years. A potentially treatable

etiologic risk factor that has been recently identified is maternal periodontal infection. In view of the persisting prevalence of preterm birth and its negative economic impact on the health care system, it is important to identify and test prevention and intervention methods in an effort to reduce the preterm birth rate.

Methods: A prospective observational cohort study was undertaken with the goal of testing an interdisciplinary patient education and treatment intervention model to determine its feasibility and potential efficacy in an at-risk population of patients. Fifty-two women were enrolled during their first trimester of pregnancy. Each enrollee was offered patient education, a dental evaluation, rooting planning and scaling as needed, and dental hygiene supplies for the duration of their pregnancies. An overall periodontal and oral health score was determined, and maternal demographic, prenatal, intrapartum, delivery, and neonatal and postnatal outcome data were obtained and recorded. Matched de-identified control data were obtained from a concurrently active March of Dimes-funded prospective observational study of perinatal risk factors.

Results: Twenty-four of the 52 women enrolled in the study attended their dental evaluation clinic appointments. Six women were excluded from analysis for various reasons, and the remaining 22 enrollees did not attend their dental evaluation appointments and were followed as a group named “intention-to-treat.” Two (8.3 percent) of the women in the treatment group delivered preterm, while three (13.6 percent) of the women in the intention to treat group delivered preterm. No women in the control group delivered a baby preterm.

Conclusions: The poor compliance of the enrollees to attend additional appointments for dental care suggests that the model of interdisciplinary patient education and treatment intervention model suggested in this study was not appropriate for the at-risk population of women seeking treatment at Yale-New Haven Hospital’s Women’s Center.

The Effects of Post-Traumatic Stress Disorder on Pregnancy Outcomes. Shari S. Rogal, Megan Smith, Karalee Porschman, Kathleen Belanger, and Kimberly A. Yonkers. Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to determine the effect of post-traumatic stress disorder (PTSD), diagnosed prospectively during pregnancy, on the occurrence of low birth weight (< 2500 grams) and pre-term delivery (< 37 weeks gestational age). A cohort of 1,362 women was recruited from prenatal care visits and screened for depression, panic disorder, PTSD, and substance use. Current episodes of PTSD were assessed using the MINI International Neuropsychiatric Interview. Pregnancy outcomes were abstracted from hospital records after delivery, and the data were analyzed using logistic regression. Two hundred sixty-two women (33 percent) were lost to follow-up due to unavailable medical records, leaving 1,100 women in the final analyses. Among those, 31 (3 percent) were found to have PTSD during pregnancy. Substance use in pregnancy, panic disorder, major and minor depressive disorders, and prior pre-term delivery were significantly associated with PTSD in the sample, while age, language spoken, and race were not. Low birth weight (LBW) was present in 6.5 percent of sampled women and was not significantly associated with a diagnosis of PTSD in pregnancy when adjusting for potential confounders. However, LBW was significantly associated with minor depressive disorder OR = 1.82 (CI = 1.01, 3.29). Pre-term delivery occurred in 7.0 percent of those without and 16.1 percent of those with PTSD ($p = .055$). Because prior pre-term delivery data were not available for 33 percent of women with PTSD, this variable was included only in secondary analyses. However, the association between PTSD and pre-term delivery depended on this variable, with OR = 2.82 (0.95, 8.38) before controlling for prior pre-term delivery and OR = 3.35 (1.04, 10.85) after controlling for prior preterm delivery. These data suggest that a possible association of PTSD and pre-term delivery was limited by the low rates of PTSD in this cohort and the inability to control for all confounders. Taken together, these findings provide limited support

for the hypothesized association between PTSD and pre-term delivery and no support for an association of PTSD with LBW.

The Effects of Menstrual Phase on the Response of Cutaneous Microvasculature. Margaret Rose, Robert Schonberger, and David Silverman. Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut.

Estrogen is well-known to protect against cardiovascular disease in women. In addition to improving lipid metabolism, it also decreases vascular resistance and enhances vascular reflexes, thereby improving vasomotor stability and increasing the arterial capacity for dilatation. Laser Doppler flowmetry (LDF) has demonstrated these changes in research trials and is emerging as having potential application in many clinical and surgical situations. In this study, our aim was to examine the impact of estrogen upon baseline blood flow as well as the response to vasodilatory interventions and to further evaluate the utility of laser Doppler as a clinical non-invasive measurement of blood flow in such contexts. We compared blood flow in the forehead cutaneous microvasculature of women during both high and low estrogen states of their menstrual cycle and compared this to the flow in male subjects. To evaluate differences in vascular reactivity, we subjected the microvasculature to two challenges: the cutaneous application of nitroglycerin to the site of the probe and transient occlusion of flow to evince a hyperemic response. Furthermore, to investigate the reproducibility of laser Doppler data, we examined both temporal and spatial variability and used each subject as his or her own control. We found significant spatial variability in the LDF measure of baseline flow rates. Temporal variability also was seen within subjects but was decreased by using median baseline values. Hormone state in females did not significantly affect baseline flow, response to topical nitroglycerin, or hyperemic response to occlusive pressure. In males, the difference between session one and session two LDF readings was not significant.

Although LDF has potential clinical applications, the clinical scenarios and patient populations must be further defined. Furthermore, the most practical technique with consistent reproducibility must be developed.

Differential Endogenous Estrogen Exposure Influences Prefrontal Cortex Response to Acute Stress. K.B. Rubinow, R.M. Shansky, and A.F. Arnsten. Department of Neurobiology, Yale University School of Medicine, New Haven, Connecticut.

The present study was conducted to determine the effect of differential endogenous estrogen exposure in rats on stress-induced changes in spatial working memory. Subjects comprised male ($n = 8$) and female ($n = 10$) Sprague-Dawley rats, which were trained to complete a T maze delayed alternation task. Performance was scored as a percentage of trials during which the correct maze arm was selected. Subjects' scores were recorded after one and two hours of restraint stress, as well as after one hour of unimpeded movement in a cage placed in the testing room. Restraint stress was effected through physical confinement within plastic, cylindrical tubing. Female subjects underwent each of the testing conditions twice, during periods of high and low endogenous estrogen exposure, as ascertained by microscopic examination of vaginal epithelial cells for estrous cycle stage determination. Females in proestrus (elevated endogenous estrogen exposure) subjected to one hour of restraint performed significantly worse than their baseline scores ($p = .0017$) or females in estrus (low endogenous estrogen exposure) after one hour of restraint ($p = .00014$). After one hour of restraint, females in proestrus also committed an increased rate of perseverative errors compared to females in estrus, although this increase did not achieve statistical significance ($p = .06$). No appreciable differences existed among subject groups in baseline performance or subsequent to two hours of restraint stress. Resultant data indicate impaired working memory among female rats under conditions of stress in the context of elevated endogenous estrogen exposure. This study, then, suggests a potential synergistic effect of

stress and estrogen in compromising prefrontal cortex function and, therefore, may lend insight into the observed sex-related disparity in the incidence of major depressive disorder and other anxiety-related mood disorders.

Upregulation of Hypoxia-Inducible Genes in Endothelial Cells to Create Artificial Vasculature. Robert Brian Schonberger, Reed Hickey, and Frank Giordano. Cardiovascular Gene Therapy Program, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

This study explored the possibility that upregulation of hypoxia inducible factor-1 (Hif-1)-responsive genes in human umbilical vein endothelial cells (HUVEC) would promote and stabilize HUVEC formation into inchoate vascular beds within artificial collagen gels. This experiment was designed to explore the above possibility by sub-cloning Hif-1 α , the related chimeric construct Hif-1 α /VP16, and the marker gene dsRed into retroviral expression vectors, producing retroviral vectors containing these genes and stably transducing HUVEC using these retroviruses. Transduced HUVEC were to be observed in cell culture as well as after implantation into artificial collagen gels that have previously supported vascular bed formation by HUVEC. Our results show, preliminarily, that HUVEC transduced with Hif-1 α /VP16 go into cell-cycle arrest. Attempts to transduce HUVEC with Hif-1 α failed to achieve high enough transduction efficiency to determine the cells' angiogenic potential. This study concluded that more experiments need to be conducted to better characterize the effects of hypoxia-responsive gene upregulation in controlling HUVEC angiogenesis and cell-cycle signaling and that straightforward transduction of HUVEC by Hif-1 α /VP16 is probably not sufficient in itself to induce *in vitro* vascular bed formation.

Routine Anal Cytology Screening for Anal Dysplasia in an Ethnically Diverse Urban HIV Clinic. Hyman Scott, Joe Khoury, Brent A. Moore, and Sharon Weissman. Section of Infectious Disease, Department of Internal Medicine, Hospital of Saint Raphael, New Haven, Connecticut. (Sponsored by David Katz, Department of Epidemiology and Public Health, Yale University School of Medicine.)

Anal cancer, like cervical cancer, is associated with human papillomavirus (HPV) infection. HIV+ patients have a 38- to 60-fold increased risk of anal cancer compared to HIV- patients, prompting many to suggest routine screening given the success of cervical Pap screening. Our goal is to describe our experience with routine anal Pap screening, determine which patients are most likely to have abnormal results, if anal disease on physical exam is predictive of cytology, and correlate cytology with histology findings. Charts of all patients with an anal Pap followed at the Hospital of Saint Raphael HIV clinic were reviewed. Demographics, immune status, sexually transmitted disease history, cytology, and histology data were extracted from medical charts. Patients with an anal Pap between November 1, 2002, and November 30, 2004, were included. Those with an insufficient sample were excluded. Analysis was done using χ^2 for comparison of proportions and student t-test for continuous variables. Overall, 265/560 HIV+ patients had at least one anal Pap. Seventy-four of these 265 patients had an abnormal anal Pap. Mean age was 44 years, and 68 percent were men. Fifty-nine percent were African American, 34 percent white, and 17 percent Hispanic. Those with an abnormal Pap were more likely to be white ($p=.03$) and gay or bisexual men ($p=.02$). They were also more likely to have lower CD4+ nadir (142 vs. 223, $p=.005$) and CD4+ at time of anal Pap (353 vs. 497, $p<.001$). Those with an abnormal anal Pap also had more anal disease (30 percent vs. 9 percent, $p<.001$), history of warts (23 percent vs. 12 percent, $p=.02$) and herpes (35 percent vs. 22 percent, $p=.02$). Anal disease on physical exam had a sensitivity of 56 percent and specificity of 77 percent for abnormal cytology findings. On histology, two patients had anal intraepithelial neoplasia (AIN) I, two AIN II, three AIN III, and two squamous cell carcinoma in situ. There was no correlation between cytology and histology. Routine anal cytology screening is a feasible

tool to incorporate into an ethnically diverse HIV clinic for identifying precancerous anal lesions, a group that has been largely overlooked. Anal disease on physical exam is a poor predictor of abnormal cytology, and there was no correlation between severity of disease on cytology and histology. However, further follow-up study is required to determine the impact on morbidity and mortality.

Patterns of Resistance to Antiretroviral Therapy Among HIV+ Patients in Clinical Care. Akash D. Shah and Michael J. Kozal. Section of Infectious Diseases, Yale AIDS Program, Yale University School of Medicine, New Haven, Connecticut.

HIV-1 antiretroviral resistance has posed major challenges to treatment advances of the last decade. However, few studies have analyzed the prevalence and time trends of drug resistance among HIV+ patients on antiretroviral therapy followed longitudinally in clinical care. The purpose of this study is to determine the cumulative prevalence of HIV genotypic drug resistance and the dynamics of resistance development in HIV+ patients in care. We hypothesized that a greater than 5 percent increase in resistance would occur per six-month period and a greater than 15 percent increase in drug resistance would occur over 18 months.

This retrospective longitudinal study consisted of patients from the two largest HIV clinics in Connecticut who were enrolled in the Options Project Study from 2000-03. HIV+ patients were consented and enrolled in the resistance substudy. HIV genotypic resistance testing was done on plasma samples available for each patient at study baseline and at approximately six month intervals for 18 months. HIV viral load and resistance data were matched to behavioral and demographic data for each patient. Genotypic drug resistance was defined according to the International AIDS Society 2004 guidelines. The chi-square test for linear trends was used to assess resistance trends.

Three hundred ninety-six HIV+ patients enrolled in the study and had archived plasma available for analysis. The cumulative prevalence of drug resistance increased from 32.1 percent to 46.3 percent for patients with 18 consecutive months of data, 31.9 percent to 50.7 percent for patients with 12 consecutive months of data, and 30.2 percent to 41.3 percent for patients with six consecutive months of data.

During the period of study for this HIV+ patient care population, the cumulative prevalence of HIV genotypic drug resistance rose dramatically. The findings emphasize the need for addressing antiretroviral resistance in a clinical setting through physician education, reduction of transmission risks, regimen adjustments, newer agents, and utilization of genotype testing.

The Prevalence of Pain in the Medical Intensive Care Unit. Jennifer Hale Smith, Kathryn Engle, and Mark D. Siegel. Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

We sought to determine the prevalence of pain among patients in the Medical Intensive Care Unit (ICU) and compare patients' responses to questions meant to identify the presence and intensity of pain and adequacy of their pain control to those of their nurses and physicians. We prospectively studied patients admitted to the Medical ICU of a university teaching hospital. Each day, patients, nurses, and physicians able to respond to questions were asked if the patient was currently in pain, to describe its severity using a 10-point numeric rating scale (0=none, 10=most severe), and to state if control was adequate. Responses were compared for interviews of patients and caregivers. Patients were interviewed about their ICU experience post-ICU discharge. We found a prevalence of pain of between 44 percent and 46 percent in the ICU. Twenty-six percent of patients in pain reported inadequate pain control. When comparing patient and caregiver interviews, both nurses and physicians had low rates of detection of patient pain. Nurses detected patients in pain 48 percent of the time, while physicians correctly did so 73 percent of the time. Nurses were unable to correctly identify any of the 23 patients who stated their pain was inadequately controlled,

while physicians correctly identified three of the seven patients who reported inadequate pain control, for an accuracy rate of 43 percent. Over 50 percent of patients who recalled their ICU experience reported experiencing pain in the ICU. When matched with their ICU interviews, 35 percent of patients interviewed at follow-up were unable to accurately recall their reports of ICU pain. At follow-up, 98 percent of patients rated their overall ICU experience a median of 8 (IQR 7 to 10). We conclude that patients are experiencing considerable pain in the ICU, although the vast majority of patients believe their pain is adequately controlled. Often, nurse and physician caregivers are unaware of their patients' pain and whether it is adequately controlled. Over one-third of patients demonstrate poor recall of their ICU pain experience. The vast majority of patients rate their overall ICU experience very highly.

A Wait-and-See Prescription for the Treatment of Acute Otitis Media: A Randomized, Controlled Trial. Khoon-Yen E. Tay, Eugene D. Shapiro, M. Douglas Baker, and David M. Spiro. Section of Pediatric Emergency Medicine, Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

Acute otitis media (AOM) is the most common diagnosis for which antibiotics are prescribed for children in the United States. Previous trials evaluating an optional antibiotic prescription are limited and have significant limitations. None have evaluated an optional prescription in the urgent care setting. We conducted a randomized, controlled trial in an urban emergency department in which children aged 6 months to 12 years diagnosed with AOM were randomly assigned a "wait-and-see prescription" (WASP) or a "standard treatment prescription" (STP). Structured phone interviews were conducted four to six, 11 to 14, and 30 to 40 days after enrollment to determine the proportion of each group that filled the antibiotic prescription and outcomes related to the clinical course. Substantially more parents in the WASP group (N=138) did not fill the antibiotic prescription compared to the STP group (N=145) (62 percent vs. 13 percent; $P < 0.001$). There were no statistically significant differences between the groups in the frequency of subsequent fever, otalgia, or unscheduled visits for medical care. Within the WASP group, both fever (OR = 4.0, 95 percent confidence interval, 1.7 to 9.5) and otalgia (OR = 4.5, 95 percent confidence interval, 1.7 to 11.5) were associated with filling the prescription. The WASP approach substantially reduced unnecessary use of antibiotics in children and is a reasonable alternative to routine use of antimicrobials for treatment of AOM.

Cellular Oxidative Efficiency: A New Approach To Calculating Theoretical P/O Ratios. Douglas G. Walled. (Sponsored by Paul K. Maciejewski.) Magnetic Resonance Research Center, Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut.

For decades, the oxidative efficiency of cellular metabolism has been under investigation. After numerous reports of varied stoichiometric measurements, consensus in the literature has begun moving toward two currently accepted theoretical P/O ratios (the number of adenosine triphosphate (ATP) molecules formed for every oxygen atom consumed): 2.5 for NADH-linked substrates and 1.5 for FADH₂-linked substrates. It is shown here, however, that the currently accepted theoretical values are inappropriately calculated underestimates and that P/O ratios of real biochemical systems are variable.

The complete oxidative metabolism of glucose, beta-hydroxybutyrate, malate, pyruvate, and succinate, utilizing three different electron shuttles (or exclusive mitochondrial metabolism) and two different values of the H⁺/ATP ratio (4 and 13/3), is examined using a new method of analysis. Calculations are made within the rigid mathematical framework of linear algebra, relying on the Law of Conservation of Matter as a first principle.

Calculated P/O values from systems modeled after cell-free mitochondrial extracts ranged from 2.711 to 3.183, or 3.000 to 3.500 depending on H⁺/ATP ratios of 13/3 or 4/1, respectively. These estimates are within the range of measured values (1.07 - 3.73) but are

higher than the commonly accepted theoretical values of ~ 2.5 and ~ 1.5 for NADH and FADH₂-linked substrates, respectively. A new view of the P/O ratio as variable, based on specific details of molecular physiology, is offered as a potentially useful means for understanding variation in measured values of the P/O ratio reported in the literature.