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Thesis Abstracts — 2002

POSITIONAL CLONING OF THE CHROMOSOMAL TRANSLOCATION BREAKPOINT IMPLICATED IN HYPOPHOSPHATEMIC RICKETS. Felix Adler, John G. Greally, David C. Ward, Thomas O. Carpenter, and Richard P. Lifton. Department of Genetics, Yale University School of Medicine, New Haven, Connecticut.

Phosphate homeostasis is controlled by a complex but poorly understood interplay of hormonal and non-hormonal mechanisms. In recent years, the identification of several genes for certain congenital forms of hypophosphatemic rickets has led to the emergence of a fascinating phosphate regulating system. We describe a patient with a rare form of hypophosphatemic rickets who carries a de novo, balanced, t(9;13)(g22;q14) translocation. The finding of a sporadic translocation in concordance with a rare phenotype strongly suggests that the translocation is causal to the disease. We used fluorescence in situ hybridization (FISH) to physically map the translocation breakpoint to within 183 kb and 147 kb on chromosomes 9 and 13, respectively, and identified a number of interesting candidate genes in the vicinity of the breakpoints. We hypothesize that the translocation is disrupting a gene required for normal phosphate metabolism, either by direct physical disturbance or by other mechanisms that alter gene expression. While we have not demonstrated direct disruption of a candidate gene, this is being evaluated by molecular genetic means. As the study of affected individuals with cytogenetic abnormalities has proven to be a powerful approach to identifying disease-causing genes, we anticipate that this pursuit will result in the identification of a new factor involved in phosphate homeostasis and will increase our understanding of related metabolic disorders.

SURVIVAL OUTCOME OF PATIENTS WITH CERVICAL CARCINOMA TREATED BY THERAPEUTIC RADIOLOGY AT THE YALE CANCER CENTER FROM 1980-2000. Arash Steven Afari, David H. Kim, Susan A. Higgins, and Barry Matthew Kacinski. Department of Therapeutic Radiology, Yale Cancer Center, Yale New-Haven Hospital and Yale University School of Medicine, New Haven Connecticut.

The aim of our study was to assess the long-term overall survival and recurrence-free survival of patients treated with primary radiation therapy and to evaluate the impact of patient and treatment-related factors on treatment efficacy.

We performed a detailed retrospective analysis from patients treated from years 1980 to 2000 for 202 consecutive cervix cancer patients treated with primary external beam radiation therapy (EBRT) and two treatments of intracavitary radiation therapy (ICRT). The mean age at diagnosis was 58.9 years (range, 26 to 94 years). The histologic characteristics of the primary lesions included squamous cell carcinoma 170 (84.16 percent), adenocarcinoma 16 (7.92 percent), adenosquamous nine (4.46 percent), and other six (0.50 percent). Patients were staged with the use of Perez modification of the International Federation of Gynecology and Obstetrics (FIGO) staging system for primary cervical carcinoma. There were 46 (22.7 percent) stage IB, 22 (10.8 percent) stage IIA, 65 (32 per-
IMPACT OF FEDERAL BIOMEDICAL RESEARCH FUNDING ON THE GROWTH OF U.S. BIOTECHNOLOGY ClUSTERS. Vishal Agrawal (Sponsored by William D. White). Section of Health Policy and Administration, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut.

Much has been said about the biotechnology industry's potential to improve healthcare and develop state or regional economies. However, there is relatively little scholarship analyzing the local effects of forces underlying the sector's rapid growth. This study examines the correlation between non-profit biomedical research activity by metropolitan area (MA) and the size of the local biotech industry "cluster." A database of current (year 2000) and cumulative (1985 to 2000) dollars granted by the National Institutes of Health (NIH) to extramural non-profit biomedical research organizations was created and mapped to corresponding MAs. Another database of over 350 US-based, publicly traded biotech parent companies and subsidiaries focused on human therapeutics was created to assess cluster sizes. SA bivariate analysis of NIH funds versus public biotech employees was plotted for each MA that either has at least one research center with a minimum $10 million in NIH funding or a public biotech company (n = 70). A statistically significant correlation (p < .0001) is observed with an \( r^2 = 68 \) percent. When a single outlier (San
Francisco Bay area) is removed the $r^2$ increases to 87 percent. These data support the notion that federal funding to academic medical centers (AMCs) and other non-profit research institutes is among the primary drivers shaping local biotech sector growth. Inspection of the data suggests, as a hypothesis for future research, that growth may be higher in MAIs where mature "anchor companies" have emerged. These may be associated with their own spin-offs, independent of traditional industry-academia collaboration.

**TRANSPLANTATION AMELIORATES THE HYPERCOAGULABILITY OF END-STAGE RENAL DISEASE.** Fred Aslan, Jane C.K. Fitch, Rex L. Mahnensmith, and Amy L Friedman. Department of Surgery, Yale University School of Medicine, New Haven, Connecticut and Department of Anesthesiology, Baylor University School of Medicine, Houston, Texas.

It has been suggested that hypercoagulability associated with ESRD may be attributable to diminished circulating levels of antithrombin III (ATIII). Whole blood clotting and rheological assessment of blood, by thromboelastography (TEG) and Sonoclot (SCT) analyses, was performed on fresh specimens from four patient groups: control (C), hemodialysis (HD), peritoneal dialysis (PD) and well-functioning kidney transplant recipients (Txp). TEG indices included $r$ (rate of thromboplastin generation), $r+$ (coagulation time), Ang (rate of clot formation), MA (clot strength), LY30 and LY60 (percent fibrinolysis at 30 and 60 minutes). SCT indices included SonACT (activation time) and SonR (rate of fibrin formation). ATIII levels were collected and assayed subsequently.

|        | C (n = 20) | PD (n = 13) | HD (n = 21) | Txp (n = 20) | p value     |
|--------|-----------|-------------|-------------|-------------|-------------|
| MA     | 64.5 ± 5.4| 77.2 ± 4.2  | 73.4 ± 6.9  | 66.5 ± 13.8 | <.001<sup>A,B,D</sup>|
| Ang    | 68.3 ± 8.8| 74.1 ± 5.6  | 74.6 ± 4.7  | 64.1 ± 14.3 | <.006<sup>C,D</sup>|
| LY30   | 2.1 ± 1.8 | 0.7 ± 0.9   | 1.3 ± 1.3   | 1.5 ± 1.9   | <.036      |
| LY60   | 5.8 ± 3.8 | 2.5 ± 2.2   | 3.2 ± 2.7   | 3.4 ± 3.3   | <.014<sup>A</sup>|
| SonR   | 16.3 ± 4.3| 32.4 ± 16.9 | 33.5 ± 29.3 | 24.5 ± 7.8  | <.001<sup>B</sup>|
| SonACT | 118.8 ± 19.2| 145 ± 35.8 | 142.6 ± 41.9| 127.6 ± 24.9| <.019      |
| ATIII  | 84.6 ± 19.4| 69.7 ± 20.6 | 68.7 ± 22.0 | 70.4 ± 22.3 | <.049      |

TEG and SCT measure quantitative and qualitative platelet and coagulation factor function. ESRD patients manifest thrombotic tendencies by TEG, SCT, and ATIII levels. Txp appears to correct these values. Lowered levels of ATIII in both dialysis groups were not normalized post-transplant. It remains to be determined whether the benefits of transplant are attributed to platelet function or other coagulation factors.

**ELEMENTARY STUDENTS’ UNDERSTANDING OF THE COMMON COLD.**
Rupal V. Badani. Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

This study examines children's understanding of the causality, treatment, and prevention of the common cold. Using a standardized, developmentally-based, semistructured interview (ASK [AIDS (acquired immunodeficiency syndrome) Survey for Kids]), 800 children (43 percent Black; 38 percent White; 18 percent Hispanic; 48 percent
female) in kindergarten through sixth grade attending six public elementary/middle schools in New Haven, Connecticut, were asked open-ended questions about the causality, treatment, and prevention of the common cold. Responses were scored for factual content. With increasing grade level, a greater percentage of students mentioned contagion and germs as causes of the cold, medicine as a means of treatment, and avoidance of casual contact as a means of prevention. Further, even some of the youngest children demonstrated some factual knowledge of each of these three illness concepts. Common misconceptions were identified across all grade levels. These misconceptions did not decrease as children acquired more factual information about colds. Additionally, these misconceptions did not appear to stem from developmental constraints in children's ability to comprehend illness concepts, indicating that health education can and should begin early in school.

STRONG WORK: THE FORCES THAT SHAPE A MEDICAL STUDENT INTO AN INTERN. Brooke Carlisle Bailey. Section of History of Medicine, Yale University School of Medicine, New Haven, Connecticut.

The study investigates how a newly matriculated medical student is shaped by his medical school training into an intern. Which challenges are common to most, if not all, students? How do they shape the students? Autobiographical accounts of medical school written between 1976 and 1999 were examined, along with a comparable sampling of first-person accounts of medical school taken from non-authors. Challenges faced by multiple reporters from diverse backgrounds, locations, and times were identified and characterized. These were: the struggle to balance the empathetic urge to identify with the patient with the need to learn to identify with the medical team; fears of inadequacy, ignorance, and failure; and the uncomfortably uncertain role and constantly shifting status of the medical student.

THE EFFECT OF AN ER-SELECTIVE CALCIUM ATPASE INHIBITOR ON NASAL POTENTIAL DIFFERENCES IN CYSTIC FIBROSIS AFFECTED MICE. Naomi J. Balamuth (Sponsored by Marie E. Egan). Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

The aim of this study was to evaluate the effect of 2,5-di-(tert-butyl)-1,4-hydroquinone (DBHQ) on chloride transport in wild-type, heterozygote, and cystic fibrosis (CF) affected mice. It has been proposed that DBHQ by altering the ER calcium concentration, interferes with the ability of chaperone proteins to recognize ΔF508-CFTR as misfolded, thereby allowing escape of the misfolded protein to the cell surface. This study will contribute to a larger investigation that is evaluating potential therapeutic agents for cystic fibrosis.

Nasal potential difference studies were performed in wild-type, heterozygote, and cystic fibrosis affected mice prior to treatment with DBHQ. As has been previously reported, CF-affected mice displayed an increased nasal potential difference, reflecting an increase in sodium reabsorption. CF affected cells with a defective CFTR are incapable of secreting chloride; therefore, the apical membrane cannot depolarize in response to isoproterenol, and the nasal potential difference does not hyperpolarize. Wild-type, heterozygote, and CF-affected mice were treated with nebulized DBHQ and nasal potential difference studies were repeated. CF-affected mice showed normalized electrophysiologic parameters following treatment with DBHQ.
YOGA INTERVENTION FOR ADULTS WITH MILD TO MODERATE ASTHMA. Sandeep Bansal, Alyse Behrman, Elaine Rodriguez, Anna-Leila Williams, and David L. Katz. Yale Prevention Research Center, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to ascertain the effectiveness of yoga as adjunctive treatment for adult patients with mild to moderate asthma. A parallel group, randomized controlled trial, double-blinded to subjects and outcomes evaluators, was conducted. Subjects were randomly allocated to an Iyengar yoga treatment group or a control condition. Both yoga and control subjects attended twice-weekly training classes for four weeks, and were then asked to continue exercises on their own for an additional three months. Yoga subjects learned breathing techniques, postures, and meditation thought to be of benefit to asthmatics. Control subjects underwent a sham intervention consisting of stretching exercises. Outcome measures included rescue inhaler use, quality of life measured by the Mini Asthma Quality of Life Questionnaire (MiniAQLQ), forced expiratory volume in one second (FEV1), daily peak expiratory flow rate (PEFR) variability, and a composite symptom score. In interim results, six of 13 subjects randomized to yoga, and six of 15 subjects randomized to control were available at their first follow-up assessment. Preliminary analysis of these data found no significant differences between treatment groups in the outcomes of interest. Data from an additional 40 subjects will be needed before the final analysis may be conducted. Despite the lack of final results, this trial overcomes limitations of previous studies by presenting a design that controls for the placebo effect received by yoga subjects. Investigators may be able to benefit from such a design when conducting future studies.

CARDIAC MECHANICS AND FLOW IN TRANSMYOCARDIAL LASER REvascularization IN A MODEL OF CHRONIC ISCHEMIA. Hany S. Bdair, Donald P. Dione, James A. Arrighi, Xenios Papademetrix, Yihua Liu, Peter Borek, Spiros Condos, Robert S. Constable, James S. Duncan, Robert T. Constable, James S. Duncan, Robert Soufer, and Albert J. Sinusas. Section of Cardiology, Department of Medicine, Yale University School of Medicine, New Haven, Connecticut.

Transmyocardial laser revascularization (TMLR) has been employed as an alternative treatment for patients with coronary artery disease, however the mechanism by which patients improve remains poorly defined. A potential mechanical effect of TMLR was evaluated by measuring changes in regional flow and function in chronically ischemic dogs before and after TMLR. TMLR was performed with an excimer laser in dogs (n = 5) six weeks post ameroid implantation. Flow was assessed with dynamic N\textsuperscript{13} ammonia PET imaging at four and 11 weeks post ameroid implantation. Absolute PET flow was assessed in 24 myocardial segments at rest and during adenosine stress. Regional and global left ventricular (LV) function was assessed with ECG-gated cine magnetic resonance (MR) imaging 5 and 12 arks post ameroid implantation. Endocardial and epicardial 3-dimensional (3D) surfaces from the MR images were segmented using a semi-automatic algorithm. Radial strains (thickening) were derived using a 3D shape tracking algorithm, finite element analysis, and an anisotropic linear elastic biomechanical model for the same 24 myocardial segments. Prior to TMLR there was a reduction in the resting flow in ischemic (IS) regions (IS: 0.36 ± 0.05 ml/min/g; non-ischemic (NI): 0.45 ± 0.03 ml/min/g; p < .05), which improved at five weeks after TMLR (IS: 0.53 ± 0.08 ml/min/g; NI: 0.59 ± 0.07 ml/min/g; p < .05 vs. pre). TMLR also tended to increase adenosine flow in IS regions (pre-TMLR: 0.90 ± 0.2 ml/min/g; post-TMLR: 1.3 ± 0.4 ml/min/g; p = ns) and NI regions
(pre-TMLR: 1.6 ± 0.4 ml/min/g; post-TMLR: 2.0 ± 0.5 ml/min/g; p = ns). TMLR improved global LV ejection fraction (pre-TMLR: 33 ± 3 percent; post-TMLR: 38 ± 1 percent; p = .07), while LV enddiastolic volume remained unchanged. Prior to TMLR, there was a reduction in resting radial strain in the ischemic regions relative to the non-ischemic regions (IS: 0.12 ± 0.05; NI: 0.16 ± 0.03; p < .05). There was a non-significant increase in radial strain in the ischemic regions and non-ischemic regions at six weeks after TMLR (IS: 0.15 ± 0.04; NI: 0.20 ± 0.02; p = ns vs. pre). TMLR significantly improved resting PET flow in the ischemic region and also tended to improve global LV function and regional myocardial thickening.

AGREEMENT BETWEEN PHYSICIANS AND PATIENTS' FAMILIES ON PROGNOSTIC ESTIMATES IN THE CRITICALLY ILL. Premila Bhat and Mark D. Siegel. Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Decisions to withhold or withdraw care have become increasingly common in intensive care units (ICUs). Disagreements between physicians, patients, and surrogates on the value of ICU care may result in conflicts when discussing the merits of continued life-sustaining treatment. One potential source of disagreement is discord between physicians and surrogates on estimates of prognosis. To determine whether physicians and surrogates agreed on prognostic estimates we asked the surrogate and primary ICU physician for each of 40 critically ill patients admitted to the Medical ICU of Yale New-Haven Hospital to estimate the likelihood that the patient would survive to hospital discharge, 28 days, and six months. Answers were elicited in a yes/no format and as a predicted percentage of the likelihood of survival. There was significant agreement between physicians and families responses for all three endpoints for yes/no responses (survival to discharge: $\kappa = 0.7532$, p < .0001; 28-day survival: $\kappa = 0.6679$, p < .0001; 6-month survival: $\kappa = 0.7106$, p < .0001). However, discord occurred more frequently when defined as a 20 percent difference between percent-estimates (survival to discharge, $\kappa = 0.383$; 28-day survival: $\kappa = 0.4795$, p < .0002; six-month survival: $\kappa = 0.3921$, p = .002). Disagreement was not significantly related to whether physicians and families had discussed prognosis. When there was discord, surrogates were usually more optimistic than physicians. In five instances, families gave prognostic estimates equal to or more than 49 percent higher than physicians. Thus while physicians and families give generally concordant estimates, there is frequent disagreement that may cause conflict and drive treatment choices when decisions about life-sustaining therapy must be made.

SCHOOL-BASED INTERVENTIONS FOR THE TREATMENT AND PREVENTION OF CHILDHOOD OBESITY. Elizabeth M. Bird, Meghan O'Connell, and David L. Katz. Yale Prevention Research Center, Derby, Connecticut.

This paper examines school based interventions designed either to prevent or treat obesity with the goal of establishing the "best practices" to date. A search for relevant studies was performed using four databases: Pubmed (2000 to 2001), HealthStar (2000 to 2001), Embase (2000 to 2001), and Cochrane Library (2000 to 2001). Twenty-four studies meeting inclusion criteria were retrieved. Quality assessment was performed independently by two reviewers utilizing techniques from the Cochrane collaboration and The Guide to Community Preventive Services developed by the Centers for Disease Control. The literature searched revealed limited data on the effectiveness of school-based obesity
prevention and management. There is evidence to support the school-based promotion of increased vigorous activity and decreased sedentary behavior, in particular, decreases in television use, both as primary and secondary prevention efforts. There is no evidence to support the broad-based cardiovascular disease prevention efforts that have gained popularity over the past fifteen years. No generalizable conclusions can be drawn as to nutrition education, food service changes, or the importance of family involvement in school-based obesity management or prevention. There continues to be a need for well-designed interventions.

**CLINICAL AND BIOLOGICAL STUDIES ON NEUROCUTANEOUS MELANOSIS.** Diana Ivette Bojorquez, Mayra Alvarez-Franco, and Miguel Reyes-Mugica. Department of Pathology, Yale University School of Medicine, New Haven, Connecticut.

Neurocutaneous melanosis (NCM) is a rare and frequently lethal neurocristopathy characterized clinically by the presence of giant and/or multiple pigmented nevi involving the midline or scalp, associated with hydrocephalus, seizures, and other neurologic abnormalities. Melanocytes arise from a transient population of precursor cells that form at the neural crest. Histologically, there is an abnormal melanocytic proliferation involving the skin, meninges and/or central nervous system. The proliferating nevus cells feature variable phenotypes ranging from well-differentiated to highly atypical melanoma-like morphology. There are two genes related to familial melanoma development: CDK4 and p16. Germline mutations in p16 have been identified in approximately 50 percent of families with familial melanoma and are common in sporadic melanomas. Two mutations are known to date involving exon 2 of the CDK4 gene in melanoma families and in some sporadic melanomas without p16 mutations. This study was directed to explore the presence of these mutations in melanocytic lesions of patients with NCM. In addition, clonality analysis of the melanocytic proliferations was also attempted. Twelve patients, nine with confirmed NCM, a one-year old girl with a congenital nevus, whose sibling died with NCM, and a three-year old girl with pigment synthesizing malignant melanoma with penetration of the dura mater were included in our study. DNA was extracted from melanocytes of normal skin, nevi, brain lesions, and/or blood samples. PCR amplification and sequencing for the 3 exons of p16 were carried out. The R24C mutation of the CDK4 gene was evaluated by restriction enzyme digestion (the mutation creates a Stu I site). No mutations were found in either p16 or CDK4. Clonality analysis using the HUMARA gene essay was carried out successfully in two girls and showed a chromosome X-inactivation pattern consistent with a monoclonal (neoplastic) proliferation in melanocytic lesions of NCM patients. A larger series of NCM cases is required to confirm these results.

**THE PREDICTIVE ACCURACY OF PRE-ADOPTION VIDEO REVIEW IN ADOPTEES FROM RUSSIAN AND EASTERN EUROPEAN ORPHANAGES.** Jon L. Boone, Margaret K. Hostetter, and Carol Cohen Weitzman. Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

The major purpose of this study was to examine whether the assessment of pre-adoption video (pre-vid) by an experienced pediatrician accurately predicts the post-adoption developmental (post-dev) status of the adoptee on arrival and to examine any difference in the extent of developmental delay between those adoptees with and those without a pre-vid review. As a foundation for the study, an extensive database for all adoptees seen at
the Yale International Adoption Clinic was created and their demographic characteristics were analyzed.

The developmental status of 20 children from Russian and Eastern European orphanages was assessed by an experienced pediatrician using a pre-vid review while the post-dev status was evaluated by a developmental-behavioral pediatrician. Using the Denver Developmental II Scoring Test (pre-vid) and the Bayley Scale of Infant Development - Second Edition (post-dev), children were scored (0, 1, 2, or 3) to indicate the degree of developmental delay in fine motor, gross motor, and language domains. A control group of international adoptees was assembled on the basis of age, gender, length of time in orphanage, length of stay in the United States before developmental exam, and country of origin. The degree of post-dev delay in the cohort with a pre-vid was then compared to that of the control group without a pre-vid using a chi-square test and Fisher's exact test.

The Pearson r coefficient between the pre-adoptive video and post-adoptive developmental ratings indicated a significant correlation, r = 0.53 and two-tailed p = .01, between the two ratings. Chi-square and Fischer test analysis examining the extent of developmental delay between the cohort and control groups were not significant.

Although there is no significant difference in the extent of developmental delay between the adoptees who did and did not receive a pre-vid assessment, results of this study show that a video review by an experienced pediatrician predicts with statistically significant accuracy the child's developmental status after arrival.

**THE ROLE OF THYROID DYSFUNCTION IN UTERINE FIBROID GROWTH.**

Hyacinth N. Browne (Sponsored by Ervin Jones). Section of Reproduction Endocrinology and Infertility, Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut.

Uterine fibroids are the most common solid pelvic tumors in women and are present in 20 to 30 percent of reproductive-age women. They represent the single most common indication for hysterectomy. Although their origins remain a mystery, attempts have been made to show factors that may control their growth and size. This study attempts to ascertain an association between hypothyroidism and uterine fibroids possibly by a mechanism that results in increased uterine cell sensitivity to and uptake of estrogen. A case-control study was performed reviewing 351 medical records of women, over the age of 18, who were hypothyroid or euthyroid to ascertain how many of these women also had uterine fibroids. Results showed that more hypothyroid women were diagnosed with uterine fibroids compared to euthyroid women (16 versus six), however this finding was not statistically significant (p = .067). Moreover, black women with hypothyroidism had a higher probability of developing uterine fibroids compared to white women (p = .018 and .892, respectively). And, hypothyroidism was shown to be the most significant risk factor associated with uterine fibroids and was the strongest predictor of fibroids in this study (p = .017). Although a significant positive association between hypothyroidism and uterine fibroids was not established in this medical record review, thyroid hormone may play an indirect role in uterine fibroid growth necessitating further investigation.
THE EFFECT AND UTILITY OF COMPUTED TOMOGRAPHIC EXAMS ON THE DIAGNOSIS OF ACUTE APPENDECTOMIES. Jeffrey Bush, Leigh Evans, and Gail D'Onofrio. Section of Emergency Medicine, Department of Surgery, Yale University School of Medicine, New Haven, Connecticut.

Background: Numerous studies have examined the utility of abdominal computed tomographic examinations (CT) in the diagnosis of acute appendicitis. Several factors must be considered: the signs and symptoms of appendicitis, the diagnostic benefit of CT with contrast and without it, the negative appendectomy rate, and the appendicitis perforation rate. In 1998, Rao et al. recommended routine CT in patients suspected of appendicitis. Numerous other studies have found that CT scans are highly sensitive, specific, and accurate at diagnosing appendicitis. However, a recent study by Flum et al. found that CT scans do not improve the negative appendectomy rate or the perforation rate. The role of routine CT scans in patients with acute appendicitis is not clear.

Objectives: 1) To determine if the proportion of patients that had abdominal CT scans performed increased from 1996 to 1999. 2) To determine if this has resulted in the improvement of diagnosing appendicitis as measured by decrease in elapsed time from emergency department presentation to operating room, decrease in perforation, and negative appendectomy rates.

Methods: A retrospective chart review study conducted at two urban teaching hospitals from January 1, 1996, to December 31, 1996, and January 1, 1999, to December 31, 1999. Patients were included if they were 18 years old or greater and underwent an appendectomy. Operative logs were reviewed during these two calendar years for patients who underwent an open appendectomy, laparoscopic appendectomy, diagnostic laparoscopy, or abdominal exploratory surgery. Patients were excluded if: 1) they underwent incidental appendectomy during a procedure for other intra-abdominal pathology; and 2) abdominal/pelvic CT was performed prior to ED arrival. The patient's entire chart was reviewed. The data points collected included age, gender, whether or not the patient had a CT scan, elapsed time from emergency department presentation to operating room, negative appendectomy rate, and perforation rate.

Results: a group of 322 patients were included in the study. In 1996, 126 patients were included. The 1999 group had 196 patients. The groups were similar in terms of age and gender. In 1996, 37 patients (29 percent) had a CT scan performed prior to surgery compared to 125 patients (64 percent) in 1999 (p < .001). The patients, from both years, who did not receive a CT scan prior to surgery had a mean elapsed time of 7.6 hours from presentation to the emergency department to operation compared to 14.25 hours for the patients who had CTs performed (p < .001). The differences in perforation rates between years (28 percent vs. 22 percent) and negative appendectomy rates (11 percent vs. 14 percent) were not statistically significant.

Conclusions: There were more CT scans performed on patients undergoing an appendectomy in 1999 than in 1996. Patients who received a CT had a longer delay in going to the operating room. There was no significant difference in the perforation or negative appendectomy rates between the two study groups of 1996 and 1999.
EFFECT OF HIGH CARBOHYDRATE AND HIGH FAT MEALS ON 24-HOUR CIRCULATING INSULIN, LEPTIN, AND FREE FATTY ACIDS. James S. Castle, James Dziura, Allison Smitten, Mary Savoye, Barbara Teague, and Sonia Caprio. Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

The effect that macronutrients have on circulating leptin levels remains unclear. We studied the effect of a high carbohydrate and high fat diet on 24-hour circulating levels of leptin, as well as glucose, insulin, C-peptide, free fatty acids, and triglycerides in ten female adolescent subjects with a wide variety of BMI (19.8 to 37.2). Previous studies have suggested a role of circulating glucose in leptin release, but this relationship was not clearly known to be due to glucose, or to the insulin secretion associated with circulating glucose. We found that 24-hour circulating leptin levels were significantly higher during the high carbohydrate diet (p < .001). Although glucose was not significantly different during the two diet days (p > .1), insulin (p < .001) and C-peptide (p < .002) were higher during the high carbohydrate day. A significant relationship was found between daytime insulin levels (9 a.m. to 4 p.m.) and evening leptin levels (5 p.m. to 12 a.m.) during both diet days (r = .66, r = .48, p < .05, p < .05), but no relationship was found between daytime glucose and evening leptin during either day (r = .05, r = .05, p > .5, p > .5). This suggests that circulating insulin may be the driving force behind leptin, not circulating glucose. Free fatty acids were significantly higher during the high fat diet than the high carbohydrate diet. These results indicate that a high carbohydrate diet results in higher circulating leptin levels, and given leptin's inhibitory role on appetite and feeding behavior, lower short-term food intake. Furthermore, given the role of free fatty acids in insulin resistance, a diet high in fat may exacerbate short-term insulin resistance.

PHYSICIANS' ATTITUDES AND PRACTICES REGARDING THE CARE OF PATIENTS WITH CHRONIC NONCANCER PAIN. Anita R. Chandrasasena and M. C. Reid. Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Chronic noncancer pain (CNCP) is common in primary care and often treated with opioid analgesics, but information regarding primary care providers' (PCPs) attitudes and practices in the care of patients with CNCP is lacking. We determined PCPs prior training in CNCP and assessed their levels of comfort caring for CNCP patients, prescribing opioid analgesics, and diagnosing/managing opioid analgesic misuse (OAM).

Participants included resident physicians (RPs) and attending physicians (APs) at a primary care clinic affiliated with an urban teaching hospital. A self-administered questionnaire was used to obtain information on PCPs' demographic status, prior training in the management of CNCP and use of opioids. We measured PCPs' levels of comfort caring for patients with CNCP and prescribing opioid analgesics, and determined their self-rated ability to diagnosis OAM. Open-ended questions were used to ascertain how PCPs diagnose and manage OAM.

Of the 57 PCPs surveyed, 53 (93 percent) responded. A majority was male (54.7 percent), the mean number of years (range) since medical graduation was 4.3 (1 to 33) and 71.7 percent were RPs. A minority of PCPs reported high levels of comfort when caring for patients with CNCP (41.5 percent) or when prescribing opioid analgesics (30.2 percent). APs expressed greater comfort than RPs in both areas (66.7 percent vs. 31.6 percent, p = .020, and 53.3 percent vs. 21.5 percent, p = .021, respectively). Only 20.8 percent of PCPs rated their ability to diagnose OAM as high. APs were more likely to rate their ability to diagnose OAM as high when compared with RPs (40 percent vs. 18.4 per-
ASTROCYTE-DERIVED VEGF MEDIATES SURVIVAL AND TUBE STABILIZATION OF HYPOXIC BRAIN MICROVASCULAR ENDOTHELIAL CELLS IN VITRO. Jen Chow. Department of Pathology, Yale University School of Medicine, New Haven, Connecticut.

Chronic sublethal hypoxia has been associated with changes in neurovascular behavior, mediated, in part, by induction of vascular endothelial growth factor-A (VEGF-A165). In this report, we demonstrate that RBE4 cells (derived from rodent cerebral microvasculature), when cultured in three-dimensional collagen gels: 1) are induced to undergo increased tube formation in response to VEGF-A165 in a dose-dependent manner; 2) undergo apoptosis under mild hypoxic conditions; 3) are rescued from the effects of hypoxia by the addition of exogenous VEGF-A165 in a dose-dependent and inhabitable manner or by co-culture with primary newborn rat astrocytes, which are induced to express increased amounts of VEGF-A in hypoxic conditions. Further, we demonstrate that: 4) the observed astrocyte-produced, VEGF-mediated protection from apoptosis (survival) is inhabitable with soluble recombinant VEGF receptor-1 (sFlt), and is associated with a robust induction of MAPK tyrosine phosphorylation. These findings illustrate the importance of VEGF in the process of neurovascular survival in response to injury in developing brain and provide insight into the signaling pathways involved.

DOES HISTORY OF TRAUMA PREDICT HYPOTHALAMIC-PITUITARY-ADRENAL DIFFERENCES AS MEASURED BY CORTISOL AND DHEA AMONG HEALTHY INDIVIDUALS FOLLOWING EXPOSURE TO STRESS? Antony Fu-Chin Chu. Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut.

Stressful events have been associated with a wide range of physiological and psychological disturbances. It is generally believed that an individual's physiological and psychological response to stress is influenced by previous stress exposure. This belief has been based, in part, upon animal and clinical studies which have demonstrated behavioral and endocrine alterations associated with stress sensitization.
In mammals, the hypothalamic-pituitary-adrenal (HPA) response to stress is an essential adaptive mechanism. It is believed that alterations in HPA responsivity to stress play a fundamental role in the pathogenesis of posttraumatic stress disorder (PTSD).

The purpose of this study was to prospectively assess whether history of trauma influences HPA axis differences (as measured by cortisol and DHEA) in healthy individuals exposed to stress. Stress sensitization data in animal and clinical studies suggest that history of trauma will predict HPA axis upregulation in healthy individuals exposed to stress.

In order to investigate our hypothesis, the current study prospectively assessed the degree to which history of trauma would predict differences in HPA axis responses among healthy individuals exposed to stress. Specifically, this group of individuals was comprised of healthy soldiers without post-traumatic stress disorder participating in combat diver training (the Combat Diver Qualification Course [CDQC]). There were three principal findings of this study. First, recovery plasma cortisol levels were significantly higher in participants with a higher number of previously experienced traumas. Second, baseline and recovery DHEA levels were elevated in participants with a greater history of previously experienced trauma. Third, we did not observe a correlation between IES score and alterations in plasma cortisol or DHEA.

We conclude that history of trauma in healthy soldiers without PTSD is associated with HPA axis upregulation (as measured by plasma cortisol and DHEA) when exposed to stress (combat diver training).

**MECHANISM OF ESTROGEN’S TRANSCRIPTIONAL REPRESSION ON THE EXPRESSION OF CELL ADHESION MOLECULES IN HUMAN ENDOTHELIAL CELLS.** Emmanuelle Marie Clerisme. Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

The protective effects of ovarian steroid hormones on the development of cardiovascular disease are mediated, in part, through inhibition of immune and inflammation cascades involving the vasculature. We have previously demonstrated that engagement of the estrogen receptor (ER) represses cytokine-mediated transcriptional activation of endothelial cell adhesion molecule (CAM) genes. Using E-selectin as the model target CAM promoter and the human endothelial ECV304 cell line, we have performed a series of promoter induction experiments co-transfecting full or truncated E-selectin promoter-luciferase reporter constructs with full length or mutant ER expression constructs to identify the mechanisms by which estrogen mediates this inhibitory effect. Cells were estrogen deprived, transfected, estrogen or vehicle-treated, IL-1 induced and analyzed for luciferase.

Estrogen (10 ng/ml) inhibited IL-1- (20 U/ml) mediated induction of E-selectin luciferase promoter only in the presence of co-transfected ER. This 50 to 100 percent repression was abrogated by the ER antagonist, ICI 182780. Use of E-selectin promoter deletion constructs revealed that the critical target(s) of repression is contained within 126 base pairs of the transcription start site. Both full-length ERα and ERβ transfected receptors were capable of mediating repression. Expressed ERα lacking either N-terminal AF-1 transactivation or the hormone-binding domain (HBD) failed to reconstitute the inhibitory response. Kinetic analyses displayed a rapid (30 minutes) repressive effect of estrogen. However, electrophoretic mobility shift assays using an E-selectin promoter based oligonucleotide target containing the critical 3 NF-κB elements demonstrated that estrogen has no effect on cytokine-induced NF-κB nuclear translocation or DNA binding.
Taken together, these data demonstrate that ligand activation of an AF-land HBD intact ER rapidly induces posttranscriptional modifications and/or complex formations which do not effect NF-κB nuclear translocation, but do impact cytokine-mediated transactivation of a critical 126 bp region of the E-selectin promoter. This may represent one of the key mechanisms through which estrogen exerts its anti-inflammatory, protective effect on cardiovascular disease.

**KOSOVAR CHILDREN’S WARTIME DRAWINGS: GENDER, AGE AND PROXIMITY TO VIOLENCE AS CORRELATES TO CONTENT IN DRAWINGS.** Aaron S. Covey (Sponsored by Linda C. Mayes). Child Study Center, Yale University School of Medicine, New Haven, Connecticut.

Since Vietnam, there has been a shift in the way war has been fought, away from soldier vs. soldier combat and into civilian populated villages. The 1999 war in Kosovo is an example of a “new age” conflict. As a result, the children of Kosovo were exposed to a high level of war violence within their own villages which included or involved killings, beatings, thievery, stealing, rape, destruction of property, forced departure from home, separation from family, etc.... Hence, these children are at risk for PTSD and other psychiatric symptoms related to war stress.

This project systematically examines 516 drawings of Kosovar refugee children who were asked to “draw a picture of your village.” Using Chi-Square and logistic linear regression analysis, we determined the differences in feature content in the children's drawings according to three categories: age, gender and proximity (in time) to the war. Though theories relating drawing features and children's emotional state remain highly speculative, our data give us an understanding of the content of war and non-war items that a large war-exposed child population decided to draw.

Fifty-three percent of children drew war images, 44 percent drew hostile images, and 19 percent drew friendly images. Older and recently exposed children were more likely to draw war images. Older kids, boys, and recently exposed kids drew hostile images more frequently, whereas older kids and boys drew more friendly images. In comparison to girls, boys drew friendly images (all three) in greater proportion than hostile images (1/4). Older children drew more friendly images (2/3) vs. hostile images, as well (1/4). In contrast, New Campers were more likely to draw all four hostile images, and none of the friendly images. This may suggest that boys, kids more removed from war and possibly older children are more likely to use a positive coping strategy in dealing with the stress of war, as “us” images, which signify identification, rather than desolation.

**SURVEY OF INTERNATIONAL HEALTH TRAINING OPPORTUNITIES IN INTERNAL MEDICINE RESIDENCY PROGRAMS.** Marc A. Davis, Anu R. Gupta, Michele Barry, and Frank J. Bia. Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to assess opportunities and support for international electives during internal medicine residency training and to identify program factors associated with these opportunities. An 18-item survey of all 389 internal medicine residency program directors in the United States and Puerto Rico was conducted between June 2001 and April 2002. The survey response rate was 49 percent (191/389). International electives were offered by 45 percent (85) of responding program directors with an additional 48 (45 percent) program directors interested in offering these opportunities. Only 51 percent of
program directors offering international electives had formal international health programs. Residency program factors associated with offering an international elective include training at a university teaching hospital (p = .012), having a larger class size (p = .037), training residents in cultural awareness (p = .049) and alternative/complementary medicine (p = .001), and having a higher percentage of yearly outpatient training (p = .022). While less than half of internal medicine residency program directors offer their residents international electives, and these electives vary widely in how they are supported by the residency programs, many more express an interest in providing these opportunities, suggesting that the interest in international health training is not being met by corresponding opportunities.

**LIVER-SPLEEN SCINTIGRAPHY IN THE NON-INVASIVE DIAGNOSIS OF COMPENSATED CIRRHOSIS.** Michelle W Diu and Guadalupe Garcia-Tsao. Department of Internal Medicine, Section of Digestive Disease, Yale University School of Medicine, New Haven, Connecticut.

The detection of compensated cirrhosis is important for the early initiation of screening, prevention, and treatment of associated complications that carry high mortality. The aim of this retrospective study was to investigate the usefulness of the liver-spleen scan (LSS), in combination with laboratory markers, in the non-invasive diagnosis of compensated cirrhosis. A total of 14 variables (five LSS parameters: liver size, spleen size, colloid shift to spleen and/or bone marrow, liver pliability, and hepatic tracer distribution; eight laboratory markers: total bilirubin, albumin, alanine and aspartate transaminase [ALT, AST], alkaline phosphatase, prothrombin time, INR, and platelet count, and age), were collected for 110 patients divided into two groups: positive cirrhosis (METAVIR Stage 4) and negative cirrhosis (METAVIR Stage 0 to 3). Using liver biopsy as the standard for comparison, stepwise logistic regression analysis identified platelet count and the LSS parameters of left-lobe prominence and colloid shift to both the spleen and bone marrow to be most significantly associated with the presence of compensated cirrhosis. Based on these three variables, we calculated relative risks (RR) of compensated cirrhosis, ranging from 1 to 254.0, and constructed a simple RR table that stratifies patients into different risk groups according to platelet count and scintigraphic evidence of the two LSS parameters. From the receiver operating characteristic curve, we selected a RR cut-point of 45.0 that has a 95 percent specificity and up to 98.2 percent positive predictive value in the diagnosis of compensated cirrhosis. In conclusion, we found that liver-spleen scintigraphy is a highly specific noninvasive modality for detecting compensated cirrhosis. When guided by clinical suspicion based on platelet count, the LSS is a useful confirmatory test for compensated cirrhosis where a liver-biopsy can be avoided.

**DIFFERENTIAL UPREGULATION OF BDNF mRNA IN THE RAT HIPPOCAMPUSS AFTER SINGLE AND RECURRENT HYPERTHERMIA-INDUCED SEIZURES.** Trac M. Doung. Department of Neurosurgery, Yale University School of Medicine, New Haven, Connecticut.

Whether febrile seizures produce the neuropathology observed in human TLE patients remains controversial. In this study, we determine the pattern of BDNF mRNA expression in the rat hippocampus after single and recurrent hyperthermia-induced seizures, using the warm-water-immersion method. BDNF mRNA was detected in hippocampal sections by in situ hybridization with an $^{35}$S-radio-labeled oligonucleotide
probe complementary to the sequence of rat BDNF mRNA. Signal from the probe was visualized using plane-film autoradiography, and the intensity was quantified by computerized densitometry. In the hippocampi of both control and hyperthermic rats, BDNF mRNA was most highly localized to the dentate granular cell layer, CA3 pyramidal cell layer, CA1 pyramidal cell layer, the hilus, the molecular layer, CA3 stratum radiatum and CA1 stratum oriens and radiatum, in descending order. The earliest increase in BDNF mRNA expression compared to controls was recorded in the granular cell layer after three seizures. By nine seizures, an upregulation of BDNF mRNAs was observed in all eight measured regions of the hippocampus. The granular cell layer demonstrated the greatest maximum increase in BDNF mRNA (4.2-fold) compared to control levels. In contrast, the CA1 and CA3 pyramidal cell layers exhibited the smallest maximum increase (1.5-fold) of the regions measured in the hippocampus.

In the dentate granular cell layer, a statistically significant increase in BDNF mRNA expression is observed between the following groups: three seizures vs. control; six seizures vs. control; nine seizures vs. control; and nine seizures vs. three seizures. A statistically significant increase in BDNF expression was observed in CA1 stratum oriens and the molecular layer of the dentate gyrus after nine seizures compared to controls. A strong positive correlation was found between the number of seizures experienced and the seizure duration. In addition, linear regression analysis revealed a strong correlation between the severity of the seizure and its duration. These findings suggest that BDNF mRNA upregulation during hyperthermic seizures protects hippocampal neurons from injury. The pattern of BDNF mRNA upregulation in the hippocampus suggests that cell populations that mount an insufficient BDNF response to seizures may be more vulnerable to injury and death during prolonged seizures. In addition to conferring neuroprotective properties, an increase in BDNF mRNA expression may enhance neuronal excitability and lengthen the seizure duration.

CHANGES IN CBF-BOLD COUPLING DETECTED BY MRI DURING AND AFTER REPEATED TRANSIENT HYPERCAPNIA IN RAT. Michael V. Dutka and John C. Gore. Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut.

The effect of hypercapnia on cerebral metabolic rate of oxygen consumption (CMRO$_2$) remains incompletely understood. This study examined the relationship between susceptibility (Blood Oxygenation Level Dependent, BOLD) and perfusion-weighted (Flow-sensitive Alternating Inversion Recovery, FAIR) MRI techniques both during induction of repeated transient hypercapnia (THC), and after return to normocapnia during whisker barrel functional activation. During induction of THC, the FAIR signal became significantly elevated over control after 100 seconds of hypercapnia (p = .039) with a trend of increasing significance to five minutes (p = .000008). The FAIR signal in the activated cortex during subsequent normocapnia was significantly increased compared to pre-THC control after each successive period of THC. The mean grouped FAIR signal increased by 81 ± 63 percent after one exposure (p = .021), by 163 ± 55 percent after the second exposure (p = .002), and by 240 ± 54 percent after the third exposure (p = .000002). The mean grouped BOLD signal trended upward, but did not increase significantly during, or after, exposure 1, 2, or 3. These data demonstrate increased uncoupling of perfusion-weighted from susceptibility imaging techniques, both in non-activated cortex during hypercapnia, and with activation after multiple exposures to THC. These results are consistent with saturation of BOLD contrast as well as with increases in CMRO$_2$ with stimulation after multiple exposures to THC.
RADIOGRAPHIC MEASUREMENTS OF THE WRIST: A DATABASE OF NORMAL CARPAL MEASUREMENTS. Kier J. Ecklund (Sponsored by Manohar M. Panjabi). Department of Orthopaedic Surgery, Yale University School of Medicine, New Haven, Connecticut.

Radiographs from 27 women and 18 men that spanned two age groups (16 to 40 years old and 41 to 80 years old) were scanned and measured using computer software to determine the carpal height ratio (CHR), revised carpal height ratio (RCHR), and a new measurement defined in our lab — the styloid metacarpal ratio (SMR). The SMR is defined as the distance from the radial styloid to the proximal convex point of the second metacarpal divided by the length of the capitate. Mean values of CHR and RCHR (0.54 ± 0.03 and 1.57 ± 0.06, respectively) were identical to those in the literature. The normal mean value of SMR was determined to be 1.10 ± 0.06. Mean ulnar variance was -0.6 ± 1.8 while radial inclination was 23.9 ± 2.7, and both were similar to previous published results. No significant difference was found between left and right wrists. Differences between left and right side for each measurement within patients were small and insignificant. Length measurements were significantly smaller in women, but RCHR, SMR, ulnar variance, and radial inclination were not different. Only radial inclination was different according to age (23.0 ± 2.4° for younger patients vs. 24.9 ± 2.7° for older patients). A number of parameters showed significant correlations (R² = 0.04 to 0.67, p < .05), with length of capitate vs. length of third metacarpal being the strongest. Normal anatomical information such as this is important for clinical diagnosis, determining prognosis, and deciding on treatment for a variety of wrist disorders including Kienbock's disease, carpal instability, distal radius fractures, and scaphoid fractures. The SMR, which has been shown to be useful for the avoidance of over-distraction in patients receiving external fixation for distal radius fractures, has been appropriately defined in the normal population.

CHILDREN WITH SPECIAL HEALTH CARE NEEDS AND WELL CHILD CARE: ASSESSING QUALITY OF MEDICAID MANAGED CARE. Amy Michelle Fahrenkopf. Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study is to determine if children with special health care needs (CSHCN) enrolled in four Massachusetts Medicaid managed care organizations (MCOs) receive preventive health care that is comparable to care provided to healthy children. A retrospective medical record review was performed of a random sample of all children enrolled in MassHealth MCOs, as well as a selection of children determined to have special health care needs through the use of diagnostic codes. Participants included 670 children aged one month to 17 years old who received Medicaid insurance benefits through the state of Massachusetts and who were enrolled in the same MCO for the period of one year. Quality of care was measured by determining the degree to which certain preventive services were completed. CSHCN were significantly more likely than healthy children to have had a physician visit (OR 1.94, 95 percent CI 1.12, 3.34), have appropriate body measurements taken, and receive indicated or catch up immunizations (OR 1.50, 95 percent CI 1.21, 1.84), lead screening (OR 3.04, 95 percent CI 1.00, 9.34), hearing screening (OR 2.65, 95 percent CI 1.20, 5.06) and vision screening (OR 2.30, 95 percent CI 1.22, 4.35). CSHCN were no more or less likely than healthy children to have a well child visit, have developmental screening, or receive anticipatory guidance for sexuality and substance abuse. CSHCN enrolled in MassHealth MCOs receive preventive health care that is at least comparable to, and often better than, healthy children enrolled in the same MCOs.
FOOT DEFORMITY IN SPASTIC HEMIPLEGIA: A RETROSPECTIVE REVIEW OF 29 PATIENTS USING GAIT ANALYSIS. Michael N. Fehm and Peter A. DeLuca (Sponsored by Peter A. DeLuca). Center for Motion Analysis, Department of Pediatric Orthopaedics, Connecticut Children's Medical Center, Hartford, Connecticut.

Foot deformities in children with cerebral palsy (CP) spastic hemiplegia are common and often require surgical intervention to restore balance to the developing foot before the onset of rigid deformities. The purpose of this retrospective study was to classify foot deformity in this population and to evaluate the outcomes of surgical treatment.

Five clinicians experienced in gait analysis examined slow motion, close-up, and planar video from gait analysis of 29 patients (average age nine years) with dynamic spastic hemiplegia. All twenty-nine patients were evaluated at the Center for Motion Analysis Gait Laboratory both pre-operatively and post-operatively (pre-post) at a mean study follow-up time of 26 months (range 6.3 to 79 months). All patients underwent soft tissue surgery for correction of foot deformity, which included equinovarus and other deformities, such as forefoot supination and forefoot/midfoot adduction.

Of these 29 patients, 13 patients received a combined split anterior tibialis tendon transfer and intramuscular posterior tibial tendon lengthening procedure (SPLATT/Frost). Simultaneous heel-cord lengthening was performed in 12 of these 13 patients. Pre-operatively, 12 of these 13 patients had supination or varus deformity or both. Postoperatively, all pre-operative hindfoot varus and forefoot supination deformities corrected to neutral foot position. We concluded, based upon review of pre-post gait analyses, that the combined SPLATT/Frost is an effective surgical package for correction of excessive dynamic forefoot supination and hindfoot varus in patients with CP spastic hemiplegia.

THE IMPACT OF PICTURE ARCHIVING AND COMMUNICATION SYSTEMS (PACS) ON RADIOLOGY SERVICES. Devesh Gandhi and Howard Forman. Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to assess if PACS improved radiology workflow, expenses, capability, and user-satisfaction. We conducted a before and after study at Yale-New Haven Hospital to assess each of the four areas — we utilized a time and motion study to assess workflow, developed two cost-accounting models to assess pre- and post-PACS expenses, used direct observation and interviewed experts to document new capabilities, and surveyed clinicians before and after PACS implementation to gauge satisfaction. PACS eliminated five steps in the radiology workflow streamlining the process. In addition, a 33 percent reduction in the scanning process time can be expected in a truly film-less environment. PACS has the potential to reduce unit CT costs 15 percent if maintenance costs turn out to be lower than projected. Third, teleradiology was a new capability engendered by PACS not possible in a film-based environment. Finally, clinicians reported a 26 percent and 28 percent increase in satisfaction in image availability and image retrieval speed with PACS respectively. We conclude that PACS has and will continue to significantly improve radiology workflow, capability, and user-satisfaction and may provide direct cost savings.
IN UTERO INDOMETHACIN ALTERS O₂ DELIVERY TO THE FETAL DUCTUS ARTERIOSUS: IMPLICATIONS FOR PERSISTENT POSTNATAL PATENCY.
Seth H. Goldbarg and Ron I. Clyman (Sponsored by George Lister). Cardiovascular Research Institute, Department of Pediatrics, University of California, San Francisco, California.

Exposure of the fetus to indomethacin produces constriction of the fetal ductus arteriosus (DA) and hypoxia in the avascular muscle media of the vessel wall. Hypoxia induces cell death, which increases the incidence of patent DA in the newborn period. We used a fetal sheep model to determine the factors that were responsible for indomethacin-induced hypoxia at various degrees of DA constriction. Indomethacin produced DA constriction in all fetuses studied in vivo. Cell death in the DA wall was directly related to the degree of indomethacin-induced DA constriction and was present at both moderate (pressure gradient across DA < 16 mmHg) and marked (≥ 16 mmHg) degrees of constriction. Indomethacin did not alter oxygen consumption in DA rings studied in vitro, indicating that oxygen demand in the constricting tissue is not significantly increased by indomethacin. Both moderate and marked degrees of DA constriction reduced vasa vasorum flow to the ductus (moderate = 69 ± 25 percent; marked = 30 ± 16 percent of preindomethacin exposure values) and increased the thickness of the ductus wall. In contrast, DA luminal blood flow was not affected by moderate degrees of constriction and was reduced only after marked constriction. Our findings suggest that changes in vasa vasorum blood flow and muscle media thickness are the primary contributors to hypoxia-induced cell death at moderate degrees of indomethacin-induced constriction. Diminished luminal blood flow only appears to contribute to the induction of cell death following the development of marked degrees of constriction. These findings help to explain why in utero exposure to indomethacin in late gestation fetuses, which depend on vasa vasorum to supply O₂ to the DA muscle media, leads to hypoxia-induced remodeling and increased incidence of postnatal patent DA.

APOLIPOPROTEIN E GENOTYPE AND SEVERITY OF COGNITIVE AND PSYCHOTIC SYMPTOMS IN ALZHEIMER'S DISEASE.
Monique Grey. Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut.

The fact that the ε4 allele of the apolipoprotein ε (apoE) gene increases the risk of developing Alzheimer's disease (AD) and decreases the age of onset of the disease suggests that it accelerates the neurodegenerative processes thought to cause AD. If this is the case, apoE genotype may be expected to affect the rate of clinical progression in AD, predicting a more severe course of cognitive and behavioral decline as the number of ε4 alleles increases. The purpose of this study was to determine if the presence and dosage of the ε4 allele of the apoE gene affects the severity of cognitive and behavioral symptoms in AD.

Three hundred and fourteen patients with AD were studied: 45 were ε4 homozygotes, 129 were ε4 heterozygotes, and 140 had no ε4 allele. Sixty-four age-matched healthy controls were also studied. For this cross-sectional study, the AD patients and healthy controls' characteristics and neuropsychiatric status were measured. The duration of the patients’ disease was estimated from review of medical records and interviews with their primary caregivers. The battery of neuropsychiatric tests and ratings used were the Mini-Mental State Exam (MMSE), Alzheimer’s Disease Assessment Scale (ADAS-Cog), Instrumental Activities of Daily Living (IADL), and Neuropsychiatric Inventory (NPI). The effect of apoE genotype on both the cognitive and non-cognitive measurements was
determined using analysis of covariance (ANCOVA). The group of ε4 homozygotes had an earlier age of onset than the ε4 heterozygotes (p = .042). Contrary to hypothesis, apoE genotype had no effect on MMSE, ADAS-Cog, IADL or total NPI scores. However, presence of the ε4 allele was strongly correlated with more severe delusions (F_{1, 210} = 7.43, p = 0.007), and subjects with two ε4 alleles had more severe delusion scores than those with one ε4 allele (F_{2, 209} = 3.77, p = .025). A trend toward more severe hallucinations was seen in patients with at least one ε4 allele (F_{1, 212} = 3.10, p = .080), but there was no statistically significant dose effect of the allele (F_{2, 211} = 2.05, p = .155). Our findings suggest that while the apoE ε4 allele is an important susceptibility gene and plays a role in the onset of the disease (as demonstrated by the earlier age of onset of AD in patients with the ε4 allele), it does not play a role in the rate of cognitive decline in AD. However, the ε4 allele is associated with more severe delusions in AD.

QUALITY OF LIFE OF PEDIATRIC AND YOUNG ADULT PATIENTS WITH TOURETTE SYNDROME. Rebekah G. Gross and James F. Leckman. Yale Child Study Center, Yale University School of Medicine, New Haven, Connecticut.

This study is the first to document quality of life (QOL) of pediatric-AGED and young adult patients with Tourette Syndrome (TS) and to investigate whether this outcome measure is informed by symptom severity or by antinuclear or antineuronal antibody status. Forty-four patients under 24 years of age meeting DSM IV diagnostic criteria for TS were included in the study. QOL was measured using the Short Form-36 Health Survey Questionnaire (SF-36), while symptom severity was gauged using the Yale Global Tic Severity Scale, the Yale-Brown Obsessive-Compulsive Scale, and the Attention Deficit/Hyperactivity Disorder Scale. Subjects' autoantibody status was detected via indirect immunofluorescence, and SPSS was used to analyze this data and to compare it with data collected for subjects within the past decade. Results indicate that SF-36 scores for this TS population approximate general U.S. population norms but are slightly higher than those reported for an older population of TS patients followed at the Institute of Neurology in London. Within the young TS study population, QOL did vary significantly with age and with symptom severity, with younger and more mildly symptomatic subjects scoring significantly better on the Social Functioning and Role Emotional subscales of the SF-36. The predictive value of autoantibodies in determining QOL was less certain, with current antibody status, but not previous antibody status or change in status over time, correlating with SF-36 scores. Overall, findings suggest that young patients with TS do not experience markedly inferior quality of life as measured by the SF-36. To the degree that scores are impaired, the effect is most evident on the Social Functioning subscale which, like the Role Emotional subscale, is influenced significantly by symptom severity. The association between autoantibodies and QOL is less convincing. A large prospective longitudinal study would be useful to clarify these relationships.

PATIENTS WITH CANCER AT THE END OF LIFE. Anna Gibb Hallemeier and Elizabeth C. Bradley. Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut.

The purposes of this study were to evaluate the frequency of documented prognosis discussions among terminally ill cancer patients, to identify correlates of having documented prognosis discussions and to describe the content of prognosis discussions as documented in patient medical records. Sample data were collected from the randomly select-
ed medical records of inpatients (n = 210) aged 65 years or older and admitted with diagnoses of brain, pancreas, liver, gall bladder, or inoperable lung cancer from six large Connecticut hospitals. A standardized instrument was used to extract data concerning patient demographics, hospital course, prognosis discussions, and evidence of advance care planning. Prognosis discussions were recorded in 79 (38 percent) of medical records and were correlated with emergency admission status (p = .004) and longer length of hospital stay (p = .003) on multivariate analysis. Of the documented prognosis discussions, 63% were within one week of admission but after the first day, and 57 percent included the patient, 76 percent included the family, 77 percent included the doctor, and 69 percent did not include another health staff member (n = 79). Life sustaining treatment discussions and DNR orders were both associated with prognosis discussions (p = .001 and p = .001, respectively) and were more often documented after the prognosis discussions. Prognosis discussions included planning for care and treatment in 33 (42 percent) of discussions documented. In conclusion, we found that prognosis discussions were infrequently documented during the hospitalization of terminally ill patients diagnosed with cancer. We also found that advance care planning, such as discussions of life-sustaining treatment and DNR orders, was significantly associated with prognosis discussions and more often occurred after prognosis was discussed.

FACTORS PREDICTING THE USE OF THE EMERGENCY DEPARTMENT: WHO, WHY, AND WHAT FOR? Dawn Harris (Sponsored by Linda Degutis). Section of Emergency Medicine, Department of Surgery, Yale University School of Medicine, New Haven, Connecticut.

This study attempted to characterize the Emergency Department (ED) population in general and also to investigate what specific criteria there may be among those who regard the ED as their usual source of care. This study took place in the ED of the Yale-New Haven Hospital, an urban, Level I trauma center, serving as a principal university teaching hospital and treating more than 95,000 emergency patients annually. More than 4,500 adult ED patients were surveyed, using a 72-question questionnaire, between December 8, 1999 and December 8, 2000. The data were compared with U.S. Census data compiled for 1990, and when available, 2000.

The factors which were most predictive of ED use by the general population included being of African-American race or of Hispanic ethnicity; having less than a high school education or having a high school diploma as a terminal degree; being single; coming from a lower-income area; and being of closer proximity to the YNHH ED. Factors that predicted the use of the ED as a usual source of care included being of male gender; being single; having no income or to a lesser extent, having an income derived from working for a salary; lacking insurance coverage; lacking a primary care physician; being from a lower-income area; being of closer proximity to the YNHH ED; and being less concerned with affording medication.

THE IMPACT OF PRENATAL COCAINE EXPOSURE ON LANGUAGE DEVELOPMENT IN PRESCHOOL-AGE CHILDREN: A MEDIATIONAL MODEL. Eric P. Hazen and Linda C. Mayes. Child Study Center, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to assess the effect of prenatal cocaine exposure on language development in preschool-age children and to identify potential mediators of this effect. A total of 359 children participated in this study. Subjects were recruited prior
to birth from patients presenting for prenatal care at the Women’s Center at Yale-New Haven Hospital, an obstetrical clinic serving a primarily uninsured population of low socioeconomic status. Subjects were categorized by exposure status based upon substance abuse history, meconium toxicology, and maternal urine toxicology. The cocaine-and other-drug-exposed (CE) group was defined as infants prenatally exposed to cocaine, with or without additional exposure to alcohol, marijuana, or tobacco. The polydrug but-not-cocaine-exposed (PE) group was defined as infants prenatally exposed to alcohol, marijuana, and/or tobacco with no evidence of cocaine exposure. Infants in the non-drug-exposed (NE) group had no evidence of exposure to cocaine, alcohol, marijuana, or tobacco. Subjects’ language development was assessed at ages 36, 48, and 60 months using the Reynell Developmental Language Scales (RDLS). Cognitive development was assessed using the Kaufman Assessment Battery for Children (K-ABC) at ages 48 and 60 months. Parents completed the Parenting Stress Inventory 24 and 54 months after their child’s birth. The NE and PE groups performed similarly on all language measures and were collapsed to form a larger control group of non-cocaine exposed (NCE) children. Compared to the NCE group, the CE group demonstrated modest deficits in receptive language scores at 36, 48, and 60 months and expressive language scores at 48 months (p < .05). The negative impact of prenatal cocaine exposure on language development was found to be mediated by less favorable perinatal outcome, increased parenting stress, and deficits in cognitive development. The significance of these findings is discussed with regard to models of cumulative risk and implications for intervention.

**EFFECTIVENESS OF CHILD DEVELOPMENT SEMINARS FOR POLICE OFFICERS, MENTAL HEALTH CLINICIANS, AND SCHOOL PROFESSIONALS.**

Heather Lee Heimerdinger (Sponsored by Robert Murphy). Department of Child Study Center, Yale University School of Medicine, New Haven, Connecticut.

Today’s children are witnesses to violence on a chronic basis. As a result, they are experiencing lasting psychological symptoms. New Haven’s Child Development Community Policing Program aims to provide police officers with increased resources and skills with which to deal with children exposed to violence. This study examined the effects of a seminar in child development provided by the CDCP to police officers, school officials, and clinicians. A pretest-posttest design was used — all participants answered questions about child development, views and actions regarding children exposed to violence, situations in which to use the CDCP services and vignettes used as examples of real-life situations of children exposed to violence. MANCOVA analysis indicated that all subjects improved their knowledge of core child development principles from pretest to posttest. Analysis of professional groups showed clinicians scoring higher than police officers at pretest with persisting elevated scores at posttest; no professional group improved significantly more than any other. Subjects’ scores on views and actions regarding children exposed to violence did not change significantly between pretest and posttest. Subjects did indicate significantly more situations in which to use CDCP services at posttest than at pretest. Overall, it appeared that participants improved in knowledge of child development and were better able to identify situations in which to use the CDCP program. Views and actions did not seem to change which may be due to limited time period between pretest and posttest in which participants could put their new skills to use. Further research needs to be conducted to elucidate the real-life effects of participation in this seminar.
MATERNAL BEHAVIOR REVISITED: CIRCUITS, GENES, AND THE CRUCIAL ROLE OF EARLY LIFE EXPERIENCE. Amy E. Herman and James F. Leckman. Child Study Center, Yale University School of Medicine, New Haven, Connecticut.

In recent years, gene knockout technology has identified specific genes associated with maternal behavior. Recent studies have also broadened our understanding of the role of environmental influences on maternal behavior. This thesis reviews recent developments in the neurobiology, genetics, and epigenetics of maternal behavior in animal model systems. It is hypothesized that specific genes encode proteins that are crucial for the development of neural substrates that underlie specific features of maternal behavior. The emergent neural circuitry is subsequently modified by early environmental influences. An understanding of the cascade of genetic factors and the resulting neural circuits required for the expression of maternal behavior may be valuable in understanding some forms of psychopathology, such as autism.

Relevant studies addressing the role of genetics and environment in maternal behavior of rodents were identified in a search of literature in peer-reviewed journals published from January 1990 to December 2000 and in a search of the Mouse Genome Informatics database at the Jackson Laboratory. Gene knockout studies were evaluated on such criteria as mouse strain, method of behavioral phenotyping, quantification of the degree of deficit of specific behaviors, and the use of “behavioral” controls. Following this review, the gene knockout data were analyzed using a cluster analysis technique designed by Eisen and colleagues (1998).

At least nine genes have been found to be necessary for the expression of one or more aspects of maternal behavior. These genes encode: three transcription factors; three enzymes, including dopamine beta hydroxylase and neuronal nitric oxide synthase; two receptors, including the prolactin receptor and the estrogen receptor, alpha; and one neuropeptide, oxytocin. Cluster analysis suggested possible relationships between specific genes. Review of recent epigenetic studies revealed a number of experimental interventions that lead to enduring consequences for adult offspring, including deficits in maternal behavior.

The review of genetic and environmental influences on maternal behavior suggests that the expression of this behavior is governed by events that occur during a critical period of early development. This work may inform models of disease pathogenesis.

THE BCL-2 PROTEIN MODIFIES SYNAPTIC TRANSMISSION. Daniel A. Hoit, Erin McCarthy, Jun Zhang, Iva Ivanovska, John A. Hickman, J. Marie Hardwick, Leonard K. Kaczmarek, and Elizabeth A. Jonas (Sponsored by Joel Dubin). Yale University School of Medicine, Department of Epidemiology and Public Health, Division of Biostatistics. New Haven, Connecticut.

The BCL-2 family protein BCL-2, found throughout mammalian brain, is believed to regulate the permeability of mitochondrial membranes. By influencing the movement of calcium and energy metabolites such as ATP across mitochondrial membranes, this protein could influence synaptic transmission. We measured the amplitude and rate of rise (mv/ms) of postsynaptic potentials evoked by stimulation of the presynaptic nerve before and after injection of BCL-2 into the squid giant synaptic terminal. Statistical analysis using linear mixed effects modeling demonstrated that several minutes after injection, the amplitude and rate of rise of the synaptic potentials were increased when compared to preinjection controls. Direct injection of ATP mimicked the effects of BCL-2, suggest-
ing that BCL-\( \text{XL} \) may act by increasing ATP release from mitochondria. In addition, ruthenium red, a mitochondrial calcium uptake blocker, decreased synaptic transmission in control cells, but its effect on BCL-\( \text{XL} \) treated cells was somewhat mitigated. To measure the BCL-\( \text{XL} \) effect on recovery from synaptic depression, cells were tetanized at 50 hz for 2 to 3 seconds. There was a significant difference in the degree of depression during tetanus in the BCL-\( \text{XL} \) treated cells when compared to controls, and the time dependent course of synaptic recovery may be somewhat different in treated cells versus controls as well. Our results suggest that BCL-\( \text{XL} \) may regulate both long and short-term changes in synaptic transmission.

\[ ^{18}\text{F}-\text{fluorodeoxyglucose} \] uptake as a marker of reversible myocardial ischemia. Joshua A. Horenstein and James A. Amghi. Section of Cardiology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to evaluate the potential of \( ^{18}\text{F}-\text{fluorodeoxyglucose} \) as a diagnostic tool for myocardial ischemia. It has been known for over two decades that acute myocardial ischemia is accompanied by increased exogenous glucose utilization in experimental models. Thus, glucose uptake serves as an indirect measure of myocardial ischemia. To measure glucose uptake by the myocardium, the positron-emitting, metabolic tracer \( ^{18}\text{F}-\text{fluorodeoxyglucose} \) is commonly used. Experiments were performed on five fasting adult mongrel dogs. An incision was made in the pericardium, and the proximal left anterior descending or circumflex coronary artery was isolated for placement of the ameroïd occlusion device, which causes a gradual reduction in coronary artery luminal diameter over time, maturing in three weeks, creating a model of chronic ischemia with minimal infarction. Ninety to 120 minutes following myocardial perfusion studies, animals were injected with 5 to 10 mCi \( ^{18}\text{F}-\text{fluorodeoxyglucose} \) for assessment of cardiac metabolism. FDG images were acquired dynamically for one hour. This study showed that FDG uptake was increased in ischemic cardiac tissue in the dog model, though there was some variability in the data in these animals. Thus, further studies in humans are warranted to determine the diagnostic utility of \( ^{18}\text{F}-\text{fluorodeoxyglucose} \) as a marker of myocardial ischemia.

Patterns of psychiatric pathology and mental health service utilization in a community sample of urban adolescents with school attendance problems. Rocco A. Iannucci (Sponsored by Mary Schwab-Stone). Child Study Center, Department of Child Psychiatry, Yale University School of Medicine, New Haven, Connecticut.

This investigation was conducted to examine the patterns of psychiatric disorder and types of mental health services used in a community sample of older adolescents with records of poor school attendance. Thirty-one students and their guardians participated in a multifaceted assessment including the administration of diagnostic interviews with multiple informants, psychiatric symptom scales, and individual cognitive testing. Approximately half of students met DSM-IV criteria for a current psychiatric disorder (48.4 percent, SE = 9.0 percent). Female non-attenders reported significantly more symptoms of depression and anxiety than males (p < .025) and more anxiety symptoms than girls from the normal school population (p < .05). Males who did not meet criteria for a current diag-
nosis had significantly lower mean nonverbal IQ than males with a current disorder (80.3 ± 8.1 vs. 101.8 ±, p < .05).

Having a current disorder was predictive of being seen in any service setting (sum of juvenile justice, psychiatric, and school settings; p < 0.05), with 95 percent of absentees being referred to some service. However, only about half of disordered subjects received any psychiatric care. When considered individually, presence of a psychiatric disorder was more predictive of juvenile justice involvement (p < .025) than of care in school or psychiatric settings.

These findings illustrate the high levels of psychiatric problems experienced by students who fail to attend school, with girls at particular risk for emotional disorders. Furthermore, disordered adolescents have insufficient access to psychiatric care. Implications for clinical practice are discussed.

ASSOCIATION OF SRDSA2 GENOTYPE AND PATHOLOGICAL CHARACTERISTICS OF PROSTATE TUMORS. Julie M. Jaffe. Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut.

The enzyme product of SRDSA2, 5α-reductase type II, is responsible for converting testosterone to the more metabolically active dihydrotestosterone, which is able to induce cell proliferation in the prostate. It is, therefore, biologically plausible that SRDSA2 may be involved in the development and growth of prostate tumors. To examine the effects of allelic variants in the gene SRDSA2 on the presentation of prostate tumors, we studied a sample of 265 primarily Caucasian men with incident prostate cancer who were treated by radical prostatectomy. We assessed the relationship of the A49T and V89L polymorphisms at SRDSA2 with clinical and pathologic tumor characteristics of these patients. We found no association of V89L genotypes with any of the characteristics studied. The presence of the A49T variant was associated with a greater frequency of extracapsular disease (OR = 3.16, 95% CI: 1.03 to 9.68) and a higher pathologic tumor-lymph node-metastasis (pTNM) stage (OR = 3.11, 95 percent CI: 1.01 to 9.65). In addition, the A49T variant was over-represented in two poor prognostic groups that have been correlated with reduced rates of biochemical disease-free survival. These included men with at least two of the following poor prognostic variables: stage T3 tumor, PSA level > 10, and/or Gleason score 7 to 10 (OR = 3.46, 95 percent CI: 1.04 to 11.49), and men with positive margins and high Gleason score (OR = 6.28, 95 percent CI: 1.05 to 37.73). Our results suggest that the A49T mutation may influence the pathological characteristics of prostate cancers, and thus may affect the prognosis of these patients.

PARENTAL PERSPECTIVES ON NEONATAL CIRCUMCISION. Amit K. Jha (Sponsored by Eve Colson). Section of Neonatology, Department of Pediatrics, Jack Weiler Hospital of the Albert Einstein College of Medicine, Bronx, New York.

Purpose: The study was designed to gain an understanding of the common factors affecting the parental decision making process with regard to neonatal circumcision, including identifying common sources of information and to document parental attitudes regarding routine neonatal circumcision.

Methods: The parents of 61 newborn boys were interviewed using a semi-structured format during June and July 1999 in the Bronx, NY. Parents were asked multiple questions regarding circumcision, including whether their son was going to be circumcised, when they made the decision, if the father of the baby was circumcised, and what their
attitudes were regarding circumcision. Chi-square analysis was used to assess for statistical significance.

Results: The overall rate of circumcision was 64 percent in the sampled population. African-American parents, fathers who were circumcised, fathers who made the circumcision decision alone, and parents who thought the circumcised penis looked better were all more likely to circumcise their sons (p < .001, p < .001, p = .03, p < .001, respectively). Hispanics, Catholics, more educated mothers, and parents who did some reading on circumcision were all less likely to circumcise their sons (p = .01, p = .005, p = .03, p = .03, respectively). The primary source of information regarding circumcision for parents was from their friends. The most common reason for circumcision was that it prevented disease and was a healthier option. The most common reason against circumcision was that the procedure was unnecessary and had no benefits.

Conclusions: Parents make the decision for or against circumcision for various reasons. However, at least some of the reasons are based on medical misconceptions. Health care providers are in a position to correct such misconceptions thereby allowing parents to make a more informed choice when deciding to circumcise their newborn sons.

AIDS REVOLUTION: THE POWER OF YOUTH. Kebba M. Jobarteh. Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut.

This study presents an exploration of alternative methods of engaging in the struggle to prevent HIV/AIDS amongst African youth. This exploration utilized the frameworks of human rights ideology in conjunction with a Freireian pedagogical approach. Historical analysis of the history of public health, human rights, education and the HIV/AIDS pandemic provides the background for this endeavor. Field research involving interviews with numerous NGOs engaged in this struggle throughout the African continent as well as with individuals engaged in said struggle provides the justification for the claims put forth.

The conclusions reached were that if the international public health community were to employ a strategy of empowering young people using a Freireian framework of dialogue and contextualization, it is possible that true behavior change with respect to the sexual lives of young Africans may occur.

HYPERTENSION AMONG PREGNANT WOMEN IN THE URBAN AREA OF YAOUNDE, CAMEROON. Damita L. Johnson-LaBorde, Yale University School of Medicine, New Haven, Connecticut.

Yaounde, the capital of Cameroon, is a large highly urbanized city in West Africa. The frequency of hypertension among 1,042 pregnant women in Yaounde was determined in the present study at the Maternal and Infant Protection Center and at the Central Hospital High Risk Pregnancy Clinic using a standard mercury sphygmomanometer. Since systolic blood pressure (SBP) predicts preeclampsia better than diastolic blood pressure, only SBP was used to classify patients as hypertensive or normotensive. Patients were grouped as hypertensive if their SBP measured greater than or equal to 140 mm Hg. A total of four measurements were taken on each patient, three on their initial visit and a fourth taken on their subsequent visit. The frequency of hypertension based on first readings was 6.04 percent, but when repeated the frequency dropped to 1.9 percent, a 69 percent reduction. The fourth measurements, taken on subsequent days, revealed a 0.58 percent frequency of hypertension in the same population. The frequency was highest among
pregnant women below the age of 20 (7.9 percent) or above the age of 40 (27.3 percent). There was a corresponding increase in SBP as gestational weeks increased among hypertensive pregnant women; however, the SBP decreased as gestational weeks increased among normotensive patients. The data also indicate that SBPs are elevated in patients who report adding salt to their food. The odds of being hypertensive among patients with a body mass index greater than or equal to 32.3, the cutoff for obesity, were 1.56 times greater than for those who were not obese. A standardized protocol improved sensitivity in Yaounde. Hypertension during pregnancy predicts preeclampsia, prematurity, placental hypoxia, and/or neonatal death. Hypertension detected and adequately managed prevents maternal strokes, seizures, and death.

**EFFECTS OF THROMBOPROPHYLAXIS ON PREGNANCY OUTCOMES IN HIGH-RISK OBSTETRIC PATIENTS.** Anita Karne, Tulin Ozcan, and Urania Magriples. Section of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to evaluate the impact of anticoagulation on pregnancy outcomes in women with thrombophilia. We performed a case-control study using retrospective medical records analysis of women who were referred to the Division of Maternal-Fetal Medicine for poor obstetric outcomes. Patients found to have thrombophilic mutations were treated with Heparin or Lovenox after confirmation of fetal viability. Demographic and clinical data on history, ultrasounds, and pathology reports were collected. Outcomes of treated and untreated pregnancies of mutation positive women versus those of the mutation negative comparison group were compared.

|               | Rx/mutation+ | No Rx/mutation+ | No Rx/mutation- | p       |
|---------------|--------------|-----------------|-----------------|---------|
| SAB           | 4%           | 49%             | 46%             | <.0001  |
| PIH           | 2%           | 18%             | 19%             | .025    |
| Good outcome  | 80%          | 26%             | 30%             | <.0001  |
| Living child  | 91%          | 40%             | 42%             | <.0001  |

There were a total of 418 pregnancies in 96 patients studied: 45 (47 percent) in the mutation positive group and 51 (53 percent) in the mutation-negative comparison group. Of the women with mutations, 30 (67 percent) were heterozygous for FVL, nine (20 percent) were heterozygous for PTG, and 17 (38 percent) were homozygous for MTHFR. There was a significant improvement in the chance of overall good outcome and birth of a living child and reduction in spontaneous abortions (SAB) and preeclampsia.

In addition, there was a significant increase in the percentage of normal ultrasounds in the treated mutation positive group compared to the non-treated mutation-positive and mutation-negative group (72 percent, 47 percent, and 46 percent; p = .016.) Specifically, there was a reduction in the percentage of abnormal Dopplers and IUGR noted in the third trimester. When placental pathology was analyzed, there were no differences with treatment, although mutation-positive patients had significantly greater rates of abnormal placentas than mutation negative patients. Mutation-positive women were more likely to have placental infarction (30 percent vs. 14.9 percent; p < .05) or intervessel thrombosis (18 percent vs. 6.0 percent; p = 0.04.)

In conclusion, Heparin or Lovenox therapy significantly improves pregnancy outcomes in women with thrombophilia.
DO SIM ETRY PARAMETERS USING ULTRASOUND-GUIDED TRANSPERINEAL IMPLANTS FOR EARLY PROSTATE CANCER. Robert Griffin Kelley. Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut.

Previous analysis has shown a strong correlation between 10-year disease-free survival rates and three-dimensional volume-dose parameters when using the retropubic prostate implant technique. This study was undertaken to determine if the newer transperineal approach for prostate implants achieves these previously established dosimetry goals. Ninety-one consecutive patients with clinical stage T1c or T2 prostate cancer underwent an ultrasound-guided transperineal prostate implant using 125-Iodine or 103-Palladium. All patients received pelvic radiography approximately one month after the implant deeds visible on the radiographs were digitized and their positions in three dimensions calculated, and volumes receiving 100 percent, 50 percent, and 150 percent of prescription dose (V100, V50, and V150, respectively) were calculated. Prostate volume by transrectal ultrasound planimetry was used to establish average prostate dimension to calculate total activity implanted per average dimension (activity/dimension). Using the older retropubic approach, 52 percent of patients achieved dose distributions greater than the values that predict superior 10-year disease-free survival. Eighty-seven percent of patients receiving the transperineal approach had implants that achieved all five dosimetry goals (V100 > 16 cc, V50 > 55 cc, V150 > 3 cc, Activity/Dimension > 30 mCi/cm, and Total Activity > 12 mCi). Ultrasound-guided transperineal implants routinely achieve three-dimensional volume-dose parameters that predict superior ten-year disease-free survival outcomes. Using the transperineal technique produces an improvement in the three-dimensional dosimetry quality indicators compared with the older retropubic implant approach.

DIFFUSION TENSOR MAGNETIC RESONANCE IMAGING IN THE HUMAN SPINAL CORD WITH A SINGLE SHOT, FAST SPIN ECHO SEQUENCE. Har-dave S. Kharbanda, David A. Hackney, and David C. Alsop (Sponsored by Adam W. Anderson). Department of Diagnostic Radiology, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania.

As the recent clinical introduction of Diffusion Tensor Magnetic Resonance Imaging (MRI) has proven to be an excellent tool for rapidly and non-invasively diagnosing certain pathologies in the brain, we wished to analyze and overcome the problem of cardiac cycle-related motion of the human spinal cord to be able to apply Diffusion Tensor MRI to the cord. We applied motion-compensation gradient pulses, designed to cancel out potential proton velocity gradients in the cord arising from bulk motion of the cord, to single shot, fast spin echo Diffusion Tensor MRI. Using a total of 672 Diffusion MRI images in our study, we found a decrease in our measurements of the diffusion trace (p < .0001), the largest diffusion eigenvalue (p < .0001), the third-largest diffusion eigenvalue (p < .005) and the principal diffusion eigenvector orientation (p < .05) when motion-compensation was applied. We did not find a significant change in our measurement of diffusion “volume index” anisotropy (p = .1983). This experiment was the first, to our knowledge, to formally demonstrate that significant proton velocity gradients do exist in the cord as a result of its complex bulk motion. Furthermore, by being able to measure diffusion trace, eigenvalues and eigenvector orientation with greater accuracy than before, we hope that this research is an important step to one day being able to non-invasively localize and diagnose stroke, multiple sclerosis, and trauma in the human spinal cord.
CAVUM SEPTI PELLUCIDI IN TOURETTE SYNDROME. Karen J. Kim and Bradley S. Peterson. Child Study Center, Yale University School of Medicine, New Haven, Connecticut.

An enlarged cavum septum pellucidum (CSP) has been associated with a variety of neuropsychiatric disorders and is a putative marker of disturbed brain development. The goal of this study was to characterize systematically the CSP and the related cavum verae in individuals with Tourette Syndrome (TS). The overall size and anteroposterior length of the CSP in 161 children (97 with TS and 64 normal pediatric controls) and 107 adults (43 with TS and 64 normal adult controls) were rated on high-resolution magnetic resonance images in the coronal view. The associations of CSP size with diagnosis and symptom severity scores were assessed using ordinal logistic regression analysis.

CSP size in TS children was significantly smaller than in normal control subjects and was inversely associated with ADHD symptom severity in the TS subjects. CSP size was not significantly associated with the comorbid diagnoses of OCD or ADHD. These results were replicated in an independent sample of TS and normal control adults. The presence of a cavum verae was not significantly associated with a diagnosis of TS. These findings suggest that the pathophysiology of TS may involve abnormalities in the early development of the CSP or in the neighboring corpus callosum, septal nuclei, or related portions of the limbic system.

POSTERIOR STABILIZATION OF THE CERVICOThorACIC SPINE: A BIOMECHANICAL EVALUATION. Jennifer Kreshak, Derek Lindsey, Daniel Kim, Andrew Kam, Scott Yerby, and Manohar Panjabi. RR&D, VA, Palo Alto, California and the Department of Biomechanical Engineering, Stanford University Stanford, California.

The cervicothoracic spine is a complex site for stabilization of traumatic and degenerative disorders and has proven to be a difficult challenge in both approach and fixation of injuries. The objective of this study was to biomechanically test three posterior cervical fixation devices and evaluate them for stability with two- and three-column injuries at the cervicothoracic junction.

Twenty-one human cadaver spines (C3-T3) were loaded in flexion/extension, lateral bending, and axial torsion. A posterior two-column injury was created at C7-T1 by transecting all posterior ligamentous elements and the posterior half of the intervertebral disc. One of three fixation systems was applied; fixation included two posterior rod/screw systems and one posterior plate/screw system, all with screws placed bilaterally at C5,C6 and T1,T2. The spines were tested again. A three-column injury was then created by transecting the remaining anterior structures, and the spines were tested a final time.

For all three systems tested in flexion/extension, there were no significant differences in stiffness between intact spines and instrumented two-column injuries, however, the three-column injury was significantly less stiff than the intact and two-column injury in extension. The range of motion and neutral zone decreased from intact to two-column injury and increased from intact to three-column. in lateral bending and axial rotation, all systems were significantly stiffer than the intact spine for both injuries; the range of motion and neutral zone were decreased for both injuries when compared to intact specimens.

These results suggest that all three systems stabilize the cervicothoracic junction with a posterior two-column injury in flexion/extension, lateral bending, and axial rotation,
however, none were adequate for a three-column injury, particularly in extension. A three-column injury at this level would warrant supplemental anterior fixation.

THE IMPACT OF THE INTERNET ON THE DOCTOR-PATIENT RELATIONSHIP. Stephen Krieger and Seth Powsner. Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut.

Purpose: There is a vast amount of medical information available on the Internet, and millions of patients go online to retrieve it each year. Many researchers and writers in popular media have stated that the Internet and World Wide Web are having a profound impact on the doctor-patient relationship, however no attempt has been made to characterize and quantify these effects. This study seeks to assess what it is patients do based on their use of the Internet, and how their use of online medical information is affecting their medical care and relationships with their physicians.

Methods: As the doctor-patient relationship is an inherently experiential phenomenon, structured interviews were used to gather both quantifiable data as well as anecdotal information. Interviews were conducted with 40 patients of the Yale Hematology-Oncology Clinic who had used the Internet for medical information.

Results: 88 percent of patients reported bringing information learned online to the attention of their doctors, and 73 percent also stated the Internet had brought up new questions to ask their physicians. Based on their use of the Internet, 33 percent of patients sought second opinions from new doctors, including 13 percent who decided to change physicians entirely. These patients were significantly more likely than the other patients in the study to have found information online that contradicted what they had been told by their doctor. Sixty-three percent of respondents reported searching for clinical trials online, and 15 percent of patients reported having been part of a clinical trial they learned about on the Internet.

Conclusions: This study’s results are incompatible with the position that patients’ use of the Internet and World Wide Web has had no measurable effect on the doctor-patient relationship. Several recommendations are made that can facilitate improved doctor-patient communication by taking into account current and potential future impact of the Internet.

DEVELOPMENT AND VALIDATION OF A NEW DEFINITION OF BIOCHEMICAL FAILURE IN PROSTATE CANCER. Tara Lagu, David Penson, Carolyn Wells, Alvan Feinstein, and John Concato. Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Different definitions of biochemical “failure” have been developed, based on levels of prostate specific antigen (PSA), to evaluate patients who receive treatment for cancer of the prostate (CaP). Two commonly used definitions are treatment-specific and have limitations. For example, the radiologic oncologic definition is cumbersome methodologically as it requires documentation of three consecutive rises in PSA level after a nadir, whereas the surgical definition considers any detectable PSA significant, increasing the likelihood of false positives. Our purpose was to define and validate a new definition of PSA failure, and to compare its performance characteristics to the existing definitions. The new definition was developed in a cohort of 180 patients diagnosed or treated for CaP at Yale-New Haven Hospital in the years 1991 to 1992. Two independent reviewers (a urologist and an internist) evaluated time vs. PSA curves constructed for each patient.
Reviewers used clinical judgement to determine whether there was evidence of PSA failure. From these data, a slope cut-off of 1 ng/mL/year was established (with sensitivity = 0.94 and specificity = 0.93) for the Yale definition of biochemical failure. This definition was then validated in a group of 238 patients diagnosed with CaP during 1991 to 1995 at eight VA medical centers. PSA failure and median time-to-failure were determined for the new definition and for definitions for prostatectomy and for radiotherapy. These definitions were applied independent of therapy. Criteria for surgical failure were met in 165 patients (69 percent) with the post-radiation definition classifying 66 patients (28 percent) as having failed. The Yale definition was intermediate between these two, identifying 112 (47 percent) as having failed. The Yale definition was also intermediate in its median time to PSA failure 3.2 months for the surgical definition vs. 13.8 months for Yale definition vs. 15.5 months for the post-radiation definition. The Yale definition of PSA failure is practical, clinically, and epidemiologically applicable regardless of treatment, and intermediate between current definitions of PSA failure.

UTILITY OF INTRAOPERATIVE PTH MONITORING IN PREDICTING METABOLIC CONTROL OF PTH LEVELS IN SECONDARY HYPERPARATHYROIDISM. Vasanthi P. Lakshminarayan, Barbara K. Kinder, and Sanziana Roman.

The purpose of this study is to evaluate whether the intraoperative PTH (iPTH) assay may be used in the surgical management of secondary hyperparathyroidism to predict metabolic control of PTH levels in patients with chronic renal failure (CRF). Between August 1999 and December 2001, 20 patients underwent surgical parathyroidectomy for secondary hyperparathyroidism at Yale-New Haven Hospital. Each patient had intraoperative PTH monitoring during parathyroidectomy with levels measured at baseline (pre-excision) and at five-minute intervals post-excision of each hyperplastic gland. Study patients had an average preoperative PTH level of 659 pg/mL (1098 percent normal PTH assumed to be 60 pg/mL) and a final intraoperative decline of 84 percent from baseline at the end of the procedure. Follow-up PTH levels (range 1 to 24 months) were obtained for 17 patients through dialysis centers. Correlation of intraoperative measures with follow-up levels indicated that final iPTH (expressed as an absolute value or percent of normal PTH) is more predictive of follow-up PTH levels (r = 0.472, p < .05) than percent decline from baseline (r = 0.244, p > 0.05). When patients were separated into two groups based on follow-up PTH levels remaining at or below versus higher than final intraoperative PTH, no statistically significant difference was seen in intraoperative PTH values (p > .05) between the two groups. Based on our data, final intraoperative PTH levels (absolute or a percentage of normal PTH levels and not percent decline from baseline) provide the best marker of follow-up levels in an individual overtime but not necessarily in the initial postoperative period. Larger numbers of patients with longer and more consistent follow-up periods are necessary to confirm that the final intraoperative PTH level can be used as a criterion for endocrine surgeons to be assured of future metabolic control in patients with secondary hyperparathyroidism.
UNMASKING CRYPTIC EPITOPEs AFTER LOSS OF IMMUNODOMINANT TUMOR ANTIGENS THROUGH EPITOPE SPREADING. Kate M. Lally\textsuperscript{a,b}, Simone Mocellin\textsuperscript{a}, Galen A. Ohnmacht\textsuperscript{c}, Mai-Britt Nielsen\textsuperscript{c}, Maria Bettinotti\textsuperscript{a}, Monica C. Panelli\textsuperscript{c}, Vladia Monsurro\textsuperscript{a}, and Francesco M. Marincola\textsuperscript{a,c} (Sponsored by Joseph Craft). \textsuperscript{a}Department of Transfusion Medicine, Clinical Center. \textsuperscript{b}HHMI-NIH Research Scholar, Howard Hughes Medical Institute, and \textsuperscript{c}Surgery Branch, Division of Clinical Sciences, NCI, National Institute of Health, Bethesda, Maryland.

The basis of intra-tumoral and systemic T-cell reactivity toward cancer remains unclear. In particular the role that peripheral stimuli play in shaping the acquired immune response toward cancer is still poorly understood. In this study we document the surfacing of systemic immunity toward a nine residue cryptic epitope from a member of the Melanoma Antigen family (MAGE-12:170-178), following temporary regression of a single melanoma metastasis, in response to vaccination against another molecule (gp100/PMel17). This emergence was unlikely to be related to unusually high expression of MAGE-12 by the tumor, or by the influence of analog epitopes to MAGE-12:170-178. Since MAGE-12 was unlikely to be expressed at sites other than the tumor, the demonstration of MAGE-12:170-178 reactivity in post- but not pre-vaccination circulating lymphocytes suggests that the systemically observed immune response was influenced by events induced by the vaccine at the tumor site or in draining lymph nodal areas. Possibly, as suggested by pre-clinical models, immunologic ignorance is the default response toward cancer unless unusual stimulatory conditions occur. Surfacing of MAGE-12 specificity occurred in association with loss of gp100/PMel 17 targeted by the vaccine. This finding suggests that vaccinations might have effects beyond their intrinsic specificity and may trigger broader immune responses through epitope spreading by inducing changes within the tumor microenvironment. This may have important practical implication for the development of immunization strategies.

MD/MBA PROGRAMS IN THE UNITED STATES: EVIDENCE OF A CHANGE IN HEALTHCARE LEADERSHIP. David B. Larson and Howard P. Forman. Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut.

Financial constraints and poor design of the healthcare delivery system are increasingly demanding the attention of medical professionals. Managerial sciences offer a rich source of potential solutions to many of these challenges. This has created a perceived need for cooperation between management and the medical profession, as well as for individuals who are members of both groups. The popular media have reported a rising number of physicians acquiring a background in management through joint MD/MBA (Master of Business Administration) degree programs. However, no recent study has analyzed these programs. The objective of this study was to measure changes in the number and nature of the affiliations between management and medicine in the form of joint MD/MBA degree programs. Surveys of admissions officers of 125 US allopathic medical schools and of the overseers of each joint MD/MBA degree program were administered in May-December 2001. The number of joint MD/MBA degree programs has grown from six to 33 since 1993; 17 more medical schools are considering establishing the joint-degree program. 10, 15, and 20 programs produced a total of 27, 42, and 61 graduates in 1999, 2000, and 2001, respectively, and over 100 students are expected to graduate per year when all 33 programs mature. Program structure and oversight indicate a spectrum of philosophies regarding the appropriate integration of the two degrees. The joint
MD/MBA degree programs apparently attempt to complement medical education with management education rather than the converse. The growth in the number of joint MD/MBA degree programs and participants indicates a relatively sudden increase in cooperation between medical and business schools and a rising interest in management education early in the careers of graduating physicians.

EFFECTS ON LIPID METABOLISM OF METFORMIN AND TROGLITAZONE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS. Ingi Le, David G. Maggs, David Katz, Geralyn R. Spollett, Stephanie L. Page, Frances S. Rife, and Silvio E. Inzucchi. Section of Endocrinology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Metformin (M), a biguanide, and troglitazone (T), a thiazolidinedione, comprise two antidiabetic classes with unique mechanisms of action. Both have lipid lowering properties, which have not been adequately compared. To determine the effects on lipid metabolism of M and T, alone and in combination (MT), subjects were randomized to receive M 1000 mg PO BID (n = 15) or T 400 mg PO QD (n = 12) for three months, followed by three months of MT. Both groups had similar baseline characteristics: mean age 53.4 years, HbAlc 9.5 percent, and BMI 33.7 kg/m². Results were as follows:

| Lipid parameter         | Treatment group | Pre-treatment | Post-treatment | Percentage change | p value |
|-------------------------|-----------------|---------------|----------------|-------------------|---------|
| HDL (mg/dL)             | M               | 40.7 ± 10.1   | 43.2 ± 15.1    | +6.0%             | NS      |
|                         | T               | 40.6 ± 8.0    | 43.1 ± 8.7     | +6.2%             | NS      |
|                         | MT              | 40.4 ± 9.1    | 45.3 ± 12.8    | +12.0%            | .0044   |
| LDL (mg/dL)             | M               | 122.4 ± 33.2  | 113.2 ± 32.5   | -7.5%             | .036    |
|                         | T               | 133.9 ± 35.0  | 144.8 ± 37.3   | +6.1%             | NS      |
|                         | MT              | 127.0 ± 30.0  | 125.0 ± 27.7   | -1.6%             | NS      |
| Fasting TG (mg/dL)      | M               | 191.3 ± 118.1 | 162.0 ± 77.9   | -15.3%            | NS      |
|                         | T               | 229.0 ± 161.2 | 191.3 ± 101.9  | -16.4%            | NS      |
|                         | MT              | 219.7 ± 145.3 | 160.5 ± 117.6  | -27.0%            | .0083   |
| Postprandial TG (mg/dL) | M               | 253.2 ± 116.6 | 228.4 ± 95.5   | -9.8%             | NS      |
|                         | T               | 290.7 ± 147.9 | 262.6 ± 128.0  | -9.7%             | NS      |
|                         | MT              | 265.2 ± 117.1 | 225.2 ± 122.6  | -15.1%            | .0059   |
| Fasting FFA (nmol/L)    | M               | .873 ± .271   | .871 ± .227    | -27.0%            | NS      |
|                         | T               | .98 ± .42     | .69 ± .24      | -30.0%            | .033    |
|                         | MT              | .94 ± .35     | .78 ± .31      | -17.3%            | .0017   |
| Postprandial FFA        | M               | .39 ± .20     | .26 ± .13      | -32.7%            | .0091   |
|                         | T               | .37 ± .21     | .19 ± .10      | -48.7%            | .0013   |
|                         | MT              | .28 ± .21     | .18 ± .12      | -53.0%            | <.0001  |

In summary, although M and T have similar glucose lowering properties, they exhibited differing effects on lipid metabolism. M decreased LDL and postprandial FFA while T decreased fasting and postprandial FFA. Meanwhile, MT demonstrated beneficial additive effects on HDL, and fasting and postprandial TG.
MANAGEMENT OF SEVERE NEONATAL NECROTIZING ENTEROCOLITIS IN EXTREMELY LOW BIRTH WEIGHT INFANTS (WEIGHING <1000 g): ROLE OF PERITONEAL DRAINAGE. Susan J. Lee and Richard A. Ehrenkranz. Section of Newborn Special Care, Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

The aim of this retrospective study was to determine whether the employment of peritoneal drainage (PD) in extremely low birth weight infants (ELBW) with severe NEC was associated with a lower or higher mortality and morbidity than that of exploratory laparotomy (EL). This study also aimed to identify those infants with severe NEC in whom PD might be the appropriate procedure of choice.

The hospital records of all ELBW infants treated for NEC at the Yale-New Haven Children's Hospital between 1991 and 1998 were reviewed. Data were abstracted from 45 patients with Stage III NEC weighing < 1 1000 g. Six of the 45 patients were treated with initial PD, and the other 39 were treated with initial EL. The following parameters were collected from the records for analysis: birth weight, gestational age, gender, Apgar scores, age at NEC diagnosis, presence or absence of preoperative risk factors, type of procedure, length of postoperative stay, postoperative management, death, and survival. Statistical analysis was performed using Fischer's test for proportional analysis and the two-tailed unpaired student's t-test for comparing continuous sample parameters.

No statistically significant differences were found between ELBW infants with NEC Stage III who underwent PD and those with NEC Stage III who underwent EL with respect to birth weight, gestational age, age at diagnosis, and age at procedure. In addition, no statistically significant differences were found for these patients in terms of the severity of the illness at the time of procedure. There was, however, a significant difference in the outcome of these patients. Of the six patients that underwent PD, five (83.3 percent) died; of those, 4 (80.0 percent) died within one week of the procedure. In comparison, of those who underwent EL, only 17 (43.6 percent) died; of those, five (29.4 percent) died within one week of the procedure. The mortality of PD patients was nearly twice as great as that of EL patients, and yet there was no difference in patient characteristics between the two groups.

This review was unable to identify clear criteria leading to the selection of an initial surgical procedure, either PD or EL. Although the outcome of infants with severe NEC and BW less than 1000 g appeared markedly improved with EL compared to PD, limitations in the sample size of our study cautions against drawing firm conclusions. Therefore, we recommend that a randomized controlled trial of PD versus EL be performed to determine the role of PD in the management of ELBW infants with severe NEC.

MICROVASCULAR OSCILLATIONS ELICITED LOCALLY BY COMBINED IONTOPHORESIS OF PHENYLEPHRINE AND ACUPRESSURE. Frederick C. Lewis, Michael Scannell, Julie Park, and David G. Silverman. Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut.

This study tested the hypothesis that organized vasomotion of the peripheral microvasculature consistent with cholinergic oscillatory control could be elicited by local iontophoresis of phenylephrine and that the response would be enhanced by acupressure at the Lung point of the ear (a method known to increase vagal tone).

Heart rate, respiration, and forehead flow (via a 1 mm² laser Doppler surface probe) were monitored in eight healthy volunteers. Forehead flow was measured at three sites receiving iontophoresed phenylephrine, iontophoresed normal saline (NS), or no ion-
ROLE FOR SIALIC ACID IN THE FORMATION OF TIGHT LYSOSOME-DERIVED VACUOLES DURING TRYPANOSOMA CRUZI INVASION. Monica E. Lopez, Chau Huynh, Luciana O. Andrade, and Norma W. Andrews. Section of Microbial Pathogenesis, Yale University School of Medicine, New Haven, Connecticut.

Previous studies have shown that sialic acid plays a role in cell invasion by Trypanosoma cruzi, the etiologic agent of Chagas disease in humans. Recently, work from our laboratory revealed that T. cruzi entry into nonphagocytic cells involves the recruitment and fusion of host cell lysosomes with the plasma membrane, which contribute to the formation of the parasitophorous vacuole. Initial electron microscopy studies of vacuole morphology showed that the membranes of the vacuole and of the parasite are very tightly apposed, resulting in very small intravacuolar volumes. We hypothesized that sialic acid, a molecule present in abundance on lysosomal membrane glycoproteins, might mediate this strong interaction. To gain insight into the role of sialic acid in the formation of these vacuoles, we studied the trypanosomal parasitophorous vacuole morphology in wild-type Chinese Hamster Ovary (CHO-K1) cells and in a sialic acid-deficient mutant cell line (Lec2) using transmission electron microscopy.

Here we confirm previous reports that sialic acid-deficient Lec2 cells are 50 percent less susceptible to invasion by T. cruzi than wild-type CHO-K1 cells. We ruled out faulty Ca\textsuperscript{2+} signaling and lysosomal exocytosis as possible mechanisms for the decreased susceptibility to T. cruzi invasion of Lec2 cells.

On transmission electron microscopy, Lec2 parasitophorous vacuoles display an atypical morphology that is characterized by a frail apposition of parasite and vacuole membranes. Stereology analysis using the point-counting method then confirmed that Lec2 vacuoles indeed have 40 percent greater "unoccupied" volume density than their wild type CHO-K1 counterparts. Furthermore, β-hexosaminidase assays detected that sialic-acid deficient Lec2 cells have a 65 percent increase in extracellular release of their lysosomal contents during T. cruzi invasion, when compared to wild-type CHO-K1 cells.
Taken together, these findings suggest that sialic acid associated with lysosomal glycophosphatidylglycoproteins is necessary for the formation of tightly-sealed parasitophorous vacuoles required for efficient invasion by *T. cruzi*.

**REACTIVE GLIOSIS FOLLOWING HIPPOCAMPAL IMPLANTATION: A BIOCOMPATIBILITY EVALUATION OF FIVE MATERIALS.** Karl A. Lozanne (Sponsored by Dennis D. Spencer). Department of Neurosurgery, Yale University School of Medicine, New Haven, Connecticut.

The present study aimed to determine the biocompatibility of several materials proposed for the development of a novel intracranial biosensor. The filial reaction induced by short-term (14 day) and long-term (90 day) implantation of potential biosensor substrates, namely carbon, silicon, gold, platinum, and Pyrex, into the hippocampus was measured and characterized. Needle shaped implants of each material, 0.5 mm in diameter, were implanted into the hippocampi of adult rats for 14 or 90 days. Glial fibrillary acidic protein immunohistochemistry coupled with mean optical density (MOD) measurements were used to determine the level of reactive gliosis following implantation. The extent of gliosis varied depending on the implant type and was lowest for platinum followed in increasing level by gold, carbon, silicon, and Pyrex. The glial reaction decreased in volume over time for each substrate except Pyrex, leaving behind a thin, porous glial membrane at the brain-implant boundary. We conclude that platinum and gold are the best substrates for a chronically implanted neural biosensor, but that carbon and silicon are also suitable. We caution against the long-term use of Pyrex as a substrate because a chronic glial reaction develops following its implantation.

**PSYCHOLOGICAL SEQUELAE AND PERCEPTION OF TRAUMATIC EXPERIENCES AMONG SURVIVORS OF TORTURE.** George Lui, Allen S. Keller, and John Concato. 1Department of Internal Medicine, New York University School of Medicine, New York, New York; and 2Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Purpose: This study evaluated survivors of torture to: 1) describe demographic characteristics and torture history, 2) quantitatively assess psychological sequelae of patients over time, and 3) qualitatively assess patients' perception of their traumatic experiences.

Methods: We interviewed patients in the Bellevue/NYU Program for Survivors of Torture at intake, three and six months. Anxiety and depression were measured with the Hopkins Symptom Checklist-25 (HSCL-25). PTSD was diagnosed by a psychologist or psychiatrist at intake and measured with the Harvard Trauma Questionnaire (HTQ) at three and six months. Open-ended questions were asked about what most bothered the patient about their traumatic experience, and their reactions to the events of September 11, 2001.

Results: At intake, 79 percent (n = 15/19) were symptomatic for anxiety (HSCL-25 > 1.75), 84 percent (n = 16/19) for depression (HSCL-25 > 1.75), and 80 percent (n = 12/15) for PTSD (by psychologist or psychiatrist). Among 10 patients with follow-up data, there was an improvement in symptoms of depression by HSCL-25 (10/10, 100 percent at baseline vs. 3/10, 30 percent at 6 months; p = .003) and of PTSD by HTQ (9/10, 90 percent at baseline vs. 0/10, 0 percent at 6 months; p < .001). Patients were most disturbed by recurrent memories of their past experience and reacted predominately with confusion and re-experiencing degradation and loss. After the events of September 11,
nine of the 11 patients responded with sympathy for the people who died. Eight patients reported increased memories of their past trauma, and seven stated that they were more afraid of discrimination after September 11.

Conclusion: This thesis suggests a high prevalence of anxiety, depression, and PTSD symptoms among survivors of torture. When receiving care in a multidisciplinary program, many of these patients showed improvement in their psychological sequelae over six months. Finally, both standardized instruments and open-ended questionnaires are useful in identifying and understanding how to treat survivors of torture.

AN APPRAISAL OF HONG KONG'S PUBLIC HOSPITAL SYSTEM IN 2001. Yee-Bun Benjamin Lui. Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut.

The Hong Kong Government established the Hospital Authority in 1990 to manage all public hospitals in Hong Kong. In so doing, the Government had followed the chief recommendations of the 1985 Scott Report to separate hospital care from primary care, and to establish a statutory body independent of the civil service structure but accountable to the Government to oversee this new public hospital system. This essay examines this important transformation in Hong Kong's public hospital system. It first provides the background and history of this public hospital system. It then examines the system's problems that had led to the Scott Report's recommendations and the subsequent creation of the Hospital Authority, and delineates the HA's objectives. Next, using multiple sources of available evidence, this essay assesses the Hospital Authority's degree of success/failure in meeting its objectives and addressing the system's problems.

This essay found that while the Hospital Authority appeared to have met some of its objectives, it has not met or only partially met some of its other objectives. Moreover, new problems have arisen from the creation of the Hospital Authority, namely 1) the vertical division between management personnel from the Head Office above and clinical personnel from the hospitals below, and 2) the further fragmentation of the public healthcare delivery structure by separating hospital care from primary care. The essay concluded, therefore, that the present management transformations embodied in the creation of the Hospital Authority could not alone solve many of the problems in Hong Kong's public hospital system. In light of this assessment, this essay gives a set of recommendations for improving Hong Kong's public hospital system.

CHRONIC RENAL FAILURE IN IRANIAN CHILDREN. Kamyar Madani and Hassan Otoukesh (Sponsored by Scott Van Why and Asghar Rastegar). Department of Nephrology, Ali-Asghar Children's Hospital, Iranian University of Medical Sciences, Tehran, Iran.

We investigated chronic renal failure (CRF) in Iranian children in order to generate baseline data including incidence, prevalence, etiologies, and modalities of renal replacement therapy, and to define strategies to identify those subjects at risk for renal disease later in life. We reviewed charts of 166 Iranian children (95 boys and 71 girls) from July 1991 to June 1999 at a tertiary referral center. The mean age at onset of CRF was 7.9 ± 4.5 years. The most common cause of CRF was congenital urological malformations (78 cases). The second most common cause of CRF was hereditary nephropathy (21 percent). High rates of cystinosis and primary hyperoxaluria were seen, and these elevated rates could be due a high prevalence of parental consanguninity. The difference in the parental
consanguinity rate for patients with non-hereditary nephropathies (24 percent) and those with hereditary nephropathies (46 percent) was statistically significant (p = .027). Eighty-six patients required renal replacement therapy, of which the majority underwent hemodialysis. The prevalence of primary reflux nephropathy as a cause of CRF was high compared to reports from Western countries. Earlier diagnosis and management of urinary tract infections in this group could reduce the prevalence of reflux as a cause of CRF in this population. Genetic counseling programs may be of benefit in the prevention of hereditary nephropathies.

REGULATION OF G-PROTEIN SIGNALING BY POST-TRANSLATION PROTEIN MODIFICATIONS. Louis A. Marotti, Jr. and Henrik G. Dohlman. Department of Pharmacology, Yale University School of Medicine. New Haven, Connecticut.

Heterotrimeric G proteins play a role in many important biological processes. Therefore, it is essential that we gain an understanding of the mechanisms underlying the regulation of their activity. One way in which protein activity can be regulated is through the addition of specific post-translational modifications. Here, we examine the effects of two post-translational modifications on G protein signaling — ubiquitination of Gpal, a yeast G protein α-subunit, and phosphorylation of Sst2, a yeast RGS protein and cognate RGS of Gpal. First, the site of ubiquitin attachment on Gpal is mapped using mass spectrometry. This information is then used to construct ubiquitination-resistant Gpal mutants, and the activities of these mutants are examined in functional assays of yeast pheromone signaling. Sst2 is phosphorylated by a mitogen-activated protein (MAP) kinase in response to pheromone stimulation. The phosphorylation takes place in a MAP kinase consensus sequence, Pro-X-Ser-Pro. Here, we evaluate the importance of the “X” residue in determining, the substrate specificity of MAP kinase phosphorylation in vivo. Substitution of the “X” residue with all 20 possible amino acids, as well as deletion of it, alters Sst2 phosphorylation. We conclude that, contrary to existing dogma, the amino acid identity of “X” is important in determining the efficiency of MAP kinase interaction. This work provides further insight into mechanisms of G protein signaling regulation.

INFLUENCES OF BACK-UP PRESCRIPTIONS ON SATISFACTION AND ANTIBIOTIC USE. Corey L. Martin and David L. Katz. Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut.

While the etiology of most diagnoses of acute rhinosinusitis is viral, many physicians continue to prescribe antibiotics for treatment of acute rhinosinusitis. This retrospective survey study sought to determine if providing patients control over the use of antibiotics, (i.e., giving a back-up prescription and guidelines for appropriate use) would decrease the inappropriate use of antibiotics, while maintaining patient satisfaction with medical treatment.

A total of 114 patients completed the survey. Seventy-six percent of patients expected antibiotic treatment for their illness. When patients expected antibiotic treatment for their illness, satisfaction rates were significantly associated with receiving an antibiotic prescription (p = .0465). Furthermore, the likelihood of not consulting another physician due to dissatisfaction was significantly associated with receiving an antibiotic prescription (p = .0111). Patients in our study group were also queried about the use of back-up prescriptions. Over two-thirds of patients (69.7 percent) preferred future treatment for acute
rhinosinusitis with a back-up antibiotic prescription. Ninety-one percent of patients (91.1 percent) stated they would wait at least one day to fill the antibiotic prescription with 52.7 percent of patients stating they would wait at least seven days to fill the prescription. Satisfaction with the concept of back-up prescriptions was not significantly different than satisfaction with conventional treatment (p = .662). Our results suggest that antibiotics are associated with satisfaction in patients who expect an antibiotic. Patients are accepting of the concept of back-up antibiotic prescriptions, and patients would have at least equal satisfaction with back-up antibiotic prescriptions versus conventional treatment for acute rhinosinusitis. By inquiring if patients expect an antibiotic we may be able to decrease antibiotic prescriptions in acute rhinosinusitis. Also, the fact that 91 percent of the patients would wait at least one day to fill their prescription and 52.7 percent of the patients would not fill their prescriptions until they had symptoms for at least seven days suggests a potential health care cost savings.

CHARACTERIZATION OF THE IMMUNE RESPONSES TO THE TUMOR-ASSOCIATED HY-ANTIGEN. Melissa A. McKirdy, Terry J. Fry, Fraia Melchionda, and Crystal L. Mackall (Sponsored by Gregory Plautz). Pediatric Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

Our purpose was to characterize the naturally occurring T cell response to a model tumor antigen. Using a tumor, MB49, that naturally expressed the male minor histocompatibility antigen, HY, we studied whether tolerance vs. immunity to HY was induced during tumor growth. Our model involved analysis of HY-specific T cell expansion using tetramers of MHC I molecules bound to the immunodominant epitope of HY, analysis of cytokine production to HY using ELISPOT, and analysis of the capacity of tumor-exposed T cells to mediate HY-disparate skin graft rejection. We found that male mice show more rapid primary tumor growth than females, that T cell depleted females show faster tumor growth than T cell replete hosts, and that reconstituting HY-specific T cell immunity controls tumor growth. Furthermore, lymph node (LN) cells from tumor-bearing hosts showed enhanced capacity to reject skin grafts following adoptive transfer. Thus, MB49 does not induce tolerance to HY; instead, naturally acquired T cell dependent and HY-specific immune responses are induced during tumor growth. However, in tumor-bearing hosts, ELISPOT revealed low-level reactivity to HY, and expansion of HY-reactive cells via tetramer were not detected. Therefore, the failure to adequately amplify anti-tumor responses limits hosts’ ability to control tumor growth. We investigated to what degree T cell active cytokines (IL-2, IL-15, IL-7) could amplify antigen-specific immune responses and found IL-7 to dramatically increase HY-reactive T cells following immunization. Thus, in an attempt to enhance the endogenous HY-specific response, IL-7 was administered to thymectomized/T cell depleted recipients of transferred LN cells that were then challenged with tumor. Although IL-7 lowered the requirement for transferred LN cells needed to achieve skin graft rejection, IL-7-treated T cells could not mediate tumor rejection. Together, these data indicate that tumor antigens weakly prime for a T cell-mediated, anti-tumor immune response but that limitations in effector cell expansion prevent control of tumor growth. Future studies are needed to identify optimal regimens for amplifying naturally occurring weak anti-tumor immunity.
CONDITIONAL EXPRESSION OF WNT-1, A REGULATOR OF GAP JUNCTIONS, IN THE MURINE HEART. Jeffrey M. Miller and Glenn I. Fishman (Sponsored by Steve Goldstein). Section of Cardiology, Department of Internal Medicine, Mount Sinai School of Medicine, New York, New York.

The goal of this study was to determine whether overexpression of the transcription factor Wnt-1 in the murine heart in vivo would induce upregulation of Connexin43 (Cx43). Cx43, the primary gap junction protein in the heart, is downregulated in several types of cardiac disease predisposing to arrhythmia, and restoration of Cx43 could theoretically reduce arrhythmogenesis. This hypothesis was tested using the tetracycline transactivator (tTA) system, which permits conditional expression of a transgene in vivo. A new line of transgenic mice harboring the tetO-wnt1 DNA construct was successfully created via transgenesis. As binding of tTA to tetO induces genes downstream of tetO, tetO-wnt1 mice were subsequently mated with a line of transgenic mice expressing tTA constitutively in cardiac myocytes. Interaction between tTA and tetO in double-transgenic mice was competitively inhibited via administration of doxycycline until adulthood, at which point doxycycline was withdrawn from drinking water to induce cardiac expression of Wnt-1.

Studies of heart lysates from double-transgenic mice via Northern and Western analysis revealed a significant doxycycline-dependent induction of Wnt-1. Initial Northern and Western analysis did not show an accompanying increase in Cx43 in response to Wnt-1 expression (18 percent decrease in Cx43 by Western, p = .50). These findings may result from a lack of secretion of Wnt-1 by the myocytes in which it is expressed, a necessary step in the Wnt-1 pathway. Interestingly, we observed that expression of tTA, an intermediary in the transgenic system, led to a significant reduction in Cx43 mRNA and protein as compared to wild-type controls (52 percent reduction by Western, p = .033; 50 percent reduction by Northern, p = .01). Further studies will seek to understand the mechanism by which tTA downregulates Cx43, and to elucidate the differences between in vitro and in vivo expression of Wnt-1.

THE USE OF PLATELET CONCENTRATE IN POSTEROLATERAL LUMBAR SPINAL FUSION: A BIOMECHANICAL, HISTOLOGIC, AND RADIOGRAPHIC ANALYSIS. Jose J. Miranda. Department of Orthopaedics and Rehabilitation, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to evaluate the potential use of platelet concentrate as an adjunct to autograft and as an autograft extender in the New Zealand white rabbit. Posterolateral fusions were performed at the L5-L6 level using two different volumes of iliac crest autograft: 1.5 cc and 3.0 cc, with and without platelet concentrate, for a total of four groups. The platelet concentrate used was prepared using blood collected from donor rabbits and had an approximate concentration of 1,000,000 platelets/μl. Animals were sacrificed five weeks after surgery, and bone growth and fusion were evaluated using radiographic, biomechanical, and histologic analysis. At the 3.0 cc graft volume, the fusion rates approached 90 percent in both the groups with and without platelet concentrate. At the 1.5 cc graft volume, the platelet concentrate group had a fusion rate of 58 percent, which was double that of autograft alone (29 percent). We therefore conclude that when the amount of bone graft is limited, platelet concentrate may function as a graft extender in posterolateral fusion with a marked increase in the fusion rate. No effect of the platelet concentrate supplementation could be established on the high fusion rates achieved with adequate volume of bone graft.
A COMPARISON OF THE RATE OF ARTERIOSCLEROSIS IN PATIENTS WITH THE MARFAN SYNDROME AND THE GENERAL POPULATION. Biren P. Modi and John A. Elefteriades. Section of Cardiothoracic Surgery, Department of Surgery, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to determine the prevalence of arteriosclerosis in patients with the Marfan syndrome in comparison to control individuals from the general population. The study arm consisted of eight patients with Marfan syndrome who had available preoperative computed tomography (CT) scans of the chest without intravenous contrast. The control arm consisted of eight age- and gender-matched patients who also had available CT scans of the chest. The CT scans were evaluated for the presence of calcium in the thoracic aorta and the coronary arteries using a semi-quantitative scale score of 0 to 3 for each artery. For all patients, a thorough chart review was conducted to search for body mass index and any history of hypertension, hypercholesterolemia, diabetes, prior stroke, prior myocardial infarction, or smoking. Though the differences were not significant, the Marfan group was younger, leaner, more likely to qualify as hypertensive due to beta-blocker administration, and less likely to be diabetic. The mean aortic calcium scores for Marfan patients and control patients were 0.000 and 0.125, respectively (p = .5). The mean coronary calcium scores for Marfan patients and control patients were 0.000 and 0.125, respectively (p = .5). These results suggest that some trends do exist which could indicate that and explain why Marfan patients have less advanced arteriosclerosis. Future studies will bear out these trends.

RADIAL SCARS OF THE BREAST: CORRELATION OF MAMMOGRAPHIC FEATURES WITH ASSOCIATED HISTOPATHOLOGY. Rashida B. N'gouamba, and Liane E. Philpotts. Section of Breast Imaging, Department of Diagnostic Radiology, Yale University, School of Medicine, New Haven, Connecticut.

This study will try to determine if there is an association between radial scars and breast cancer and the correlation with mammographic features.

Pathology reports of breast biopsies performed at our institution (1988 to 1998) were reviewed to identify cases of radial scars. The pre-biopsy mammograms were available in 154 of these cases. These were blindly reviewed to assess the mammographic lesions (mass [with or without calcifications], calcifications, or architectural distortions). The associated histopathologic findings were categorized as malignant, borderline (atypical ductal/lobular hyperplasia or lobular carcinoma in situ), or benign. The mammographic features were correlated with the pathologic findings.

Of the 154 cases, the mammographic features were calcifications in 80 (52 percent), masses in 54 (35.1 percent), and architectural distortion in 20 (13 percent). The associated pathology revealed 28 (18.2 percent) carcinomas (39.3 percent invasive carcinoma and 60.7 percent ductal carcinoma in situ), 28 (18.2 percent) borderline, and 98 (63.6 percent) benign lesions. Of the calcifications, 17 (21.3 percent) were malignant and 1 (21.3 percent) were borderline. Eight (14.8 percent) of the masses were malignant, and 7 (13 percent) were borderline. Of the architectural distortions, three (15 percent) were malignant, and four 20 percent were borderline.

Radial scars diagnosed on breast biopsy were found associated with malignancy (18.2 percent) or borderline (18.2 percent) histology in more than a third of cases. The incidence of associated malignancy was similar for all mammographic features.
FETAL RENAL DOPPLER PEAK SYSTOLIC VELOCITY AND PERINATAL OUTCOME IN INTRAUTERINE GROWTH RESTRICTION. Hung Dinh Nguyen and Raymond Bahado-Singh. Section of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut.

The purpose of our study is to evaluate the clinical usefulness of the renal artery Doppler peak systolic velocity in predicting small for gestational age fetuses (SGA), severe SGA, and perinatal complications resulting from poor fetal growth. In addition, we also wanted to compare the diagnostic accuracy of the peak systolic velocity (PSV) with that of the resistance index (RI), an angle-independent Doppler index. Renal artery Doppler PSV and RI were measured prospectively in fetuses at risk for small for gestational age. Maternal and neonatal outcome data were extracted from hospital charts and recorded. Normative data were generated from appropriately grown fetuses delivering at 37 weeks or more without complications. The Doppler indices were expressed as multiples of the normal median (MOM) for gestational age. Using receiver operator characteristics curves, optimal Doppler thresholds for the detection of SGA cases, severe SGA cases, and adverse perinatal outcome were determined. Stepwise logistic regression analyses were used to compare the diagnostic accuracy of the PSV with that of the RI. There were 406 study patients of which 119 (29.3 percent) were SGA and 78 (19.2 percent) were severe SGA. The renal artery Doppler PSV was a statistically significant predictor of SGA, severe SGA, and perinatal complications. The areas under the curve (p value) were 0.572 (.023), 0.581 (0.026), and 0.630 (< .001), respectively. When compared to the renal artery RI, the PSV was a superior predictor of severe SGA and perinatal complications with p values of .014 and .021, respectively. In conclusion, our study demonstrated that the renal artery PSV is a significant independent predictor of SGA, severe SGA, and perinatal complications resulting from fetal growth restriction. Furthermore, the renal artery PSV is a better predictor of severe SGA and perinatal complications when compared to the renal artery RI, a traditional angle-independent measure.

USE OF SPECT DIFFERENCE IMAGING TO ASSESS SUBCORTICAL BLOOD FLOW CHANGES DURING EPILEPTIC SEIZURES. Andrew D. Norden and Hal Blumenfeld. Departments of Neurology and Neurobiology, Yale University School of Medicine, New Haven, Connecticut.

Seizures are thought to arise primarily from the cerebral cortex. However, the propagation and behavioral manifestations of seizures involve a network of both cortical and subcortical structures. The medial thalamus and upper brainstem reticular formation are crucial areas for the maintenance of normal consciousness. Bilateral involvement of these structures may be responsible for loss of consciousness during partial seizures. Therefore, we sought to investigate the role of the medial thalamus and brainstem in seizures. We performed SPECT ictal-interictal difference imaging co-registered with high-resolution MRI scans to localize regions of cerebral blood flow changes in patients undergoing inpatient monitoring for epilepsy. Ictal-interictal SPECT scans from 43 seizures in 40 patients were analyzed. The medial thalami showed SPECT difference imaging changes of more than 20 percent in 18 patients. Of patients with medial thalamic changes, the majority (13 of 18) had seizure onset in the temporal lobe, while only one had confirmed onset in extratemporal structures, and the remainder were non-localized. In contrast, in the 22 patients without greater than 20 percent SPECT changes in the medial thalami, six had extratemporal onset, six had temporal onset, and the remainder were non-localized. In
patients with temporal lobe seizures, the side of greater medial thalamic and brainstem reticular formation involvement was strongly related to SPECT injection timing such that there was a sequential pattern of ipsilateral followed by contralateral changes. Brainstem structures showed greater than 20 percent SPECT changes in 27 of 43 seizures with no clear relation to temporal or extratemporal onset. We conclude that the medial thalamus is preferentially involved in seizures arising from the temporal lobes, possibly reflecting the strong connections between limbic temporal structures and the medial thalamus. Sequential involvement of ipsilateral followed by contralateral structures in the medial thalamus and upper brainstem may explain how seizures produce peri-ictal loss of consciousness despite incomplete involvement of the cerebral cortex.

RISK FACTORS FOR DELAYED DIAGNOSIS OF SUBARACHNOID AND INTRACEREBRAL HEMORRHAGE. Joyce M. Oen-Hsiao, Walter M. Kernan, Catherine M. Viscoli, and Lawrence M. Brass. Yale University School of Medicine, New Haven, Connecticut; Lewis B. Morgenstern, University of Texas School of Medicine, Houston, Texas; Issam A. Awad, Yale University School of Medicine, New Haven, Connecticut; Janet L. Wilterdink and Edward Feldmann, Brown University School of Medicine, Providence, Rhode Island; Thomas Brott, Mayo Medical School, Rochester, Minnesota; Ralph I. Horwitz, Yale University School of Medicine, New Haven, Connecticut.

To identify risk factors for delayed diagnosis of subarachnoid (SAH) or intracerebral (ICH) hemorrhage in younger patients (ages 18 to 49), we performed a subsidiary case-control study among 702 subjects from the Hemorrhagic Stroke Project (HSP). Case subjects were the 54 HSP patients (7.7 percent) who did not receive an appropriate diagnostic evaluation (brain CT scan, and if CT negative, LP) within 24 hours of consulting a physician for symptoms consistent with hemorrhagic stroke. For each case subject with a delayed diagnosis, we identified two subjects from the HSP with a prompt diagnosis, all successfully matched on recruitment site. We calculated odds ratios (ORs) for the association between risk factors and delayed diagnosis.

Four features were associated with risk for delayed diagnosis (criteria: OR > 2.0 or < 0.5): initial evaluation in a physician’s office (OR = 23.1), absence of alarm symptoms (photophobia, loss of consciousness, focal weakness) (OR = 4.6), no effortful activity preceding focal time (OR = 5.5), and Hispanic ethnicity (OR = 2.4). Risk factors associated with delayed diagnosis were different in patients who presented to the hospital compared to patients who presented to an office. In a separate analysis, risk factors associated with delayed diagnosis were different for patients with SAH compared with patients with ICH.

In conclusion, patients with SAH or ICH are at greater risk for a delay in their diagnosis if they do not have alarm symptoms, especially if they present to an office rather than a hospital emergency department. Efforts to reduce delayed diagnosis should be directed at primary care physicians who see low-risk patients with milder symptoms. Our findings also indicate that there are different risk factors associated with delayed diagnosis of hemorrhagic stroke based on location of presentation and on stroke type. Future research to understand and prevent delayed diagnosis must consider location of presentation and stroke type.
ABILITY OF PERIORBITALLY APPLIED ANTI-GLARE PRODUCTS TO IMPROVE CONTRAST SENSITIVITY IN CONDITIONS OF SUNLIGHT EXPOSURE. Patricia J. Pahk and Brian M DeBroff. Department of Ophthalmology and Visual Science, Yale University School of Medicine, New Haven, Connecticut.

Sun glare decreases an athlete’s contrast sensitivity and impairs his ability to distinguish objects from background. Many commercial products claim to reduce glare but have not been proven effective in clinical studies. We determined whether glare-reducing products such as EyeBlack grease and No Glare sticker reduce glare and improve contrast sensitivity during sunlight exposure.

Forty-six students were tested for contrast sensitivity using a Pelli Robson Contrast Chart. Each subject served as an internal control and was initially tested using no product. Each was then tested again after being randomized to either application of EyeBlack grease (n = 16), No Glare sticker (n = 14), or Vaseline (placebo, n = 16) on the skin at the level of the infraorbital rim. All testing was performed in conditions of direct and unobstructed sunlight exposure to the subject. ANOVA test revealed a significant difference between EyeBlack grease (Pelli Robson value 1.87 ± 0.09) and No Glare sticker (1.75 ± 0.14) in binocular testing (p = .0182). No statistical difference was found between the groups in the right eye, left eye or in the combined data of the right and left eyes. Paired T-test demonstrated a significant difference between control (1.77 ± 0.14) and EyeBlack grease (1.87 ± 0.09) in binocular testing (p = .0364). There was also a significant difference between control (1.65 ± 0.05) and EyeBlack grease (1.67 ± 0.06) in the combined data of the right and left eyes (p = .0208). There was no statistical difference found between control and treatment group in any other combination.

Our data suggest that EyeBlack grease reduces glare and improves contrast sensitivity in conditions of sunlight exposure as compared to control and to No Glare sticker in binocular testing. Further testing with larger sample sizes and controlled glare conditions are needed to determine if glare reduction occurs in a manner that would reduce sun glare in actual athletic conditions.

PREGNANCY AND CHILDBIRTH PRACTICES AND POPULAR LITERATURE IN TWENTIETH-CENTURY AMERICA: HISTORICAL AND SOCIAL PERSPECTIVES. Jacqueline J. Park (Sponsored by Susan E. Lederer). Section of the History of Medicine, Yale University School of Medicine, New Haven, Connecticut.

The purpose of the study was to demonstrate how pregnancy and childbirth practices and popular literature throughout twentieth-century America served as agents that expressed, affirmed, and challenged cultural ideologies regarding motherhood, femininity, and gender roles, and to demonstrate how historical, social, and cultural contexts influenced pregnancy and childbirth practices.

Primary sources consisted of instructional pregnancy and childbirth handbooks, as well as works of advocacy that endorsed particular pregnancy and childbirth methods or philosophies. Representative text and images that reflected the influence of contemporaneous cultural contexts, as well as historical and social contexts, were selected, documented, and analyzed.

Data were organized into five periods. In the early twentieth century, Victorian notions of femininity and sexual propriety were evident in the dictates of practical handbooks for pregnant women. During the twilight sleep debate of 1914 to 1915, doctrines linked to first wave feminism and the women's suffrage movement were manifest in demands for childbirth reform. The 1950s-era Natural Childbirth method's glorification of
pregnancy and childbirth reflected postwar ideals of a “feminine mystique” of motherhood and domesticity. In the 1960s, the popularity of the Lamaze technique defined a more active role for women in labor and delivery, and allowed for greater male participation. Finally, the home birth and midwifery movement in the 1970s to early 1980s articulated aims of the women’s liberation movement and the counterculture’s suspicion of traditional institutions.

As pregnancy and childbirth practices changed form throughout the century, each successive development bore the imprints of a unique combination of social forces that were discernible in the text and images of popular pregnancy and childbirth literature.

**POST-MASTECTOMY CHEST WALL RECURRENT: PROGNOSTIC SIGNIFICANCE OF CLINICAL AND IMMUNOHISTOCHEMICAL VARIABLES.** Analene Pentopoulos and Bruce Haffty. Department of Therapeutic Radiology, Yale University School of Medicine, New Haven Connecticut.

**Purpose:** To determine survival (OS), distant metastasis (DM) and chest wall progression (CWP) following isolated postmastectomy chest wall relapses (PM_CWR) treated with radiation therapy (RT) and to evaluate the prognostic significance of immunohistochemical (IHC) markers at the time of PM-CWR.

**Methods and Materials:** Between 1979 and 2000, 113 patients presented with a PM_CWR for treatment with RT. Paraffin-embedded blocks of the recurrent tumor for 43 cases were arranged into a tissue micro-array and processed for IHC staining of ER, PR, N53 and HER-2-neu (H2N). Based on intensity and percentage of tumor staining, each case was as classified as positive or negative.

**Results:** As of September 2001, median follow-up from the time of PM_CWR was 11 years. At five years following PM_CWR, OS was 46 percent, DM was 51 percent, and CWP was 21 percent. Patients sustaining a PM_CWR within two years of initial diagnosis fared poorly. ER and PR negativity correlated with early PM_CWR. PR+ correlated most significantly with DM following CWR with DM observed in eight percent of PRY compared to 60 percent of PR- (p < .01) at five years. CWP significantly correlated with H2N. with 14 percent H2N- patients progressing locally compared to 46 percent H2N+ (p < .01).

**Conclusions:** For patients with PM_CWR, PR negativity in the recurrent tumor is a poor prognostic factor. PR+ patients had later PM_CWR and survived longer without DM than PR- patients. H2N+ was associated with CWP. These preliminary findings have potential implications for local and systemic management of PM_CWR.

**CERVICAL CANCER INFORMATION ON THE INTERNET: HEALTH INFORMATION SEEKERS AT RISK.** Nikki Pinkerton (Sponsored by Ervin Jones, Michael Berman, and Frederick Haeseler). Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut.

A cross-sectional survey was designed to reveal what health information consumers are likely to find about cervical cancer on the Internet. Do web sites address common questions, and is their information accurate? Do common indicators of fundamental site quality, such as authorship, help health information consumers identify higher quality websites? And, do some search engines find more relevant websites than others? Two standardized rating instruments were developed. The first measured relevancy and quali-
ty by evaluating website's coverage of 55 elemental responses derived from nine cervical cancer-related topics.

More than 50 percent of the 242 unique websites located using 12 popular search engines were irrelevant by failing to address a single elemental response and a single search engine, Google significantly outperformed the other search engines. Only a minority (41.6 percent) of key elements deemed important were covered by websites (mean Quality of Information score: 22.9 out of 55) and to varying degrees, potential misinformation was found on every topic surveyed. The second rating instrument measured eight indicators of fundamental website quality (mean score 6.51 out of 12).

Higher overall Quality of Information scores were not correlated with higher quality information, but a single indicator, the ownership of the website, was correlated with higher quality websites. In summary, relevancy of cervical cancer-related information depends in part on the search engine used to locate the website; the quality of information varies greatly among websites; and Indicators of Fundamental Quality are insufficient for evaluating websites with respect to quality of information, with the possible exception of university ownership. Consumers who use the Internet as their sole source of health information are truly at risk because they are ill-prepared to make critical health care decisions based upon the largely irrelevant, variable quality of health information on the Internet that may be conflicting, incomplete, and potentially harmful.

EFFECTS OF BRAIN REGION AND GENDER ON PROTON MAGNETIC RESONANCE SPECTROSCOPY IN NORMAL SUBJECTS. Marlyanne M. Pol-Rodriguez and Robert K. Fulbright. Section of Neuroradiology, Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to acquire spectra using proton magnetic resonance spectroscopy (MRS) with a long echo time (TE) to measure clinically important brain metabolites in normal subjects. We aimed to determine whether these metabolites vary across brain regions and between men and women. The results of this study will constitute a normative database that will be used as a reference for MRS studies of patients with neurological disease.

Single voxel proton (1H) spectra were acquired in 72 subjects ranging in age from 20 to 44 years. Ten brain regions were examined. Six gray matter sites in the cerebrum included four cortical areas in the frontal, parietal, temporal, and occipital lobes, and two deep nuclear sites in the basal ganglia and the thalamus. Two cortical white matter regions were in the parietal and the frontal lobes. Two posterior fossa sites included the pons and the cerebellum. For each spectrum, the metabolites N-acetyl aspartate (NAA), creatine (Cr) and choline (Ch) were identified. Ratios of NAA/Cr and Ch/Cr were calculated for each brain region. A multifactorial analysis of variance was performed with the two metabolic ratios as dependent variables and with brain region and gender as independent variables. Posthoc statistical analysis consisted of the Scheffe's F statistic for significant difference between pairs of brain regions for both metabolic ratios.

There was significant regional variation for both the NAA/Cr ratio (p < .0001) and the Ch/Cr ratio (p < .0001). The NAA/Cr ratio was consistent within cortical gray and white matter but differed between cortical gray (smaller ratio) and white matter (larger ratio). The Ch/Cr ratio was variable in the gray matter, differed between some but not all gray and white matter regions, but was consistent within cortical white matter regions. There was no difference between men and women for either metabolic ratio. These find-
ings provide the requisite normative values to use single voxel, long TE MRS in adult patients with neurological disorders.

A HISTORY OF QUALITY OF LIFE MEASUREMENTS. Jordan M. Prutkin and Alvan R. Feinstein (Sponsored by Harlan M. Krumholz). Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Purpose: To review the origins and early development of “quality of life” measurements in the medical literature.

Methods: a comprehensive literature review of Medline from 1966 to 1986 examining articles with “quality of life” as a subject heading. Studies were included if they were the original article describing a scale’s development or used scales developed in the social science literature.

Results: The measurements have been derived from two separate sources: a transfer and expansion of medical appraisals for “health status,” and an application of sociometric and psychometric methods for populational assessment of happiness, well-being, and other “affects.” Neither source of measurements used the basic principle that a person’s “quality of life” is a state of mind, not a state of health, and that a suitable personal expression should allow the opportunity to cite distinctive individual feelings. In addition, the existing approaches are often unsatisfactory for denoting changes.

Conclusions: Since “quality of life” of individual patients was not directly sought with the two original sources, its appraisal may be improved with an old clinical method of asking patients what they believe.

A NOVEL MODEL FOR STUDYING MECHANISMS OF FEAR/STRESS IN RATS: INVESTIGATION OF A PREDATOR ODOR. Andy J. Redmond, Bret A. Morrow, John D. Elsworth and Robert H. Roth. Laboratory of Neuropsychopharmacology, Departments of Psychiatry and Pharmacology, Yale University School of Medicine, New Haven, Connecticut.

Dysregulation of the neurochemical fear response pathways may be the basis of psychiatric disorders such as panic disorder and post-traumatic disorder (PTSD). Traditional stress-inducing procedures alter working memory and increase serum corticosterone levels, immediate-early gene expression in the brain, and dopamine (DA) turnover in the stress-sensitive mesoprefrontal dopaminergic neurons. In these experiments, we used a novel approach, examining the effects of a predator odor, 2,5-dihydro-2,4,5-trimethylthiazoline (TMT) on the fear response in rats. TMT results in a unique pattern of biochemical activation. Both conditioned fear and acute TMT exposure increased serum corticosterone and DA metabolism in the mPFC; however TMT, but not conditioned fear, activated DA turnover in the amygdala, but not the nucleus accumbens core and shell. Conditioned fear, but not TMT, increased typical behaviors associated with the fear response. Second, we used a spontaneous, delayed, non-matching-to-sample task to assess working memory after TMT exposure. Rats demonstrated a robust working memory in the absence of TMT. Exposure to TMT during a 15-minute delay disrupted working memory without altering exploratory behavior. Finally, we examined the effects of TMT on the expression of the immediate-early gene product, Fos, in the amygdala, and in the midbrain, presumably on DA neurons. Both TMT and footshock activated Fos in the lateral and basolateral nuclei of the amygdala, and in the A10, but not the A9 neurons. We conclude that TMT,
is an ethologically relevant, nonpainful, stressor that fulfills basic criteria for studying mechanisms of fear in rats.

**CALCITROPIC HORMONES AND BONE RESORPTION MARKERS IN HEALTHY OLDER MEN.** Sarah R. Rettinger, Amy Arnold, and Barbara Gulanski. Yale University School of Medicine, New Haven, Connecticut and VA Connecticut Healthcare System, Section of Endocrinology, West Haven, Connecticut.

In the past two decades many studies have investigated the formidable problem of osteoporosis in post-menopausal women. Yet osteoporosis and osteoporotic fractures represent tremendous health challenges in older men as well. NHANES III estimated that three to six percent of American men over 50 years of age have osteoporosis, 28 to 47 percent have osteopenia, and one in eight men over 50 experiences a fragility-related fracture in his lifetime (Looker, 1997). The mechanisms of age-related bone loss in men remain unclear. Little or conflicting data exist addressing the role of calcitropic hormones in age-related bone loss and the changes in biochemical markers of bone metabolism in older men. In this study, we measured the calcitropic hormones, gonadal steroids, interleukin-6 (IL-6), markers of bone turnover, and bone mineral density (BMD) of healthy, community-dwelling men over age 50. Seventeen healthy, eugonadal subjects were included in the final analysis. None had secondary causes of bone loss or took medications known to affect bone metabolism. Study patients had a mean age of 68 (range 50 to 90) and were predominately (94 percent) Caucasian. Thirty-six percent of subjects had either osteopenia (12/17) or osteoporosis (2/17). Elevated serum PTH values were found in 5/17 (29 percent) subjects. The group’s 1,25 dihydroxyvitamin D levels demonstrated a wide range, but all were within the normal limits. Urinary excretion of type I collagen N-telopeptide (NTX), a marker of bone resorption, was above the upper limit of normal in 4/17 (24 percent) subjects. Serum IL-6 was well above the normal limit in 14/17 (82 percent) subjects, with a mean value of 6.3 (± 3.5) pg/mL (normal < 3 pg/mL). IL-6 and PTH demonstrated a significant positive correlation (r = 0.56, p ≤ .02) while IL-6 and 1,25 dihydroxyvitamin D demonstrated an even stronger positive correlation (r = 0.71, p < .02). Similarly, urinary excretion of type I collagen N-telopeptide (NTX) was associated with PTH (r = 0.69, p < .002), but more strongly associated with 1,25 dihydroxyvitamin D (r = 0.81, p < .002). Finally, IL-6 demonstrated significant strong correlation with bone resorption marker NTX (r = 0.82) but no correlation with bone formation marker osteocalcin. Larger studies are required to assess the impact of these biochemical findings on bone density.

**DIFFERENCES IN PATHOLOGICAL AND MOLECULAR FEATURES OF INTRADUCTAL BREAST CANCER BETWEEN YOUNGER AND OLDER WOMEN.** Neesha A. Rodrigues, Deborah Dillon, Darryl Carter, Nicole Parisot, and Bruce Haffty. Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut.

Young age at diagnosis has been reported to be a risk factor for local recurrence in patients with ductal carcinoma in situ (DCIS) of the breast treated with breast-conserving therapy (BCT). What confers this greater risk, however, is still unclear. We compared various pathological and molecular features of DCIS arising in a cohort of young women to those of DCIS arising in a cohort of older women to identify potential biological differences that could help to explain why younger patients have a worse prognosis. Our study population consisted of 20 patients ≤ 42 years of age and 34 patients ≥ 60 years of age
who were treated at our institution with BCT and whose archival paraffin blocks were available and had sufficient tumor for staining. One representative specimen block from each case was obtained. Pathological characteristics evaluated included histology, grade, and presence of necrosis. Paraffin-embedded sections were immunohistochemically evaluated for expression of HER-2/neu, ER, PR, bcl-2, cyclin D1, ki-67, and p-53. Although there was no difference in pathological features of the tumors between the two groups, HER-2/neu was overexpressed in a greater percentage of the younger population (p = .06). There was no difference in expression of the other markers. Of note, HER-2/neu expression was correlated with high nuclear grade (p = .004), necrosis (p = .06), and ER and PR negativity (p = .01 and .03 respectively) in the combined population. Our data suggest that HER-2/neu overexpression in younger patients may characterize a biological difference in their tumor and may partially contribute to their higher risk of recurrence. Further studies are needed to assess whether this difference holds independent of grade and to evaluate the prognostic significance of HER2/neu overexpression in DCIS.

HEALTH NEEDS OF WOMEN PRESENTING TO THE EMERGENCY DEPARTMENT: HIGH-RISK BEHAVIORS AND PREVENTABLE CONDITIONS. Sandra M. Scott, Gail D’Onofrio, and Linda C. DeGutis. Section of Emergency Medicine, Department of Surgery, Yale University School of Medicine, New Haven, CT.

This study was designed to identify unmet health needs of women presenting to the Emergency Department (ED). A convenient sample of patients presenting to the Yale-New Haven ED were interviewed by multicultural community-based health promotion advocates (HPAs). A Health Needs History elicited socio-demographic characteristics, high-risk behaviors, health care utilization patterns, and use of standard preventive screening. Between 12/08/99 and 12/07/00, 3033 women were screened. 15.3 percent of women were without health insurance, and the majority (62.1 percent) said they could not afford medication. Many women (15.7 percent) reported that they did not have a regular physician, and 9.9 percent either used the ED for regular care or had no usual source of care. Standard screening rates for disease prevention among women were on or above population norms: in the last year 74 percent reported having a Papanicolaou smear, and 54.2 percent over 40 reported having a mammogram. A usual source of medical care and health insurance coverage were significantly associated with having had each of these preventive tests. High-risk behaviors and conditions among women surveyed included. smoking (33.9 percent), failure to use seat belts (12.3 percent), lack of safe sex practices (54.2 percent), illicit drug use (11.9 percent), depression (25.7 percent), domestic abuse (9.7 percent), alcohol consumption (32.4 percent), unsafe alcohol use (51.3 percent of female drinkers), and alcohol dependence (10.7 percent). Women were more likely than men to inconsistently use condoms, report intimate partner violence, and take pills for depression or nerves. More risk behaviors than expected were greatest in women in the middle (30 to 54) as opposed to the youngest (29 and under) age group. In conclusion, high-risk behaviors and preventable conditions pose health threats to women presenting to the ED. Rates of standard clinical prevention measures, while similar to national norms, need improvement. The ED visit offers an opportunity for detection, intervention, and referral.
URINE AND SERUM DETECTION OF SURVIVIN, AN ANTI-APOPTOSIS PROTEIN, IN GENITOURINARY MALIGNANCY. Jennifer D. Sharp, Marcia A. Wheeler, and Robert M. Weiss. Division of Urology, Department of Surgery, Yale University School of Medicine, New Haven, Connecticut.

Survivin, an apoptosis inhibitor, is over-expressed in numerous human cancers and correlates with aggressive disease and unfavorable outcomes. Previously, survivin has been isolated from the urine of patients with bladder cancer. Detection of urinary survivin may be a sensitive, specific, and noninvasive tool in the diagnosis of genitourinary malignancies. Further, detection of serum survivin may provide important predictive/prognostic information. Survivin levels of urine and serum samples from five groups (bladder cancer, prostate cancer, other genitourinary malignancy, benign genitourinary disease, and normal controls) were assayed via an antibody-based detection system. Urine survivin was detected in 14 of 17 patients with bladder cancer, seven of 11 with prostate cancer, four of five with other malignancies, three of 11 with benign genitourinary disease, and one of 13 normal volunteers; overall, sensitivity and specificity for malignancy were 76 percent (82 percent for bladder cancer) and 83 percent, respectively. Patients with bladder or prostate cancer had significantly higher urine survivin levels than patients with benign genitourinary disease and normal controls (p < .0001, p < .005). Serum survivin was detected in 14 of 17 patients with bladder cancer, seven of 10 with prostate cancer, five of five with other malignancies, nine of 11 with benign disease, and three of 10 normal volunteers; serum survivin did not significantly correlate with presence of malignancy, stage of disease, or urine survivin levels. Urine survivin detection appears to be a sensitive, specific, and noninvasive test to identify patients with new or recurrent genitourinary malignancies. High levels of urinary survivin correlate positively with advanced grade and/or stage of genitourinary malignancy.

ANTI-INFLAMMATORY AND WOUND-HEALING PROPERTIES OF THYMOSIN β4 PEPTIDES IN THE SKIN. Michael Sherlinga, Efstathios Theodoridisb, Renata Filla, Adrian Haydayb, Robert Tigelaarb, and Michael Girardi2. aDepartment of Dermatology, Yale School of Medicine, New Haven, Connecticut; and bDept of Immunobiology, Guy's Hospital, London, United Kingdom.

Pro-thymosin-s4 (pTβ4) was recently identified as a major transcript in a serial analysis of gene expression (SAGE) library of gut intraepithelial lymphocytes (IELs). To determine whether dendritic epidermal T cells (DETCs), the IELs of the skin, produce pTβ4, quantitative reverse transcriptase polymerase chain reaction (RT-PCR) was performed on freshly isolated DETCs. DETCs produced both splice variants of Tβ4, lymphoid-Tβ4 (LTβ4) and ubiquitous-Tβ4 (UTβ4), and LTβ4 was selectively up-regulated with activation. To study the relative anti-inflammatory properties of LTβ4 and UTβ4 in the skin, the peptides were synthesized and tested in 8 to 10 week-old BALB/c and FVB mice. Three different models of cutaneous inflammation were utilized: neutrophil infiltration by foot-pad λ-carrageenan injection, irritant contact dermatitis (ICD) to α-methoxy-α-(trifluoromethyl) phenylacetic acid (TPA), and allergic contact dermatitis (ACD) to 2,4 dinitrofluorobenzene (DNFB). In all cases, mice received intradermal and intraperitoneal (IP) injections of either UTβ4 or LTβ4, methionated ubiquitous-Tβ4 (mUTβ4) or methionated lymphoid-Tβ4 (mLTβ4), or PBS vehicle prior to elicitation, and peptide IP six hr later. Footpad or ear thickness was measured at 0, 6, 24, 48, and 72 hr. In the λ-carrageenan model, LTβ4 suppressed footpad swelling 40 percent more than UTβ4 at 24 hr (.22 ± .03 mm vs. .37 ± .03 mm, p < .001), and much more than saline at
6 hr (.47 ± .04 mm vs .60 ± .02 mm, p < .01), 24 hr (.22 ± .03 mm vs .53 ± .03 mm, p < .0001) and 48 hr (.34 ± .04 mm vs .58 ± .05 mm, p < .00001). Likewise, mLTB4 suppressed footpad swelling 30 percent more than mUTB4 at 6 hr (.36 ± .06 mm vs .51 ± .05 mm, p < .03), and 26 percent more at 24 hr (.28 ± .04 mm vs .38 ± .01 mm, p < .02), and much more than saline at 6 hr (.36 ± .06 mm vs .72 ± .06 mm, p < .001), 24 hr (.28 ± .04 mm vs .69 ± .03 mm, p < .0001) and 48 hr (.55 ± .03 mm vs .53 ± .03 mm, p < .01). In the ICD model, mLTB4 decreased ear swelling by more than 25 percent vs. mUTB4 at 6 hr (.18 ± .02 mm vs .24 ± .02 mm, p < .01) and much more than saline at 6 hr (.18 ± .02 mm vs .31 ± .01 mm, p < .0001), and at 24 hrs (.17 ± .02 mm vs .22 ± .02 mm, p < .02). In the ACD model, LTB4 suppressed ear swelling 16 percent more than UTB4 at 24 hrs (.19 ± .01 mm, vs .23 ± .01 mm, p < .02), and 22 percent more at 72 hr (.15 ± .01 mm vs .20 ± .01 mm, p < .002), and more than saline at 24 hrs (.19 ± .01 mm vs .24 ± .01 mm, p < .001), and 72 hrs (.15 ± .01 mm vs .20 ± .01 mm, p < .001). Likewise, mLTB4 suppressed ear swelling 17 percent more than mUTB4 at 24 hr (.17 ± .00 mm, vs .20 ± .02 mm, p < .03), and 18 percent more at 72 hr (.15 ± .00 mm vs .20 ± .02 mm, p < .01), and more than saline at 24 hrs (.17 ± .00 mm vs .23 ± .01 mm, p < .0001), and 72 hr (.15 ± .00 mm vs .26 ± .01 mm, p < .0001). These studies indicate that LTB4 is an effective anti-inflammatory factor in the skin in vivo and is more potent than UTB4; in addition, they suggest that one of the mechanisms of DETC down-regulation of cutaneous inflammation is the production and secretion of LTB4.

**THYMIDINE PHOSPHORYLASE/PD-ECGF AND CYTOSKELETAL CO-LOCALIZATION IN HUMAN KERATINOCYTES IN VITRO.** Shannon M. Sheu, Rosalind L. Russell, John G. Haggerty, and Pauline M. Schwartz. Department of Dermatology, West Haven Veterans Affairs, West Haven, Connecticut.

Thymidine phosphorylase/platelet-derived endothelial cell growth factor (TPase/PD-ECGF) is active in human keratinocytes in vitro and in vivo. As keratinocytes differentiate, TPase activity increases and intracellular localization changes. The aim of this study was to better characterize the sub-cellular localization of TPase/PD-ECGF in keratinocytes. Immunofluorescence studies suggested that TPase/PD-ECGF has a filamentous distribution in cultured keratinocytes maintained under low calcium conditions. Dual-labeled immunofluorescence was employed to examine the possible colocalization of TPase/PD-ECGF with microfilaments, microtubules, intermediate filaments, and mitochondria. From these results, it appears that the intermediate filaments keratin and vimentin co-localize with TPase in cultured keratinocytes grown under low and high calcium conditions. An immunoprecipitation studied verified colocalization of TPase with vimentin under low and high calcium conditions, and with keratin under low calcium conditions. Thus, as TPase appears to associate with such intermediate filaments, it may participate in keratinocyte structure, differentiation, and in wound healing. The relationship between the filamentous localization of TPase and its possible mechanism of action in keratinocytes requires further extensive study.
GENETIC RISK FACTORS IN TAMOXIFEN-ASSOCIATED THROMBOEMBOLIC EVENTS DURING BREAST CANCER ADJUNCT THERAPY. Nara Chi Sun Shin. Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Over the past decade, venous thrombosis has been characterized as a multifactorial disease with both genetic and acquired risk factors. The most prevalent genetic risk factors are the Factor V (FV) Leiden (G1691a) mutation and the Factor II (FII) prothrombin gene (G20210A) mutation. A likely acquired risk factor is treatment with tamoxifen, a selective estrogen-receptor, as an increased incidence of thromboembolic events was observed in treatment arms involving tamoxifen therapy for breast cancer. To test our hypothesis that these patients with thromboembolic events were more likely to have underlying genetic risk factors, we examined 189 blood samples from breast cancer patients on adjuvant tamoxifen therapy for the FV Leiden and FII prothrombin gene mutations. For every patient who experienced thrombosis, there were two age- and stage-matched patients without thrombosis serving as controls. Mutations were easily detected using multiplex PCR and RFLP with restriction enzymes MnII and HindIII. Of the 189 patient samples, there were 16 FV heterozygotes, eight FII heterozygotes, and three FV and FII double heterozygotes; the remaining 162 samples were wild-type. This was a double-blinded study, and sample acquisition has not yet been completed. Consequently, it is unfortunately not yet possible to identify cases and controls in order to analyze the relative risk of thrombosis in patients with FV Leiden and FII prothrombin mutations. The two potential outcomes of this statistical analysis are: 1) the prevalence of FV and FII mutations is significantly greater in patients who experienced a thromboembolic event than in control patients, or 2) there is no statistically significant difference in the prevalence of these mutations among the two groups. If the former is found to be true, then this study would bear important clinical significance. Screening for these two mutations is inexpensive, and pre-treatment testing could allow either the choice of nonhormonal therapeutic agents or the possible incorporation of anticoagulant therapy for patients who carry these mutations. The benefits of this intervention should substantially reduce morbidity and mortality from venous thromboembolism and be cost-effective. If the latter is found to be true, then no association could be made between these genetic mutations and the risk of thrombosis during tamoxifen therapy. However, the overall higher prevalence of FV and FII heterozygotes in this study population versus the general population warrants an explanation. One possibility is an association between these genetic mutations and the predisposition to developing breast cancer.

ATTITUDES TOWARDS CROSS-CULTURAL MEDICINE AMONG MEDICAL STUDENTS IN THE STATE OF CONNECTICUT. Nathan Siegel, Liza Cariaga-Lo, and Forrester Lee. Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Purpose of Study: a survey of medical students enrolled at the University of Connecticut and Yale University sought to determine: (1) how supportive medical students are of cross-cultural medicine; (2) how useful and relevant they believe cross-cultural medicine will be in their future medical practices; (3) how comfortable students are in dealing with cross-cultural issues; (4) the interest in, satisfaction with, and impediments to, cultural competency training; and (5) what influence demographic factors have on students' attitudes towards cultural competency.
Methods: All medical students at the University of Connecticut and Yale University in their first through fourth years of study, or medical students from these schools that were on extended study but currently doing clinical training were eligible. A three-page survey was developed, and the finished, anonymous questionnaire distributed in April of 2001. Univariate and bivariate statistical analysis of the data was conducted.

Results: The cumulative response rate from the two schools was 49.3 percent yielding 373 completed questionnaires. Students were broadly supportive of cross-cultural medicine. However, students on the whole did not report confidence in their cross-cultural knowledge. Medical students tended to be more tolerant of alternative health practices that were more familiar to them. Overall, students expressed a qualified interest in cross-cultural training. A respondent's political philosophy highly correlated with multiple survey responses. Liberal students supported cultural competency concepts, belief in the physician's important role in cross-cultural interactions, and acceptance of cross-cultural education when compared to moderate and conservative students. Students in both preclinical and clinical stages of training agreed that cross-cultural issues were important, but clinical stage student responses reflected a more constrained, practical approach to its application. Minority ethnicity was independently and significantly associated with positive attitudes towards cross-cultural medicine. In univariate analysis, female students expressed more positive attitudes towards cultural competency, but after controlling for political persuasion, no gender difference was observed. Life experiences, volunteer activities, peer-to-peer discussions, and clinical exposure significantly influenced cross-cultural attitudes whole formal courses and lectures were least influential. However, students supported the introduction of curriculum features addressing cultural competency.

Conclusions: In general, medical students in Connecticut believe that cross-cultural medicine is an important component of the medical encounter and express qualified support for cross-cultural education training programs. Positive attitudes were most strongly expressed by politically liberal students, ethnic minorities, and students in the pre-clinical stages of medical school. Students also expressed qualified support for introducing aspects of cross-cultural education into the curriculum but acknowledged that their attitudes are more strongly influenced by personal and clinical experiences than lectures or courses on cross-cultural issues. These findings should help guide the development of appropriate curricular materials in cross-cultural medical education.

THE RISK OF INJURY TO PAKISTANI CHILDREN. Michael S. Singera and Abdul Ghaffarb (Sponsored by David Katz). aYale University School of Medicine, New Haven, Connecticut; and bMinistry of Health, Islamabad, Pakistan.

Injury is responsible for one million child fatalities every year, 98 percent of which occur in developing countries. There is a critical need to determine how these children are injured, who is most at risk, and when. Pakistan, home to 60 million children, is ideal for this work. Our Specific Aims were (1) to determine the primary causes of injury to Pakistani children; (2) identify demographic factors that predispose children to injury; (3) test when, in the context of their schedules, children were more likely to be injured, and whether these patterns differed for preschool versus school children; (4) interview families for the circumstances and consequences of injuries; and (5) distill our findings into culturally and economically feasible recommendations. We interviewed 300 inpatients at the Children's Hospital in Islamabad: 150 injury patients and 150 controls. For each Specific Aim, responses were analyzed by appropriate descriptive, case-control, or cohort methods. The most common causes of injury were falls (59 percent), road collisions (16 percent), and burns (13 percent). Most children (79 percent) were unsupervised. Except
for burns, boys outnumbered girls 2:1. The case-control study found differences in (1) the mother's level of education, (2) size of the home, and (3) number of children in the home (all p < .05). The most perilous time of day was 3 to 6 p.m. Compared to preschoolers, school children showed elevated risk on weekends (OR = 4.0, p < .001) and reduced risk during school (OR = 0.2, p < .0001). The risk for preschoolers remained stable over the week. In summary, poor supervision, poor education, and crowded homes contributed to injury in our sample of Pakistani children. We discuss steps to (1) keep children off roofs and isolate them from fires and traffic, (2) promote supervision, (3) educate parents, and (4) provide safe play options.

COMMUNITY-BASED NUTRITION INTERVENTIONS FOR THE TREATMENT OF OBESITY IN ADULTS. Jennifer Solomon, Meghan O'Connell, and David L. Katz. The Yale Prevention Research Center, Derby, Connecticut.

This systematic review examines nutrition-based randomized controlled trials for the treatment of obesity in adults. The objective is to discern "best practices" to date. The study search was performed in 2000 to 2001 utilizing Pubmed, HealthStar, Embase, and Cochrane Library. Twenty-one retrieved studies met the inclusion criteria. Quality assessment was done by two independent reviewers using techniques developed by the Centers for Disease Control. Study quality and divergence precluded the use of meta-analysis. Best practices suggested by current data are that prolonged group follow up is helpful in prolonging weight loss and in slowing the process of weight regain. Total caloric intake rather than macronutrient composition of diet is more predictive of weight loss. Specific approaches, such as providing shopping lists, meal plans, food storage protocols, plate size, etc., are more effective than general behavior therapies. Weight loss research in this area remains rather sketchy and non-amenable to meta-analysis. Consistency in interventions and outcome measures in future studies would allow for meta-analysis and potentially more conclusive data.

THE TEMPORAL RELATIONSHIP BETWEEN PEDIATRIC ASTHMA ADMISSIONS AND POLLEN COUNTS. Steven J. Song (Sponsored by Ramsay Fuleihan). Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

This study was intended to analyze pediatric admissions to Yale-New Haven Children's Hospital in relation to the counts of four different types of pollen. In a retrospective study, we determined the number of pediatric admissions for asthma to Yale New Haven Children's Hospital (YNHCH) over a period of three years (1998 through 2000). For each year, pollen counts for trees, weeds, grasses, and molds were averaged per week and plotted against the total number of admissions for asthma at YNHCH for that week. At that point, we examined the plots to see if there was a correlation between the various pollen counts and the number of admissions for each week. During mid-May, there was a consistent spike in admissions over the three years studied, while the end of September and beginning of October revealed a larger spike in admissions. Tree pollen counts only spiked in early May, while weeds only spiked in September. Plotting admissions vs. pollen counts revealed a consistent one to two week lag between the mid-May admission spike and the tree pollen count spike, and a two to four week lag between the September/October admission spike and the weed pollen count spike. Based on the current understanding of the
IgE-mediated basis of asthma, we concluded that a Type-I hypersensitivity reaction alone could not have produced the admission spike in mid-May and September/October.

SEQUENCE AND EXPRESSION ANALYSIS OF A13-1, AN IL-3 AND RETINOIC ACID RESPONSE GENE EXPRESSED IN MYELOID DIFFERENTIATION. Charles P. Stowell, Noel A. Maun, David K. Thomas, Nathan D. Lawson, and Nancy Berliner. Section of Hematology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

IL-3 and all-trans retinoic acid (ATRA) induce myeloid differentiation of the murine multipotential, stem cell factor-dependent hematopoietic cell line EML (Erythroid, myeloid, and lymphoid potential). Prior to this study, in a search for genes guiding myeloid differentiation, cDNA representation difference analysis (RDA) was used to identify immediate-early genes expressed during induction of EML cells with IL-3 and ATRA. Two RDA fragments were identified whose pattern of expression by Northern blot analysis revealed optimal expression in the presence of a combination of IL-3 and ATRA, suggesting a synergistic mode of induction. Sequence analysis revealed one fragment to be from the murine homologue of B-box protein EBBP. The second fragment was a fragment from a novel gene, designated A13-1 (ATRA and IL-3 induced gene 1). The second fragment was used to probe a λ-Zap cDNA library derived from RNA of EML cells following short-term induction, and we identified three clones. In this study, we performed sequence analysis on these three clones in an attempt to better characterize the structure and function of A13-1. We also sought to characterize the pattern of expression of A13-1 by Northern blot analysis of RNA isolated from murine hematopoietic cell lines and other murine tissues. A13-1 encodes a protein of 524 amino acids with a hydropathy profile consistent with a molecule spanning the cell membrane seven times. Sequence homology searches placed A13-1 in a subclass of the secretin-like family of G-protein-coupled receptors. Northern blot analysis confirmed the synergistic induction of A13-1 by IL-3 and ATRA in EMLs and suggested that A13-1 is expressed at several of the stages of myelopoiesis examined as well as in spleen and lung.

MEDICAL COSTS OF CHILD MALTREATMENT: YALE-NEW HAVEN HOSPITAL AND CONNECTICUT. K. Claire Stylianopoulos, Bonnie D. Kerker, Karen Santucci, and John M. Leventhal. Departments of Pediatrics and Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut.

Purpose: The purpose of this study was to estimate the medical costs of child maltreatment at Yale-New Haven Hospital and in Connecticut.

Methods: Several approaches were used to estimate maltreatment costs: (1) Costs at Yale-New Haven Hospital (YNHH) were obtained from hospital discharge data, chart review, emergency department (ED) logs, pediatric billing office and hospital financial data. Inpatient costs were estimated between 1/1/96 and 12/31/98. ED costs were estimated for the 1997 to 1998 fiscal year; (2) Maltreatment admissions in Connecticut were estimated from hospitalization incidences for maltreatment at YNHH, the maltreatment literature, and the Connecticut hospital administrative database; (3) ED evaluations in Connecticut were estimated by adjusting maltreatment evaluations at YNHH to total pediatric ED evaluations in the state; (4) Costs in Connecticut were estimated by adjusting YNHH costs to admissions and ED evaluations in the state.
Results: Costs at YNHH. There were 15 maltreatment admissions per year between 1/1/96 and 12/31/98, and 121 ED evaluations during the 1997 to 1998 fiscal year. Average cost of a maltreatment admission was $25,731, and average cost of an ED evaluation was $513. Total annual cost at YNHH, including hospitalizations, ED evaluations, follow-up appointments, and sexual abuse clinic was estimated to be $833,848. Costs in Connecticut. We estimated 76 to 79 maltreatment admissions and 1,397 ED evaluations per year. Annual cost in Connecticut, including hospitalizations, ED evaluations. follow-up, sexual abuse evaluations, and neglect evaluations in the primary care setting was estimated to be $6.3 million.

Conclusions: Maltreatment evaluations in the hospital, ED and outpatient setting are costly. Pediatricians and child advocates must continue to implement and support programs targeted towards the prevention of child maltreatment.

A STUDY OF HEPATITIS C SEROPREVALENCE IN HIV-INFECTED CHILDREN AT YALE-NEW HAVEN CHILDREN'S HOSPITAL. Scott M. Sutherland and Warren A. Andiman. Section of Infectious Diseases, Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

This study was designed to determine the prevalence of hepatitis C virus (HCV) infection in the pediatric HIV-infected population at Yale-New Haven Hospital and to examine the potential for HCV co-infection to accelerate the progression of HIV disease. As a correlate, alanine aminotransferase (ALT) levels were examined to determine whether ALT elevations might be used to predict HCV infection in this population. Stored serum samples from a living cohort of HIV-infected children (n = 66) and a deceased cohort of HIV-infected children (n = 40) were screened for antibodies to HCV using a third generation Enzyme Linked ImmunoSorbent Assay (ELISA) and subjected to confirmatory testing using a 3rd generation Recombinant Immunoblot Assay (RIBA). HIV disease progression parameters, such as age at which an AIDS-defining illness developed and age at death, as well as ALT values, were collected to compare HCV-Infected and HCV-uninfected HIV-positive children. None of the 66 living patients and one of the 40 deceased patients (2.5 percent) had serological evidence of HCV infection. 4.5 percent of living patients and 65.4 percent of deceased patients had elevated ALT levels. The prevalence of HCV infection was negligible in the pediatric HIV-infected population in New Haven. Due to the low prevalence of HCV infection, it was not possible to investigate whether HCV infection hastens HIV disease progression. However, it was evident that elevated ALT levels in this population do not correlate with HCV infection status and that these abnormalities cannot be attributed to HCV-mediated liver damage.

AXON REGENERATION AFTER SPINAL CORD INJURY IN ADULT RATS. Bayan T. Takizawa and Stephen M. Strittmatter. Department of Neurology, Yale University. School of Medicine, New Haven, Connecticut.

The purpose of this study was to determine whether axon regeneration can be induced in the injured spinal cord by administration of the Clostridium botulinum C3 exoenzyme, an inactivator of the Rho protein, or the drug Y-27632, an inhibitor of the protein kinase p160ROCK, a downstream effector of Rho. To evaluate this, the posterior two thirds of the spinal cord at T3-4 was transected in adult rats. An osmotic pump with a small catheter was used to deliver the C3 protein, the Y-27632 drug, or an appropriate control to the injured spinal cord. Behavioral studies showed that the C3 exoenzymetreated
rats had a poorer outcome and that the ROCK inhibitor-treated rats walked better than their respective controls immediately after the surgery and over the ensuing three weeks. The behavioral tests from the fourth week showed almost complete recovery by all three groups, with insignificant differences. The ROCK inhibitor-treatment group showed significant increases in corticospinal axon sprouting in the gray matter above and below the lesion. There were also a few fibers observed entering the lesion site and passing through it. The C3 experiments were inconclusive and need to be re-explored, while the ROCK-inhibitor experiments are promising, as the animals did better functionally and histologically.

THE DIAGNOSTIC ACCURACY OF KERNIG’S SIGN, BRUDZINSKI’S SIGN, AND NUCHAL RIGIDITY IN ADULTS WITH SUSPECTED MENINGITIS. Karen E. Thomas, Rodrigo Hasbun, James Jekel, and Vincent J. Quagliarello. Departments of Internal Medicine and Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut.

To determine the diagnostic accuracy of Kernig’s sign, Brudzinski’s sign, and nuchal rigidity, 297 adults with suspected meningitis were prospectively evaluated for the presence of these meningeal signs before lumbar puncture. Kernig’s sign (sensitivity = 5 percent, likelihood ratio positive = 0.97), Brudzinski’s sign (sensitivity = 5 percent, likelihood ratio positive = 0.97), and nuchal rigidity (sensitivity = 30 percent, likelihood ratio positive = 0.94) did not accurately discriminate patients with and without meningitis (≥ 6 white blood cells [WBC]/ml of cerebrospinal fluid [CSF]). The diagnostic accuracy of these signs did not significantly improve in the subset of patients with moderate meningeal inflammation (≥ 100 WBC/ml of CSF) or in the subset of patients with microbiologic evidence of CSF infection. Only in four patients with severe meningeal inflammation (≥ 1000 WBC/ml of CSF) did nuchal rigidity show diagnostic value (sensitivity = 100 percent, negative predictive value = 100 percent). In adults with suspected meningitis, neither the presence nor absence of these classic meningeal signs reliably indicate the presence or absence of meningitis; better bedside diagnostic signs are needed.

ANESTHESIA OF CHORDA TYMPANI NERVE AND EFFECT ON ORAL PAIN. Karen Tie, Katherine Fast, John Kveton, Zachary Cohen, Valerie Duffy, Jordan Prutkin, Barry Green, and Linda Bartoshuk. Department of Otolaryngology, Yale University School of Medicine, New Haven, Connecticut.

Two nerves innervate the fungiform papillae on the anterior (mobile) tongue: the chorda tympani (CN VII, taste) and the trigeminal nerves (CN V, pain) with CN V accounting for 75 percent of the innervation. There is genetic variation in the density of fungiform papillae and the ability to taste the compound, 6-n-propylthiouracil (PROP). Supertasters have the greatest density of fungiform papillae, perceive the greatest intensity from oral irritants and the greatest bitterness from PROP. Previous research has shown inhibitory interactions within taste areas in the central nervous system; input via CN VII inhibits that via CN IX (glossopharyngeal nerve; taste, posterior tongue), resulting in increased perceived intensity of taste stimuli as well as taste phantoms at areas innervated by CN IX when CN VII is anesthetized or damaged.

The data in the present study suggest inhibitory interactions between taste and oral pain. Seventeen subjects underwent unilateral anesthesia of CN VII (in separate experiments, CN VII was anesthetized on each side). Anesthesia of the chorda tympani nerve
resulted in contralateral intensification of burn sensation with 10 ppm and 100 ppm capsaicin. The magnitudes of these effects depended on genetic taste status (i.e., density of fungiform papillae): supertasters experienced the greatest intensification. We conclude from the contralateral intensification that input via CN VII normally inhibits that via CN V. These data suggest that supertasters may be at special risk for oral pain disorders as the result of damage to CN VII because of the loss of that inhibition.

THE RECOGNITION AND DETERMINANTS OF DEPRESSION AT A SOUTH AFRICAN PRIMARY CARE CLINIC. Virginia A. Triant, Beverley R. Schweitzer, and Jeffrey M. Levine. Division of Primary Health Care and Family Medicine, University of Cape Town, Cape Town, South Africa. Departments of Psychiatry and Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Depression leads to substantial morbidity and mortality on a global scale, but it is frequently under-recognized in primary care settings, particularly in under-resourced settings. This study attempts to determine rates of recognition and treatment of depressive disorders at a community clinic in the Cape Flats, South Africa.

The diagnostic instrument PRIME-MD was administered and charts reviewed for a sample of 222 patients presenting to the Lotus River Community Health Centre. Outcomes sought were (1) the prevalence of depressive disorders and (2) rates of detection and treatment as indicated by antidepressant prescription.

The prevalence of depressive disorders in the group was found to be 32 percent (n = 70), with 13 percent meeting criteria for major depressive disorder (n = 29). There was a statistically significant correlation between a diagnosis of depression and prescription of a tricyclic antidepressant (TCA) (p = .028). The sensitivity and specificity of a TCA prescription for depression were 20 percent and 91 percent, respectively. Multiple logistic regression analysis demonstrated that the most predictive factor of either a diagnosis of depression or a prescription of an antidepressant was the presence of somatic symptoms.

In this primary care setting, patients with depressive diagnoses were frequently distinguished from those without depression as indicated by a significant correlation between depression and antidepressant receipt. Physicians appeared to respond primarily to somatic rather than psychological presentations. While depressed patients received antidepressants more frequently than non-depressed, only a minority of depressed patients was actually recognized as such. Analyzing patterns of detection requires an understanding not only of physician practices but also of the cultural setting and the health care system.

AROUND-THE-CLOCK EMERGENCY RADIOLOGY ATTENDING COVERAGE IN THE INTERPRETATION OF ABDOMINAL CT SCANS. Jeanne K. Tyan, Harry C. Moscovitz, and Howard P. Forman. Section of Emergency Medicine, Department of Surgery and Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut.

Our study examined the effect of two recent interventions instituted by the Department of Radiology at Yale-New Haven Hospital on reducing the error rate in the interpretation of radiological studies in the emergency department (ED). The first intervention increased coverage of on-site board-certified radiologists to 24 hours a day, every day. The second required those radiologists to provide a finalized dictation contemporaneous with the clinical case and also required an over-read of every study done in the ED within 24 hours by a radiologist specializing in that type of film. We compared the finalized radiol-
ogy reports of patients who had abdominal CT scans during the three time periods surrounding the two interventions with the documentation of the ED scan which represents the radiology interpretation by which management and diagnosis was based in the emergency department. We analyzed a total of 670 patients in these three groups and found that major discrepancy rates between the initial and final interpretations were significantly decreased by both of these two interventions (p = .018). This effect was especially significant during weekends and nights (5 p.m. to 8 a.m.) (p = .006). Our study proves that the institution of a two-phase QI process can significantly reduce the rate of errors in interpretation and communication of CT scans. It is hypothesized that these changes might result in improved patient care.

FACE PERCEPTION: DEVELOPING A PARADIGM USING FUNCTIONAL MRI TO ASSESS AUTISTIC DISORDER. M. Reza Vagefi and Robert T. Schultz. Child Study Center, Yale University School of Medicine, New Haven, Connecticut.

Autistic disorder is a pervasive developmental disorder diagnosed in infancy or early childhood. The current understanding of face perception has served as an initial modality for elucidating the neuro-pathophysiology of the autistic brain. Studies of individuals with autism have demonstrated deficits that suggest a failure of holistic processing mechanism when perceiving faces. A functional Magnetic Resonance Imaging (fMRI) study on seven normal controls was performed to assess the role that the fusiform face area (FFA) plays in configural versus featural processing of faces. The new task attempted to demonstrate the priority and affinity that the FFA has for configural information by comparing how faces presented as wholes and separately as parts are processed. Behavioral results from the study's task showed a fair amount of inter-subject variability with significant main effects for subjects, image types, and response types, as well as two-way and three-way interactions between these factors. Response accuracy for the group showed that correct responses were given for more often for whole face stimuli than any other stimuli and more incorrect answers were given for cut face stimuli. Reaction times indicated that most subjects were fastest at processing objects, followed by whole faces, and slowest at processing cut faces. Analysis of composite and individual fMRI's surprisingly revealed that the cut face stimuli not only activated the object areas of the brain as hypothesized, but also engaged the FFA over whole face stimuli. These results question the specificity of the FFA for holistic processing. Several suggestions are offered as to why this may have occurred, as well as, comments on improving the task and its applicability to an autistic population.

TRANSCRIPTION FACTOR XBP-1 IS ESSENTIAL FOR TERMINAL DIFFERENTIATION OF B CELLS INTO IMMUNOGLOBULIN SECRETING PLASMA CELLS. Prashanth Vallabhajosyula, Andreas Reimold, Neal Iwakoshi, John Manis, Ahn Wee, Ellen Gravallese, Daniel Friend, Michael Grusby, Frederick Alt, and Laurie Glimcher (Sponsored by Sankar Ghosh). Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, Massachusetts.

B cell differentiation is a complex process marked by antigen independent and antigen dependent maturation processes. Transcription factors play important roles in regulating the various stages of B cell differentiation. Though several such factors have been shown to be important in regulating the various stages of B cell development, very few
CT angiography (CTA) has been shown to predict penampullary tumor resectability, but whether CTA is useful in anticipating survival after pancreaticoduodenectomy for pancreatic cancer is unknown. Vascular involvement of penampullary neoplasms was scored by CTA (0 = not involved to 4 = encased). From February 1996 to September 2000, 73 patients with histologically proven pancreatic adenocarcinoma and CTA score 0 to 3 were explored for pancreaticoduodenectomy, with 57 patients found to be resectable. Hazard ratios for all covariates were estimated using Cox’s Regression, and survival was estimated by the Kaplan-Meier method. Overall resectability was 78 percent, with a median survival after resection of 25 months. In multivariate analysis, only poor differentiation predicted poor outcome (HR = 2.81, p = .014), while CTA score did not (p = .250). For patients with CTA score 0, Stage III disease had a worse prognosis than Stage I (HR = 6.56, p = .004). For Stage I disease, CTA score 1 to 3 compared with CTA score 0 trended to poorer outcome (HR = 4.99, p = .054). Surprisingly, for Stage III disease, a CTA score 1 to 3 had better survival than score 0 (HR = 0.23, p = .010). CTA alone is not an independent predictor of survival. The paradoxical finding that with Stage III disease, CTA score 1 to 3 fared better than 0 suggests that evidence of vascular involvement by CTA in pancreatic adenocarcinoma is not a contraindication to resection in terms of expected outcome. Preoperative CTA not only predicts resectability but may also be a valuable adjunct to tumor staging for predicting survival after pancreaticoduodenectomy for pancreatic cancer.
THE LONG-TERM EFFECTS OF MALNUTRITION ON IQ AND ADAPTIVE BEHAVIOR IN INDONESIAN CHILDREN. Kinari E. Webb, Sara S. Sparrow, Nicholas J. Horton, Paul Geary, and David L. Katz. Yale Child Study Center and Yale University Department of Psychology, New Haven, Connecticut; Department of Biostatistics, Section of General Internal Medicine, Boston University School of Public Health and School of Medicine, Boston Massachusetts; Section of Internal Medicine, Bethesda Mission Hospital, West Kalimantan, Indonesia; Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut.

This research explored the relationship between malnutrition, environmental factors, and the cognitive and developmental skills of Dyak children in West Kalimantan, Indonesia. We compared a child’s stature with their IQ and adaptive behavior skills at age seven to eight years old as measured by the Test of Non-Verbal Intelligence, third revision, and the Vineland adaptive behavior skills test (n = 92). The effect of timing and duration of malnutrition on IQ and adaptive behavior was also examined by using anthropometric data that had been collected monthly during the children’s first five years of life (n = 38). Shorter children were found to have decreased IQs and composite adaptive behavior scores although these associations were not significant after the confounding effects of parental IQ, schooling, and economic variables were taken into account. Shorter children had poorer scores in the motor skills subsection of the Vineland and this effect remained after controlling for environmental factors. Children with low weight-for-age z-scores at 17 and 30 months had decreased IQs and children who weighed less at 48 months had reduced adaptive behavior scores. This suggests that malnutrition at different ages may have differential effects on cognitive and developmental outcomes. Children with an increased duration of malnutrition had lower IQs but this effect did not remain when environmental factors were included in the analyses. The complex interactions and potential causal relationships between measures of nutritional status, other environmental variables, and cognitive and developmental skills are discussed. While malnutrition may have detrimental effects on cognitive and developmental skills, these effects appear to be relatively small in comparison to the large negative effects of other risk factors such as lack of schooling.

EVALUATION OF AN EMERGENCY RADIOLOGY QUALITY ASSURANCE PROGRAM AT A LEVEL ONE TRAUMA CENTER. Luke S. Yoon and Howard P. Forman. Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to evaluate the use of a redundant system in improving quality of care in the trauma setting by examining a subset of our Quality Assurance (QA) program. 531 consecutive abdominal/pelvic CT studies performed on trauma patients in a Level I trauma center from 08/22/99 to 08/21/00 were retrospectively reviewed. Each case was initially interpreted by a board-certified or board-eligible radiologist during the emergency department evaluation and was subsequently reviewed by a subspecialty abdominal imaging radiologist as part of a QA program. Nineteen were excluded due to incomplete information being available, resulting in 512 in our study. Cases with discordant interpretations had follow-up to discern management change. Of the 512 trauma cases, 153 cases showed discordant readings (29.9 percent). Review of patient records demonstrated changes in patient management in 12 cases (12/153; 7.8 percent). Three cases (3/153; 7.8 percent) were reviewed in morbidity and mortality records.
of the Department of Trauma Surgery as a direct result of misinterpretations. Six cases had additional diagnostic imaging studies for re-evaluation; Four of six cases confirmed the QA reader's interpretation while two of six cases were shown to favor the initial interpretations. Our experience suggests that discordant radiologic interpretations most often do not result in a change in patient management and outcome. However, the QA program did identify and lead to changes in management of a number of cases by providing clinically significant additional findings.