Yale University School of Medicine 
Thesis Abstracts — 2005

Ascending Aortic Aneurysm Protects Against Systemic Atherosclerosis. 
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The purpose of this study is to determine whether there is a negative association between ascending thoracic aneurysms and systemic atherosclerosis.

The degree of atherosclerosis was compared in 64 patients with aortic root aneurysm (31 annuloaortic ectasia and 33 Type-A dissection) vs. 86 matched controls. Atherosclerosis was quantified by evaluating non-contrast computerized tomographic images of the chest and scoring the degree of calcifications in the coronary arteries and aorta. Multivariable analysis was applied to determine the relative effect of cardiac risk factors and presence of aortic aneurysms on atherosclerosis. Smoking, dyslipidemia, diabetes, and age were all found to increase the degree of atherosclerosis (p < .01 to .05). Controlling for all risk factors, mean differences in the overall degree of calcification demonstrated that patients with annuloaortic ectasia and Type-A dissection were found to be protected against atherosclerosis (p = .03 and p < .0001).

Concluding, patients with aortic root pathology (aneurysm or dissection) exhibit significantly less systemic atherosclerosis than a matched control population. It is possible that these patients are inherently protected against atherosclerosis by the same genetic mutations predisposing them to ascending aortic aneurysms. The future characterization of these mutations could help elucidate the pathophysiology of atherosclerosis.

Abortion Access and AIDS Incidence in United States Women. Yuri Agrawal and Kirk Blankenship. Center for Interdisciplinary Research on AIDS, Yale University School of Medicine, New Haven, Connecticut.

We determined the effect of ease of access to abortion services on the change in AIDS incidence rates between 1996 and 2000 among women in each of the states in the United States and Washington, D.C. Data on barriers to abortion access, including mandatory waiting period laws, parental notification laws for minors and lack of public funding of abortion services were collected from each of the United States, and were combined into one variable representing ease of abortion access. Multiple linear regression analyses were performed with the abortion access variable as an independent variable and change in AIDS incidence rates as the dependent variable, with adjustment for possible confounders. A unit increase in abortion access was associated with a decrease in AIDS incidence rates in females of 4.59 cases per 100,000 (95 percent confidence interval 1.27 to 7.90; p < .05). This association was greater in states with higher percentages of African-American women. A lack of access to abortion services may increase AIDS incidence by leading to higher rates of female household headship, economic vulnerability, and engagement in high-risk transactional sex.

Activation of 5’AMP-Activated Protein Kinase Kinase in the Ischemic Myocardium. Suzanne Baron, Ji Li, Raymond R. Russell, III, and Lawrence H. Young. Section of Cardiology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

The 5’-AMP-activated Protein Kinase (AMPK) is a heterotrimeric serine-threonine protein kinase that becomes activated during physiological stress and acts to conserve ATP.
by modulating a variety of cellular energy pathways. The activation of AMPK has been
directly linked with phosphorylation by AMP-activated protein kinase kinase (AMPKK) at
a site deemed Threonine 172 (Thr\textsuperscript{172}) on the catalytic subunit of the protein. Nevertheless,
the role that AMPKK plays in regulating AMPK activity has remained unclear as recent
research has suggested that AMPKK may be constitutively active. Therefore, we isolated
AMPKK in ischemic myocardial tissue induced by either \textit{in vivo} regional ischemia or by \textit{in vitro}
low-flow ischemia in isolated working hearts and evaluated AMPKK activity, as mea-
sured by phosphorylation of Thr\textsuperscript{172} on synthetic AMPK 1 subunits or on recombinant heter-
otrimeric AMPK proteins. We found that levels of phosphorylated Thr\textsuperscript{172} on endogenous
AMPK were increased 2-fold (p < .03) during \textit{in vivo} ischemia and 2.6-fold (p < .01) dur-
ing \textit{in vitro} ischemia when compared to control conditions. Furthermore, Thr\textsuperscript{172} phos-
phorylation of recombinant AMPK proteins was increased after incubation with AMPKK iso-
lated from ischemic tissue (p < .15 for \textit{in vivo} ischemia and p < .04 for \textit{in vitro} ischemia with
recombinant AMPK 1 subunits; p < .04 for \textit{in vivo} ischemia and p < .01 for \textit{in vitro} ischemia
with recombinant heterotrimeric AMPK). These results demonstrate that ischemia increas-
es cardiac AMPKK activity, thereby suggesting that Thr\textsuperscript{172} phosphorylation and AMPK
activity are modulated by upstream kinases as opposed to phosphatase actions.

Infant Sleep Position and Related Care Practices in Low-Income, Primarily
African-American Infant Caregivers. Cristina Baseggio, Amy Margolis, and Eve
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Haven, Connecticut.

The purpose of this study was to determine infant sleep position and other practices
related to Sudden Infant Death Syndrome (SIDS) used by low-income, primarily African-
American mothers, whose infants are at high risk of SIDS. We conducted face-to-face
interviews of a convenience sample of mothers at a Women, Infants, and Children center
in New Haven between June and September 2004. Mothers were eligible if they spoke
English and had infants under eight-months-old. We interviewed 182 mothers; 50 percent
were African-American. Of participants, 10 percent reported that they usually placed their
infants in the prone position and 29 percent reported that they ever (usually, sometimes,
last night) placed their infants in the prone position. Mothers were more likely to place
their infants in the prone position at least sometimes if an important friend or relative rec-
ommended the prone position (odds-ratio [OR] 3.93; 95 percent CI 1.39 to 11.09) or they
placed a previous child in the prone position (OR 5.71; 95 percent CI 1.88 to 17.39).
Mothers were more likely to usually place their infants in the supine position if they
believed babies were most comfortable in the supine position (OR 5.91; 95 percent CI
2.02 to 17.31), received a recommendation for the supine position from a doctor or nurse
(OR 2.91; 95 percent CI 1.15 to 7.35), or trusted medical professionals (OR 2.37; 95 per-
cent CI 1.18 to 4.74). Advice from trusted sources, as well as knowledge and opinions on
comfort and safety, are important to mothers. Results from this study can be used to
inform interventions to reduce the prevalence of the prone sleep position in inner city, pri-
marily African-American infants.

Of Pills and Needles: Involuntarily Medicating the Psychotic Inmate When
Execution Looms. Julie D. Cantor (Sponsored by Dr. Howard Zonana). Depart-
ment of Psychiatry, Yale University School of Medicine, New Haven, Connecticut.

This thesis explores the case of Charles Laverne Singleton, an Arkansas man who
was convicted of robbery and murder and sentenced to death for his crimes. During his
incarceration on death row, he became psychotic and needed psychotropic medications to
control his symptoms of paranoid schizophrenia. At times, Singleton refused to take those
medications, and his psychotic delusions and hallucinations would return. It is well established in constitutional law that if an inmate is a danger to himself and others, and if physicians determine that particular medications would be in his medical interest, that such medications may be given to the inmate on an involuntary basis. It is also clear, from a constitutional perspective, that an inmate must be mentally competent before he can be executed. That is, he must understand the nature of the punishment he is to endure and the reason he is to be punished. What happens when a side-effect of those psychotropic drugs is that an otherwise psychotic inmate becomes sane enough to execute? Is it ethical and legal to continue to force that inmate — Charles Singleton — to ingest those medications? This thesis analyzes the relevant case law and the ethical and legal arguments that animate those opinions to support its conclusion that not only is it legal to medicate Singleton, but it is the most ethical course as well. Because reasonable physicians may disagree with this analysis and its conclusion, the thesis also offers rational steps those individuals can take to alleviate their sense of conflict, beyond making pronouncements that medicating Singleton is a breach of medical ethics.

**Association Between Human Sperm Morphology and Aneuploidy Using Fluorescent in Situ.** Jillian S. Catalanotti, Ciler Celik-Ozenci, and Gabor Huszar. Sperm Physiology Laboratory, Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut.

With the increased use of assisted reproduction technology requiring manual sperm selection based on sperm shape, such as intracytoplasmic sperm injection (ICSI), a potential relationship between sperm morphology and chromosomal abnormalities is a major concern. In order to assess the feasibility of simultaneous evaluation of both attributes in an individual sperm cell, we investigated whether sperm shape is preserved after decondensation and denaturation as required for fluorescent in situ hybridization (FISH). We studied 395 spermatozoa using computer-assisted morphometry, considering various head size, shape, and roundness parameters. Decondensation and denaturation were then performed, and sperm that were studied initially were re-localized and measured. To establish whether sperm of normal and abnormal shapes would behave in a similar manner in response to decondensation, the sperm were classified according to their head shapes into symmetrical (n = 115), asymmetrical (n = 115), irregular (n = 115) and amorphous (n = 50) categories. Initial shape was preserved in all morphological categories as measured either by shape factor (asymmetrical: 0 percent change, p > 0.05; irregular: 1.2 percent change, p > .05), by roundness ratio (symmetrical: 0 percent change, p > .05), or by both (amorphous: 0 percent change in roundness ratio, p > .05, 1.3 percent change in shape factor, p > .05). Overall, decondensation according to the FISH protocol does not significantly change sperm shape. FISH can be used to evaluate a potential relationship between sperm morphology and numerical chromosomal abnormalities in an individual sperm.

**Characterization of the Immunogenicity of Novel HLA-A2-Restricted Nef CD8 T Cell Epitopes in HIV-1+ Adults and Children.** Rohit Chandwani, Kim A. Jordan, Johan K. Sandberg, and Douglas F. Nixon. Gladstone Institute of Virology and Immunology, University of California-San Francisco. (Sponsored by John Rose, Department of Pathology, Yale University School of Medicine)

The CD8 T cell response is fundamental to the host defense against human immunodeficiency type 1 (HIV-1) infection. The Nef protein of HIV-1 is an important determinant of HIV pathogenesis. These two points illustrate the potential role that Nef CD8 T cell epitopes can play in the development of an epitope-based vaccine. This paper describes the antigenic characterization of five HLA-A2 restricted Nef CD8 T cell epitopes that were
identified in HLA-A2 transgenic mice and described in Sandberg (2000). These epitopes include peptides 83-91 (AALDL SHFL), 42-50 (ALTSSNTAA), 79-87 (MTYKAALDL), 137-145 (LTGFWCFL), and 181-189 (LEWRFDSRL). The novel Amplispot technique, which is based on the ELISpot, was used here to quantitate CD8 T cell responses directed against each of the peptides in PBMC samples from HIV-1 infected individuals. PBMC samples from 40 HLA-A2+ HIV-infected individuals (19 adults, 21 children) were obtained. Analysis of the magnitude and frequency of epitope recognition revealed the 83-91 peptide to be immunodominant, stimulating the strongest CD8 T-cell responses with a mean of 387 SFCs/10^6 PBMCs in 44 of samples. Overall, all five peptides were able to elicit CD8 T cell responses averaging at least 100 to 150 SFC/10^6 PBMC in a minimum of 25 percent of the HLA-A2+ patients. Substantial variation between CD8 T cell responses was observed between samples and, in particular, between adult and pediatric cohorts, with the latter having limited magnitude and breadth of the immune response. The characterization of epitopes in this study (1) validates the utility of the Amplispot technique, (2) illustrates the limited CD8 T cell response in HIV-1 infected children, and (3) identifies promising candidates for consideration in an epitope-based HIV-1 vaccine.

**Effects of cAMP on Carbachol-Induced Zymogen Activation, Secretion, and Injury in Pancreatic Acini.** Anamika Chaudhuri, Thomas Kolodecik, and Fred Gorelick. Department of Internal Medicine, Section of Digestive Diseases. Yale University School of Medicine, New Haven, Connecticut.

A hallmark of acute pancreatitis is premature activation and retention of enzymes within the acinar cell. This study examines the effects of the cholinergic agonist, carbachol, and agents that increase cAMP on zymogen activation, secretion, and cellular injury in isolated pancreatic acini. We found that secretin caused a dose-dependent enhancement in zymogen activation at physiologic (1 mm) doses of carbachol. Even at a high concentration, secretin(100 nm) produced only slight enhancement of zymogen activation with supraphysiologic (1 mm) carbachol. In contrast, 8-Br-cAMP caused a concentration-dependent enhancement in zymogen activation, peaking at 500 mM, with both physiologic and supraphysiologic carbachol. Both secretin and 8-Br-cAMP also enhanced physiologic carbachol-induced amylase secretion. However, only 8-Br-cAMP enhanced secretion at supraphysiologic carbachol. When activated enzyme secretion was evaluated, 8-Br-cAMP, but not secretin, increased chymotrypsin and carboxypeptidase secretion compared to supraphysiologic carbachol. When injury was investigated by LDH release and trypan blue retention, secretin was observed to decrease injury caused by physiologic carbachol and slightly increase injury caused by supraphysiologic carbachol. 8-Br-cAMP reduced injury at both concentrations of carbachol. Evaluation of morphologic indicators of injury demonstrated similar patterns. By examining PKA substrate phosphorylation and investigating the effects of PKA inhibitors, it was determined that PKA is partly responsible for the effects of 8-Br-cAMP. Furthermore, stimulation of the Epac pathway was found to sensitize to zymogen activation and amylase secretion caused by supraphysiologic carbachol. These results suggest that cAMP-stimulated pathways, mediated by PKA and Epac, may reduce cellular injury by causing secretion of activated enzymes.

**On the Moral Development of Medical Professionals: Can Virtue Be Taught?**

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Medical students, physicians, and scientists often find themselves in situations where they can cheat, fabricate data, and profit. Therefore, the moral character of medical professionals matters. Integrity, *inter alia*, matters. The philosophical approach to ethics that emphasizes moral character is called Virtue Ethics; virtue, in turn, is a stable disposition to do what
is right and love what is good. The purpose of this inquiry was to answer the following questions: can virtue be taught? If so, how? The methods employed were (1) philosophical reflection, (2) literature review, and (3) discussion with colleagues. The results were as follows:

1. Education, habituation, and imitation are severely limited in their ability to produce lasting changes in moral character;
2. Moral truths are objective; they are not dependent on instincts, societal conventions, or individual preferences;
3. One's will is of fundamental importance to becoming virtuous;
4. Pride and humility are foundational traits in moral development;
5. Progress toward virtue involves a fundamental reordering of one's loves.

This study concludes that moral agents are free to spurn all forms of external moral training. Nevertheless, growth toward virtue can be achieved through an acknowledgement of objective moral realities, a proper exercise of one's will, a pursuit of honesty leading to humility, and a habitual self-assessment leading to a proper re-ordering of one's loves.

**Differentiated Myeloid Cell Lines as Models for Neutrophil Functional Activation.** Jeffrey Chi, Peter Gaines, and Nancy Berliner. Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Neutrophil responses to bacterial and fungal infections are mediated by migration, phagocytosis, respiratory burst, and granule release. Functional responses of ATRA-responsive myeloid EPRO and MPRO cells were compared to 32Dc13 cells induced with G-CSF, and to HL60 and NB4 cells, each induced with ATRA. Respiratory burst was tested using a luminol derivative (Diogenes) to measure reactive oxygen species (ROS) generated by NADPH-oxidase during phorbol12-myristate 13-acetate (PMA) stimulation. Flow cytometry was utilized in a surrogate assay for secondary granule release via increased CD11/CD11b (MAC-1) expression on the cell surface in response to stimuli. Phagocytic activity using fluorescein-labelled opsonized zymosan particles was assessed under fluorescence microscopy. Migration in response to chemokines was also visualized across a porous membrane within chemotaxis chambers. EPRO and MPRO cell lines both showed upregulation of MAC-1 cell surface expression with significant respiratory burst, phagocytosis and chemotactic activity when appropriately stimulated. Both NB4 and HL-60 cells were fully capable of phagocytosis and respiratory burst activity but showed poor chemotaxis. An unexpectedly high MAC-1 surface expression was seen in HL-60 cells, but negligible change was seen in NB4 cells. 32Dc13 cells showed upregulation of the secondary granule protein genes, significant phagocytosis, and moderate chemotaxis, but absent respiratory burst. Gp91phox is a subunit of the NADPH-oxidase complex. Gp91phox mRNA and protein were deficient in 32Dc13 cells, shown by Northern and Western analysis, respectively. However, no abnormalities of Gp91phox were found by Southern blot analysis. Collectively, these studies imply that MPRO and EPRO cells possess a relatively complete phenotypic profile of neutrophil function in comparison to the other myeloid cell lines studied. This would suggest that the MPRO and EPRO lines represent valid models of neutrophil functional maturation and may be the best lines to use to study the impact of genetic manipulation on neutrophil functional capabilities.

**Autonomic Modulation of Cutaneous Sensory Thresholds in Children and Adolescents.** Richard J. Chung, Clorinda Schenck, Molly Waring, Mabel Djang, David Zurakowski, and Charles B. Berde. Department of Anesthesia, Children's Hospital Boston, Harvard University, Boston, Massachusetts. (Sponsored by Zeev N. Kain, Department of Anesthesiology, Yale University School of Medicine.)

The purpose of the present study was to investigate the effects of cutaneous sympathetic nervous system activity, modulated through whole-body warming and cooling, on
cutaneous thermal and mechanical sensory thresholds in healthy children and adolescents. This study is part of a research program designed to elucidate the role of the sympathetic nervous system in the pathogenesis of specific types of neuropathic pain.

In a group of twelve subjects, cutaneous sympathetic withdrawal and outflow were elicited through whole-body warming and cooling using a forced-air device. Cutaneous indices of sympathetic activity, including skin temperature and laser Doppler flowmetry, were measured throughout all testing phases. Quantitative sensory testing (QST) was performed at room temperature, during warming, and during cooling. The specific sensory thresholds assessed were cold sensation, warm sensation, cold pain, heat pain, vibratory sensation, and dorsal and plantar foot surface von Frey hair sensation.

The results were analyzed using non-parametric methods for related samples data (Friedman test). The Friedman test result for cold sensation was statistically significant (p = .046). The other parameters did not exhibit significant differences across temperature settings based on within-subject comparisons.

Despite the likely involvement of cutaneous sympathetic activity in certain types of neuropathic pain, the present results indicate that sympathetic modulation does not appreciably affect cutaneous sensory thresholds in healthy children and adolescents without neuropathic pain. The present study involved twelve subjects and served as a pilot in developing the specific methodologies used. As such, extension of the present protocol to a larger cohort is necessary to build upon the results presented herein.

CD8 T Cell Responses to Recombinant Vesicular Stomatitis Virus Vaccines in CD4 T-Cell Deficient Mice. Dagan E. Coppock, Elizabeth A. Ramsburg, Jean Publicover, and John K. Rose. Department of Pathology, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to determine if a recombinant vesicular stomatitis virus (rVSV) vaccine, expressing human immunodeficiency virus (HIV) EnvG, could elicit CD8 T cell responses in the absence of CD4 T cell help. If CD8 responses were deficient, we then planned to determine if they could be augmented or restored through the addition of cytokines to the vaccine vector.

Both wild-type and CD4 deficient mice received rVSV vaccine expressing HIV-EnvG. Lymphocytes were harvested post-infection on days of peak CD8 T cell response, both in primarily infected animals and animals that received a boost at thirty days post primary immunization. The frequency of antigen-specific CD8 T cells was enumerated by MHC class I tetramer staining.

Our experiments demonstrated that, though reduced in quantity, antigen-specific CD8 T cells were present, both centrally and peripherally, in CD4 deficient mice. Furthermore, when comparing cytolysis of target cells, the primary CD8 T cells in the deficient group showed a similar function to those CD8 T cells in the wild-type group.

We have concluded that our vaccine is able to induce a functional, though reduced, CD8 T cell response in CD4-deficient deficient mice. Though rVSV vectors containing cytokines have been created, further studies need to be performed to determine if these vectors can quantitatively augment or restore the CD8 T cell response.

Optimal Management of Melanoma in Situ and Stage I Melanoma: A Retrospective Case Review. Nicholas B. Countryman and David J. Leffell. Department of Dermatology, Yale University School of Medicine, New Haven, Connecticut.

The incidence of cutaneous melanoma is on the rise. While a significant amount of work has been, no study has comprehensively evaluated clinical treatment information of melanoma in situ and stage I. We performed a retrospective case review of the outpatient
management of 208 lesions of melanoma in situ and stage I melanoma. This included 137 melanoma in situ lesions and 71 stage I melanoma lesions. Male patients had 53.85 percent of the lesions, while 46.15 percent of the lesions were diagnosed in female patients. The mean age of the entire patient population was 65.57 years. Overall, the mean lesion size was 13.90 mm in diameter. The mean size of all of the melanoma in situ lesions was 14.50 mm, while the mean size of all lesions diagnosed as malignant melanoma was 11.68 mm with a mean depth of 0.42 mm.

Stage I melanoma, melanoma in situ, and all lesions considered in aggregate show a statistically significant predilection to the head and neck areas. When comparing stage I melanoma to melanoma in situ, the former show a significant propensity for the trunk. Melanoma in situ lesions of the trunk showed a significant propensity for the right side. We demonstrated a low local recurrence rate of 4.38 percent for melanoma in situ lesions and a 1.41 percent local recurrence rate for stage I lesions. Our data indicate that all of the local recurrence occurred on the head and neck. Analysis suggests that lesions of the head and neck are more likely to recur than lesions elsewhere on the body. Further analysis did not suggest a difference of local recurrence rates between those patients treated with currently recommended clinical surgical margins of 5 mm in melanoma in situ and 1 cm in stage I melanoma. All recurrences in our study occurred in patients treated with the recommended surgical margins.

### Risks and Benefits of Exercise in Patients with Implantable Cardioverter-Defibrillators

Jennifer Davids and Rachel Lampert. Section of Cardiology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Although most patients with implantable cardioverter-defibrillators (ICDs) have underlying cardiovascular disease, and would, therefore, benefit from exercise, current guidelines restrict patients with ICDs from vigorous exercise, based on postulated risks of injury to the patient and/or device.

The purpose of this study was to determine whether exercise is safe for patients with ICDs, and whether an exercise regimen facilitated by a cardiac rehabilitation program is beneficial in reducing shock occurrence and maintaining patients' exercise routines. A telephone survey was conducted among all 314 living patients ≤70 years old with ICDs implanted between 6/1997 and 6/2001 at Yale-New Haven Hospital; 164 completed the survey.

Study participants described the intensity and potential danger of activities they performed, as well as shocks during exercise, which occurred in 23 people. In all but one shock event, the first shock delivered by the device successfully restored normal rhythm; no ventricular tachycardia failed to be converted with a high-energy shock. The only injuries sustained during shock episodes were two skin breaks due to falling.

The role of cardiac rehabilitation in shock prevention and maintenance of exercise routine was evaluated in the subset of ICD patients with coronary artery disease (n = 82). Patients who participated in a cardiac rehabilitation program were significantly more likely than non-participants to exercise at a moderate to vigorous intensity (50 percent vs. 20 percent), and to receive fewer shocks during exercise (zero percent vs. 16 percent).

Although shocks during vigorous exercise do occur, they are unlikely to cause injury, as seen in this single-center population of ICD patients. Sports may be safer for ICD patients than previously considered. ICD patients with coronary artery disease who participate in cardiac rehabilitation programs benefit from shock prevention and maintenance of their exercise routines. These data should help guide clinicians in promoting exercise through cardiac rehabilitation in patients with ICDs.
Characterizing T Cell Responsiveness in Human Lupus. Matthew S. Davids and Joseph Craft. Section of Rheumatology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

Although intrinsic abnormalities in lupus T cells likely contribute to their hyperresponsiveness, a fundamental difference in the distribution of naïve, central memory, and effector memory T cell subpopulations may also be important. In this study, we investigated whether skewing of T cell subpopulations is present in SLE patients by performing four color staining of mixed PBMC samples from 16 lupus patients and 12 age/sex-matched controls with anti-CCR7 and anti-CD45RA antibodies. CD4+ T cell subpopulations in lupus patients consistently showed higher percentages of effector memory cells and lower percentages of naïve cells. CD8+ T cell populations in lupus patients surprisingly also showed increased levels of effector memory cells and decreased levels of naïve cells. Subgroup analysis by age revealed that over time, both patients and controls shift their T cell subpopulations from naïve to effector memory cells. We also examined T cell proliferation with [3H] thymidine incorporation and CFSE dilution experiments, which showed that aggregate lupus CD4+ T cell populations respond more vigorously to anti-CD3 stimulation than controls and that lupus T cells often undergo three cell divisions in the time it takes control cells to undergo two cell divisions. CD8+ T cells, in contrast, showed a slightly hyporesponsive phenotype. One experiment suggested that the most hyperresponsive subpopulation is the effector memory CD4+ T cell. Another experiment demonstrated the feasibility of physically separating T cell subpopulations using a cell sorter. Finally, the cytokine profile of lupus T cells was characterized using a cytokometric bead assay, which showed a Th2 cytokine dominance in lupus patients. Interestingly, levels of IL-10 in lupus patients were found to be consistently depressed, providing initial evidence that recent studies in lupus-prone mice showing decreased IL-10 leading to an exacerbated disease phenotype are applicable to human SLE.

The Role of CD1d-Bound Lipid in Activating Hepatic T Lymphocytes in Allergic Contact Dermatitis. Neelendu Dey and Philip W. Askenase. Section of Allergy and Clinical Immunology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Allergic contact dermatitis, or contact sensitivity (CS), is the localized inflammation that occurs when a sensitized host is topically exposed to an allergen. Primed T lymphocytes are able to mediate a localized response at the site of exposure to allergen because of events initiated early in sensitization by hepatic natural killer T (NKT) cells. NKT cells are CD1d-restricted (lipid-reactive) lymphocytes that secrete IL-4 as early as 7 minutes after initial topical exposure to allergen. I investigated the roles of hepatic lipids and CD1d to elucidate their roles in activating hepatic NKT cells in CS. I utilized adoptive cell transfer techniques and a variety of knockout mice to engineer situations in which the effects of lipids or CD1d could be analyzed. Here I show that lipids are critical in activating NKT cells, but that CD1d expression by hepatocytes per se is not. Hepatic NKT cells themselves may activate one another. Other liver mononuclear cells such as dendritic cells may also play a role.

Tight Diabetes Control is Associated with Lower Risk of Postoperative Infection. Annika S. Dronge (Sponsored by Ronnie A. Rosenthal). Department of Surgery, Yale University School of Medicine, New Haven, Connecticut.

Tight postoperative glucose control is associated with decreased mortality and morbidity, including infections. This study will investigate whether long-term preoperative glycemic control, as indicated by Hemoglobin Alc (HgbAlc) <7 percent, decreases the risk of postoperative infections. A retrospective observational study of the West Haven Department of Vet-
erans Affairs National Surgical Quality Improvement Program (NSQIP) dataset from January 1, 2000, to September 30, 2003, was conducted to include all diabetic patients who underwent major surgery, excluding cardiac surgery, and those who had a HgbA1c level within 180 days prior to surgery. The patient's age, race, diabetic therapy, American Society of Anesthesiologists (ASA) class, Activities of Daily Living (ADL), case urgency, wound classification, and operative length were recorded. Infectious complication included wound infection (superficial or deep), urinary tract infection, pneumonia, and sepsis. Baseline and outcome variables were collected and reviewed from the NSQIP and the inpatient treatment files. The primary analysis examined the association of preoperative HgbA1c levels with infectious postoperative complications. Adjustment was made for all other factors using logistic regression. During the time period from January 1, 2000, to September 30, 2003, there were a total of 490 diabetic patients undergoing major surgery with a reported HgbA1c. In bivariate analysis, age, ASA classification, ADL, operative urgency, wound class, operative length, and HgbA1c were significantly associated with postoperative infections. In multivariable analysis, HgbA1C >7 percent was associated with a significantly higher rate of infections (OR 2.133, CI 1.229 to 3.703, p < .0071). Long-term glucose control, as indicated by a preoperative HgbA1c level less than 7 percent, prior to surgery, is associated with a reduced rate of postoperative infectious complications in a diverse group of surgical patients.

Racial and Gender Variations in Insulin Sensitivity: A Clinical Study of Asians and Caucasians, Men and Women. Jing Feng and Kitt Falk Petersen. Section of Endocrinology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Insulin resistance (IR) is a state of impaired insulin-stimulated glucose utilization and is the best predictor for developing type 2 diabetes. Insulin sensitivity was examined via an Oral Glucose Tolerance Test (OGTT) in healthy, young, lean, non-smoking, sedentary subjects (Asians and Caucasians, men and women), after matching for age, weight, height and body mass index (BMI). The Insulin Sensitivity Index (ISI) was calculated from the plasma glucose and insulin concentrations. Since IR correlates with intramyocellular lipid (IMCL) content, 1H MR spectroscopy was used to non-invasively determine IMCL and intrahepatic lipid (IHL) content. Circulating factors implicated in IR: free fatty acids (FFA) leptin, ghrelin, adiponectin, and resistin were also studied.

The percentage of IR subjects were higher in the Asian compared to the Caucasian group. In a multivariate analysis accounting for race and gender (adjusting for BMI, age, and family history of diabetes), racial differences were still a significant independent correlate of insulin sensitivity, whereas gender was not. As a group, the Asians had significantly elevated plasma insulin concentrations (during the OGTT), lower ISI and higher IHL content than the Caucasians. In the Asian group, ISI correlated better with IHL than with IMCL. In contrast, the relationship between IHL and ISI was not seen in the Caucasians. FFAs and fasting levels of resistin, adiponectin and ghrelin were similar between Asians and Caucasians. Our data show that unlike the Caucasian subjects, IHL accumulation is a feature of insulin resistance in the Asians, which may play a major role in their decreased insulin sensitivity.

Gene Discovery in Developmental Neuropsychiatric Disorders: Clues from Chromosomal Rearrangements. Thomas Fernandez, Thomas Morgan, Nicole Davis, Ami Klin, and Matthew W. State. Department of Genetics, and Child Study Center, Department of Developmental and Molecular Neurobiology, Yale University School of Medicine, New Haven, Connecticut.

The molecular characterization of rare affected individuals presenting with chromosomal abnormalities has made recent important contributions to disease gene identifica-
tion in developmental disorders and autism. Here we review the success of this approach compared to more traditional approaches toward disease gene identification for complex developmental neuropsychiatric disorders. We report on cases of children affected by autism and pervasive developmental disorder (PDD) with different balanced chromosomal translocations. By using fluorescent in situ hybridization (FISH) to fine-map the breakpoints of these chromosomal rearrangements, we discovered the physical disruption of one gene transcript (Contactin4 [CNTN4]) in a boy with PDD and a phenotype consistent with 3p deletion syndrome. Our results demonstrate the association of CNTN4 disruption with the 3p deletion syndrome phenotype, strongly suggest a causal relationship, and point to an important role for CNTN4 in normal and abnormal CNS development. We subsequently screened a cohort of patients (n = 97) with autism and autism spectrum disorders (ASDs) and normal karyotypes, along with control subjects (n = 234), for mutations in coding regions of this gene. One missense mutation was identified in a multiplex ASD family and not found in controls, although this mutation did not co-segregate with affected status. Finally, by mapping the breakpoints of an inherited (4;11) translocation in three autistic siblings, we identified an interesting candidate gene for autism susceptibility that warrants additional study.

**Effect of Language Barriers on Clearance of Cervical Spine Injuries in the Emergency Department.** Michele C. Flagge and Phillip A. Brewer. Section of Emergency Medicine, Department of Surgery, Yale University School of Medicine, New Haven, Connecticut.

Introduction: Clinical clearance of injuries to the cervical spine in the Emergency Department (ED) requires that the patient be able to understand and respond to the examiner's questions, presenting a dilemma to Limited English Proficient patients. We hypothesized that non-English speakers brought to the ED with spinal immobilization following trauma would have longer times between arrival and clearance of the cervical spine and would be more likely to require radiologic examination for clearance.

Methods: A prospective cohort study was done based on chart review of all cases of motor vehicle crash victims with spinal immobilization arriving during hours of full ED operation. Approval of the Human Investigation Committee was obtained prior to initiating the six-week study. The age, gender, race, and language proficiency of each subject was recorded, as was the ED census during full operation hours. The following times were obtained: Crash, ED arrival, physician exam, clearance (clinical or radiographic), and discharge. In addition, clinical versus radiographic clearance was noted.

Results: A total of 101 cases were entered, including 78 English speakers and 23 non-English speakers. Average time from arrival to physician exam were 28 minutes for each group. Forty-seven English speakers (60 percent) were clinically cleared compared to 11 (48 percent) non-English speakers. The likelihood of clinical clearance were higher for English speakers (OR = 1.84). Average times from ED arrival to clinical cervical spine clearance were 33.5 minutes for the English speaking group and 39.9 minutes for the non-English speaking group, and average times for x-ray clearance was 55.2 minutes for the English speaking group and 57.6 minutes for the non-English speaking group. Average time in ED was 184.5 minutes for the English speaking group, with 157.7 minutes, and 229.9 minutes for clinical and radiographic clearance, respectively. Average time in ED was 207.3 minutes, with 149.2 minutes and 260.5 minutes for clinical and radiographic clearance, respectively. Interpreters were used in 11 cases (48 percent).

Conclusions: Non-fluency in English increased the likelihood of requiring x-rays for cervical spine clearance. This is possibly because language barriers prevent the examiner from confidently excluding cervical spine injury based solely on history taking and phys-
ical examination. Non-English speakers had a non-statistically significant increase in the average time to clinical c-spine clearance. English speakers had a non-statistically significant increase in average time to radiographic clearance. Given the increase in overall length of stay and discomfort of prolonged periods of cervical spine immobilization, it is incumbent upon the hospital to provide adequate language services to increase the rate at which non-English speakers are clinically cleared.

**Uncoupling Protein 2 Expression and Its Association with Atherosclerotic Disease Severity.** John K. Forrest, J. Dawn Abbott, Kerry S. Russell, and Raymond R. Russell. Section of Cardiology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Uncoupling proteins (UCPs) are inner mitochondrial membrane channels that dissipate the proton gradient generated by the respiratory chain, and have been shown to play an important role in attenuating reactive oxygen species (ROS) generation. Animal studies suggest that changes in UCP expression in circulating monocytes may effect atherogenesis by regulating the production of ROS known to cause endothelial damage. However, the association between mononuclear cell UCP expression in humans and coronary artery disease has not been assessed. The purpose of this study was to investigate the association between mononuclear cell uncoupling protein 2 (UCP2) expression and the severity of coronary artery disease in patients undergoing coronary angiography. Peripheral blood samples were obtained from 103 enrolled patients undergoing coronary angiography. Coronary atherosclerotic disease burden was assessed using a 15-segment stenosis scoring system. Messenger RNA was isolated from the peripheral mononuclear cells, and real-time PCR was performed to evaluate UCP2 expression. In patients with severe coronary artery disease (stenosis score >25) there was a 35 percent decrease (p < .02) in monocyte UCP2 mRNA expression compared to patients with no to mild coronary artery disease (stenosis score 0 to 10). There was no significant difference in the monocyte expression of UCP2 mRNA in patients with moderate disease (stenosis score 11 to 25) compared to patients with no to mild coronary artery disease. This study demonstrates that decreased monocyte UCP2 expression correlates with increased atherosclerotic disease burden in patients, and supports the hypothesis that changes in monocyte in UCP2 expression may modulate vascular oxidant stress and play a role in atherogenesis.

**Stopping the Cycle of Violence in Adolescents: Mediating Factors Through the High School Transition.** Ariel S. Frey, Vladislav Ruchkin, and Mary Schwab-Stone. Section of Child Psychiatry, Yale Child Study Center, Yale University School of Medicine, New Haven, Connecticut.

Adolescence is a time when young people are at particular risk for disengagement from school and for involvement in problem behaviors. A longitudinal study, using the Social and Health Assessment survey, was conducted with 652 students (54 percent African-American, 23 percent Hispanic, and 10 percent Caucasian) in 8th grade and one year later in their first year of high school. The aim of this study was to determine the role of school attachment, teacher support, parental control, and exposure to community violence as predictors one year later of involvement in violent behavior, development of aggressive attitudes, perception of school climate, and academic motivation. Family and school factors were mediating factors that were differentially associated with negative outcomes. School attachment was negatively associated with violent delinquency (p < .05) and aggressive beliefs (p < .001), and was positively associated with academic motivation (p < .001). Perceived teacher support was positively related to school climate and academic motivation over time (p < .001 for each). Reported high parental control was
negatively associated with violent behavior and high parental control was positively associated with academic motivation (p < .001 for each). Violence exposure was related to violent behavior (p < .001) and negative perception of school climate (p < .01). In order to create effective school reform that enables our society to break the cycle of violence in inner-city environments, all of these factors must be considered so that the resulting school reform is successful in promoting optimal developmental progress.

**Apoptotic Cleavage of Vimentin: A Direct, in Vivo, Assessment of Ovarian Carcinoma Chemosensitivity.** Adam Gafni-Kane, Ayesha Alvero, and Gil Mor. Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut.

We report the successful development of an enzyme-linked immunosorbent assay (ELISA) for the *in vitro* and the *in vivo* assessment of ovarian carcinoma chemosensitivity based on the presence of extracellular fragments of the intermediate filament vimentin secondary to chemotherapy-induced apoptosis. A time-dependent rise in proteolytic fragments of vimentin was identified via ELISA first intra- and then extra-cellularly among A2780 ovarian carcinoma cells treated with paclitaxel *in vitro*. The *in vitro* ELISA results correlated with upregulation of caspase-3 activity, and Western blot confirmed that the vimentin peptides were of the sizes generated as byproducts of apoptosis. Applied *in vivo*, the ELISA properly identified known responders to treatment, exhibiting radiologic evidence of either disease regression or stabilization, as they were the only ovarian carcinoma patients to manifest a rise in serum vimentin that was of a statistically significant difference compared to a prior reading. Patients were assessed over the first cycle of chemotherapy, indicating that chemosensitivity may be assessed earlier than current practices dictate. The identification of protein fragments resulting from apoptosis has great potential in the development of measures to assess ovarian carcinoma response to treatment *in vivo*, a venture made worthwhile by the grim prognoses faced by patients suffering from ovarian carcinoma.

**Spirituality and Medicine: A Historical Perspective and The Creation and Analysis of a Course at Yale.** Katherine A. Gergen-Barnett and Auguste H. Fortin, VI. Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

For centuries, physicians addressed a patient's spiritual and religious beliefs as a part of his healing. Today, patients' beliefs are viewed as peripheral to the medical encounter. This paper addresses the history of the mind-body-spirit connection in medicine, the current recommendations to reincorporate spirituality into medicine and medical education, and how a workshop designed and implemented at Yale may help heed this call.

We designed and implemented a mandatory workshop for second-year medical students and primary care internal medicine residents. The workshop used multiple educational strategies to illustrate how and when to take a spiritual history, to discuss the differences between spirituality and religion, and to provide an overview of the research showing an association between spirituality/religion and health outcomes. Learners completed pre- and post-workshop surveys consisting of six statements rated on a five-point Likert scale and a space for learners to write their definitions of spirituality and medicine, as well as provide feedback. Non-parametric methods, the Wilcoxon Rank-Sum test, the Mann-Whitney U test, and the constant comparative method of qualitative data analysis were utilized to evaluate these surveys. Participants significantly increased their agreement with the appropriateness of inquiring about spiritual and religious beliefs as part of the medical encounter, their perceived competence in taking a spiritual history, their
knowledge of the differences between spirituality and religion, and their knowledge of available pastoral care resources. Though there is still much work to be done, workshops such as these can help physicians and medical students know their patients more fully and allow the religious or spiritual patient to place his illness in a context of personal meaning.

**Health Status of Coronary Artery Disease Patients One Year after Hospitalization.** Sharon K. Gill, Judith H. Lichtman, Joan M. Amatruda, Jennifer A. Mattera, Sarah A. Roumanis, and Harlan M. Krumholz. Section of Cardiology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Most studies of cardiovascular disease report acute events and mortality as outcomes and few focus on patient-centered outcomes such as improved symptom burden, general health, or functional status. We sought to examine health status patterns in patients with coronary artery disease (CAD) according to their baseline demographic and clinical characteristics.

Participants were selected from patients hospitalized with CAD who participated in a trial of a cholesterol education intervention (n = 624). Patients were stratified by method of revascularization and presence or absence of myocardial infarction (MI) at index admission. Outcomes at one-year were chest pain in past year, unfavorable general health (“fair” or “poor”), and unfavorable functional status (“limited a lot” on at least one activity), determined by follow-up interview. To determine which baseline characteristics were independently associated with each outcome, we used multivariate logistic regression.

Nearly 16 percent of participants had unfavorable functional status, and 21 percent had unfavorable general health at one-year follow-up. Overall, 30 percent reported chest pain at follow-up, with higher chest pain rates for younger patients (less than 65 years). Prevalence of unfavorable outcomes varied widely by revascularization method and MI history: unfavorable general health 16 to 36 percent, unfavorable functional status 9 to 33 percent, and reported chest pain 15 to 55 percent. Logistic regression identified female sex and history of revascularization as independent predictors of worse health status across all three outcomes. Potentially modifiable risk factors that predicted at least one unfavorable outcome were: smoking, emotional distress (depression/anxiety), and below-median emotional support.

Women and those with a hospitalization for CAD have a substantial risk for unfavorable health status outcomes across a variety of domains at one year after discharge. However, the overall heterogeneity of health status outcomes across patient characteristics underscores the importance of further characterizing patients who are likely to do poorly after hospitalization, with the ultimate goal of improving health status outcomes.

**Cervical Spine Ligament Injury During Simulated Frontal Impacts.** Elena Gimenez Gmdzinski, Adam M. Pearson, Shigeki Ito, Paul C. Ivancic, Yasuhiro Tominaga, Manohar Panjabi. Department of Orthopedics and Rehabilitation, Yale University School of Medicine, New Haven Connecticut.

The supraspinous and interspinous ligaments, ligamentum flavum, capsular and posterior longitudinal ligament strains were monitored during simulated frontal impact of whole cervical spine specimens with muscle force replication, and compared to corresponding physiological strain limits. The objective was to quantify the strains in the cervical spine ligaments during simulated frontal impact, and investigate injury mechanisms. Clinical and biomechanical studies have documented injuries to cervical spine ligaments during frontal impact. There are no biomechanical studies investigating subfailure injury mechanisms to these ligaments during simulated frontal impacts of increasing severity.
The whole cervical spine with muscle force replication model and a bench-top sled were used to simulate frontal impacts at 4, 6, 8 and 10 g horizontal accelerations of the T1 vertebra. The peak ligament strains during frontal impacts were compared to physiological strain limits determined during intact flexibility testing. Significant increases (p < .05) in the supraspinous and interspinous ligaments, and the ligamentum flavum strains beyond physiological limits were observed throughout the cervical spine, with the highest strains occurring at C3 to C4. Significant increases were observed in the capsular ligament strains only during the 10 g impact, while the posterior longitudinal ligament strains did not exceed physiological limits. The supraspinous and interspinous ligaments and the ligamentum flavum may be at risk for injury due to excessive strains during frontal impacts.

A Role for Mayan Community Health Promoters in Tuberculosis Control in the State of Chiapas, Mexico. Michael Herce, Jacob Chapman, Arachu Castro, Jorge Gabriel Garcia Salyano, and Kaveh Khosnood. School of Epidemiology and Public Health and Yale School of Medicine, Yale University, New Haven, Connecticut and Harvard School of Public Health, Boston, Massachusetts; Brigham and Women's Hospital, Department of Emergency Medicine, Boston, Massachusetts; Program in Infectious Disease and Social Change, Department of Social Medicine, Harvard Medical School and Partners in Health, Boston, Massachusetts; Team for the Support of Community Health and Education (EAPSEC), San Cristobal de las Casas, Chiapas, Mexico; and Division of Epidemiology of Microbial Diseases, Department of Epidemiology and Public Health, Yale University School of Medicine.

In order to characterize the work of community health workers, known as health promoters, operating in Chiapas, Mexico and to identify qualities of their services applicable to community-based tuberculosis (TB) control programs, we conducted a qualitative study employing structured interviews with 38 health promoters from twelve rural Chiapas municipalities. We report here that health promoters self-identify as being of Mayan Indian ethnicity. They volunteer 11 hours each week to conduct clinical and public health work in their communities. Most health promoters are bilingual, speaking Spanish and one of four indigenous Mayan languages native to Chiapas. Over half (53 percent) work with a botiquin, a medicine cabinet stocked with essential medicines. Fifty-three percent identify TB as a major problem affecting the health of their communities, with one-fifth (21 percent) of promoters reporting experience caring for patients with known or suspected TB and 29 percent having attended to patients with hemoptysis. One-third of health promoters have access to antibiotics (32 percent) and one-half have experience with their administration; 55 percent use traditional Mayan medicinal plant therapies in the care of their patients. We describe how health promoters employ both traditional and allopathic medicine to treat the symptoms and diseases they encounter most frequently which include fever, diarrhea, and parasitic infections. We contend that given the complex sociopolitical climate in Chiapas and the state’s growing TB epidemic and paucity of health care infrastructure, efforts to implement comprehensive, community-based TB control would benefit from employing the services of health promoters.

Clinical Yield of Computed Tomography Brain Scans in Older General Medical Patients. Liaime A. Hirano, Sanjay Saluja, Linda Leo-Summers, Sidney T. Bogardus, Jr., and Sharon K. Inouye. Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Despite being rapid and non-invasive, computed tomographic (CT) scanning of the brain remains a costly diagnostic tool, the yield of which remains controversial. Since elderly patients often present with a range of symptoms that prompt physicians to order
brain CT scans, we evaluated the ordering, findings, and clinical yield of brain CT scans in a sample of patients drawn from a previous prospective cohort study of 919 hospitalized patients age ≥70 years. Of the 919 patients, 117 underwent more than one brain CT scan. We reviewed the medical and radiological records of the first brain CT scan in these 117 patients for indications for ordering and clinically significant brain abnormalities (CSBA). Medical records of patients with brain CT scans with CSBA were reviewed for two weeks following the scan for changes in medical management resulting from scan findings. Three independent reviewers adjudicated the presence of CSBA and resulting changes in management. Of the 117 brain CT scans, 32 (27 percent) were ordered to rule out (R/O) intracranial hemorrhage (ICH), 30 (26 percent) for R/O cerebrovascular accident (CVA), 16 (14 percent) for falls, 15 (13 percent) for syncope, 7 (6 percent) for R/O subdural hemorrhage, 5 (4 percent) for mental status change, and the remaining 12 (10 percent) for other reasons. Of the 117 brain CT scans, 29 (25 percent) had a CSBA, including old CVA, age-indeterminate CVA, acute CVA, ICH, and other abnormalities. Only 10 (9 percent of all scans, and 34 percent of abnormal scans) resulted in management changes (including consultations, further imaging, stroke work-ups, and drug changes). The presence of focal neurological deficits was significantly associated with management changes following CT scans (OR = 5.5, 95 percent CI 1.3 to 23.8).

These results suggest that the overall clinical yield of brain CT scans is low. Targeting scans toward patients with focal neurological deficits will help to improve clinical yield.

**Onchocerciasis: A Potential Risk Factor for Glaucoma.** Douglas William Jacobson (Sponsored by Susan Forster). Department of Ophthalmology, Yale University School of Medicine, New Haven, Connecticut.

Onchocerciasis is a microfilarial disease that causes ocular manifestations and blindness. Previous evidence of an association between onchocerciasis and glaucoma has been mixed. This study aims to further investigate and strengthen the association between onchocerciasis and glaucoma.

All subjects were patients at the Bishop John Ackon Christian Eye Centre in Ghana, West Africa undergoing either trabeculectomy for advanced glaucoma or extracapsular extraction for cataracts, who also had a skin snip biopsy for onchocerciasis. A cross-sectional case-control study was performed to assess the difference in onchocerciasis prevalence between the two study groups.

The prevalence of onchocerciasis was 10.6 percent in those with glaucoma compared with 2.6 percent in those with cataracts (OR, 4.45 [95 percent CI percent 1.48 to 13.43]). The mean age in the glaucoma group was significantly younger than in the cataract group (59 and 65 respectively). The groups were not significantly different with respect to gender or region of residence. In models adjusted for age, region, and gender, subjects with glaucoma had over three times the odds of testing positive for onchocerciasis (OR, 3.50 [95 percent CI 11.10 to 11.18]).

This study has shown a positive association between sub-clinical onchocerciasis and glaucoma. This finding emphasizes the importance of eradication of onchocerciasis from West Africa.

**Germs of Progress: Schistosomiasis in Senegal: The Ethics, Politics and Economics of International Health Research and Development at the End of the Twentieth Century.** Kohar Jones (Sponsored by John Harley Warner and Kaveh Khoshnood). Department of History of Medicine and School of Public Health, Yale University School of Medicine, New Haven, Connecticut.

What are the links between development and disease? What is the role of international health research in shaping global health? Do international ethical guidelines for human experimentation adequately protect people in developing countries? These questions are examined in this five-chapter historical case study of schistosomiasis in Senegal.
“Schistosomiasis, Silent Scourge of Development: Dams and Disease in the 20th Century,” introduces schistosomiasis and Senegal. It provides a history of international health as told through schistosomiasis, from the germ theory of disease to imperial medicine, the pharmaceutical revolution and the hope of “Health for All by the Year 2000.” Though medical experts warned that schistosomiasis, the “germ of progress,” followed the dams and irrigated agricultural development projects of the Green Revolution, Senegalese politicians pushed for dam development, schistosomiasis be damned.

“Future Shock: the Politics of Predicting the Future: Schistosomiasis Prevention in Senegal, 1972-1987,” examines the relationship between health research and policy planning before the dams’ construction, as an American consulting firm and Yale researchers, separately supported by USAID funds, came to drastically different conclusions about the potential for schistosomiasis outbreak with the dams. Political expediency combined with financial factors to determine how their research results were reported, publicized, and used in policy planning. The appearance of disease with dams was expected and measures could have been taken to prevent it.

“ESPOIR: Hope as Public Health: The Creation of a Program to Combat Schistosomiasis in Senegal: 1988-1998” describes the outbreak of schistosomiasis and the Senegalese health system's response. In 1989, the regional governor invited a French schistosomiasis vaccine researcher to participate in a research/prevention program against schistosomiasis. This led to the European Special Program for Operational and Integrated Research (ESPOIR), a multinational, multidisciplinary network of researchers that had difficulty negotiating its roles and responsibilities in the health system's response to the outbreak. There was tension between disease control and research objectives. Funding dictated the choices made. Immunological research geared towards vaccine trials took precedence over community health.

“Developing Ethical Guidelines for International Biomedical Research” examines human experimentation across history, describing the attempts to find a balance between the needs of science, the good of society and the rights of human subjects. The age of science in medicine and the pharmaceutical revolution led to an explosion in human experimentation in the latter half of the twentieth century. By the 1970’s, the U.S. scientists and bioethicists who created ethical guidelines for human research placed responsibility for ensuring ethical experimentation in the hands of institutional review boards. At the end of the 20th century, difficult moral questions associated most visibly with AIDS research in Africa led to revisions of international guidelines that placed responsibility for resolving difficult ethical questions on often inexperienced ethical review committees in developing countries whose members often had significant conflicts of interest. The fifth chapter summarizes the ethical quandaries encountered with schistosomiasis research in Senegal, describes the limitations of the current solutions, and suggests possible solutions for the future.

Carotid Endarterectomy Among The Elderly: Variations In Utilization Based On Age, Sex and Race. Niya A. Jones, Harlan M. Krumholz, Yun Wang, Lawrence M. Brass and Judith H. Lichtman. Section of Chronic Disease Epidemiology, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut.

The primary aim of the present investigation is to determine carotid end arterectomy (CEA) rates among elderly individuals by age, sex and racial subgroups. Secondly, temporal patterns in CEA utilization will be characterized and compared within these subgroups.

A retrospective cohort study was conducted using Medicare administrative data. The population consists of elderly, fee-for-service Medicare beneficiaries hospitalized, during 1992 through 1999, with a primary diagnosis of ischemic stroke based on International Classification of Disease, Ninth Revision (ICD-9) codes 433-437. Crude rates of annual
CEA use were calculated for the entire cohort and then by subgroup. Risk-adjustment was subsequently performed to take demographic and clinical factors into account.

Women make up 57.5 percent of the cohort. 86.5 percent of the population is white, 9.7 percent is black and 3.8 percent is identified as other race. The mean age of the population is 79 years old. Overall, CEA rates increased from 11.1 percent in 1992 to 15.9 percent in 1995 with relatively little change from 1995 through 1999. Though beneficiaries aged 65 to 74 years old were more likely to receive CEA than those in other age groups (p < .0001), cohort members who were 85 and older experienced the largest comparative increase in CEA utilization. Men were virtually twice as likely to undergo CEA as women during the eight-year period (p < .0001). Whites were nearly four times more likely to receive CEA than blacks over the course of the study (p < .0001).

Beneficiaries 74 years old and younger, males and whites were more likely to undergo CEA relative to other members of their respective subgroups despite risk-adjustment. Patterns of CEA use generally remained stable when examined by subgroup such that differences in CEA rates within each group persisted over time. Additional research is necessary to contextualize these variations in procedure utilization.

DNA Ploidy Analysis for the Detection of Minimal Residual Disease in Acute Lymphoblastic Leukemia. Barton C. Kenney, Arthur Zieske, and Brian R. Smith. Section of Hematopathology, Department of Laboratory Medicine, Yale University School of Medicine, New Haven, Connecticut.

The detection of minimal residual disease (MRD) in acute lymphoblastic leukemia (ALL) has clear prognostic implications, as MRD-positivity during or after induction chemotherapy is associated with poor outcome and increased risk of leukemic relapse. However, the detection of MRD in B-lineage ALL by flow cytometric immunophenotyping can be difficult in the post-therapy bone marrow, due to an increase in normal B-cell precursors that can be confused with leukemic blasts. The aim of this study was to assess whether flow cytometric DNA ploidy analysis, in tandem with flow cytometric immunophenotyping, can be used as a sensitive means of detecting residual or relapsed ALL in patients with previously documented aneuploid cell populations. We retrospectively studied all cases of ALL at our institution over a 12-year period from 1991 to 2003 (n = 114). Aneuploid clonal populations were present in 32 percent of patients (n = 37). Of this group, 24 had “normal” immunophenotypes, as defined by phenotypic similarity of the leukemic clone with normal precursor B-cells, and 13 had “aberrant” immunophenotypes predominantly manifest as simultaneous expression of myeloid markers. Aneuploidy detected the presence of residual or relapsed disease in all cases where disease was found by flow immunophenotyping (normal n = 8; aberrant n = 7). In the group with normal immunophenotype, aneuploidy detected post-remission disease in three patients and MRD in one patient in whom the diagnosis could not be made with confidence by immunophenotyping. In the aberrant group, aneuploidy detected MRD in two patients in whom immunophenotyping failed to show positivity, likely because of downregulation of myeloid antigens on leukemic blasts. These results suggest that flow cytometric DNA ploidy analysis may be a useful and sensitive adjunct in determining relapse or presence of MRD in patients with B-lineage ALL.

Quantification of Gated Single Photon Emission Computerized Tomography: Methodology and Validation of the Yale Approach and Its Comparison to the QGS Method. Daniel Khaimov. Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut.

Recently a new method for the quantitative assessment of left ventricular (LV) volumes and ejection fraction (EF) from ECG-gated single photon emission computerized
tomography (SPECT) was developed at Yale Nuclear Cardiac Imaging Laboratory. The aim of this study was to present the methodology, to validate the Yale method using phantoms, and to compare it to the widely used Quantitative Gated SPECT (QGS) method.

A simple thresholding technique was used to generate binary images from non-gated SPECT images. The K-means cluster classification algorithm was employed to separate the LV region from non-LV regions on the binary images. A counts- and geometry-based algorithm was applied to define endocardial and epicardial boundaries for calculation of LV volumes and LVEF. The correlations between SPECT and actual volumes in phantoms without perfusion defects were excellent using both methods (Yale $r = 0.97$, $SEE = 9.99$; QGS $r = 0.99$, $SEE = 3.52$). However, mean estimation error in estimation of the phantom volume with the Yale method was significantly smaller ($p = 0.03$) than that with QGS (Yale mean error $= -1.67$; QGS mean error $= 7.36$). In phantoms with defects, the correlations between SPECT and actual volumes were also excellent for both methods (Yale $r = 0.99$, $SEE = 6.97$; QGS $r = 0.99$, $SEE = 2.6$). The mean error in estimation of phantom volumes using the Yale method was smaller than that using QGS, but it was not statistically significant ($p = .08$) (Yale mean error $= -2.85$; QGS mean error $= 6.36$).

In conclusion, the Yale gated SPECT quantification method provides reliable and accurate assessments of LV volumes and LVEF and may have advantages over the widely used QGS. The Yale method can be used as an alternative analysis tool in detection of abnormality of LV function.

Activity-dependent Modulation of Neuronal Sodium Channel Expression.
Joshua P. Klein and Stephen G. Waxman. Department of Neurology, Yale University School of Medicine, New Haven, Connecticut.

Action potentials initiate via the voltage-dependent opening of plasma membrane-associated sodium channels. The number and type of sodium channels in a neuronal membrane determine the quantity of sodium current that results from a given stimulus. The expression of sodium channels in neurons is plastic, and is not only altered by injury and disease, but also by subtle changes in physiologic environment. In this dissertation, the effect of neuronal activity level on the expression and function of sodium channels is explored within several neuronal populations. First I examine the response of vasopressin-producing magnocellular neurosecretory cells of the supraoptic nucleus to the hyperosmotic setting of chronic diabetes mellitus. Evidence for up-regulation of sodium channels, and metabolic overactivation leading to apoptosis, in these neurons is presented. Second, I test the effect of electrical stimulation on expression of sodium channels in cultured sensory neurons. And lastly, I demonstrate that there is dysregulated sodium channel expression within cortical neurons in a specific region of the brain in a model of absence epilepsy.

Together, the results of these experiments support the hypothesis that the activity level of a neuron influences its rate of production and expression of sodium channels. Identification of this phenomenon could lead to new therapeutic strategies for 1) limiting end-organ pathogenesis in diabetes (by reducing magnocellular neurosecretory cell sodium channel activity, thereby preventing chronically up-regulated vasopressin secretion), 2) treating pain (by using stimulation to normalize post-injury sodium channel expression and reduce neuronal hyperexcitability), and 3) treating epilepsy (by targeted modulation or block of seizure-initiating sodium channel activity). Development of novel therapeutic approaches will depend on further characterization of the regulatory feedback mechanism that links changes in neuronal activity level with modulation of sodium channel expression.
The Effect of Aging on the Skeletal Response to Intermittent Treatment with Parathyroid Hormone. Eleanor Knopp, a Nancy Troiano, b Mary Bouxsein, c Benhua Sun, a Karen Lostritto, a Caren Gundberg, b James Dziura, a Karl Insogna, a a Departments of Internal Medicine and b Orthopaedics, Yale University School of Medicine, New Haven, Connecticut and the c Department of Orthopaedics, Beth Israel Deaconess Medical Center, Boston, Massachusetts.

Little is known about the modifying effects of age on the skeletal response to intermittent treatment with PTH. We therefore compared the response of 63 aged (18-month old) and 61 young-adult (3-month old) C57BL/6 mice to 4 weeks of daily subcutaneous injections of either vehicle or h(l-34)PTH at a dose of 95 ng/g body weight. The increase in total body-bone mineral density as compared to vehicle-treated animals was similar in aged and young-adult mice (+5.6 percent vs. +6.3 percent). Aged animals demonstrated a greater increase in spinal BMD than their younger counterparts (+12.0 percent vs. +5.1 percent, p = .01); absolute increment: $57 \times 10^4$ vs. $28 \times 10^4$ gms/cm$^2$). MicroCT analyses in a subset of the vertebrae showed a trend toward higher L5 trabecular bone volume fraction (BV/TV) in the PTH-treated aged animals (+40.2 percent vs. +19.6 percent). Vertebral histomorphometry demonstrated a greater PTH-induced increase in osteoblast number in aged vs. young-adult animals (694 vs. 396 cells/mm$^2$). In contrast, in the femur the PTH-induced increase in BMD tended to be greater in the young-adult than in the aged animals although this did not reach statistical significance (8.1 percent vs. 4.2 percent). The numbers of osteoblast progenitors and mineralizing colonies in cultured marrow were unaffected by PTH treatment in either group. We conclude that aging differentially impacts the regional skeletal response to PTH such that the increase in BMD in the spine is augmented while that in the femur is unaffected. Effects on osteoblast progenitor recruitment do not seem to be the basis for these changes.

Predictors of Error Reporting. Mandy Krauthamer, Barrett Kitch, Joel Weissman, Eric Campbell, and David Bates. Institute for Health Policy at Massachusetts General Hospital, Boston Massachusetts (Sponsored by David Paltiel, Department of Health Policy, Yale University School of Epidemiology and Public Health, Yale University School of Medicine).

Error reporting systems can enhance quality and safety in health care by helping identify hazardous situations, making it possible to prevent reoccurring errors. Increased information regarding who currently utilizes the event reporting systems and what cultural factors may influence utilization are important when seeking to focus interventions to improve the event report submission rate and the capture of every type of error. METHODS: We administered the Agency for Healthcare Research and Quality’s “Hospital Survey on Patient Safety Culture” to a random sample of 802 physicians and nurses from four acute care hospitals. The survey measured the number of events reported in the past 12 months, respondent characteristics, and the individual perceptions of twelve dimensions of safety culture. RESULTS: The overall response rate was 41 percent; physician and nurse response rates were 37 percent and 46 percent, respectively. Seventy-three percent of nurses reported having filed an event report in the past 12 months compared to only 35 percent of physicians (p < .001). However, reporting practices varied substantially by nurse and physician specialty. While 46 percent of surgeons reported having filed at least one event report, only 21 percent of internal medicine and pediatric physicians filed an event report (p < .001). Physicians who reported filing event reports perceived higher levels of teamwork, communication openness, and management commitment to safety than physicians who never submitted an event report. Nurses perceived a higher level of communication openness, reporting a greater ability to “speak up if they see something that
may negatively affect patient care” compared to physicians, although we found no association between nurses’ perceptions of culture and their reporting practices. CONCLUSION: We found significant variation in the error reporting practices across specialty with surgeons and surgical nurses being more likely to have participated in event reporting. Among physicians, a more positive safety culture may promote event reporting. Continuing to rely on traditional event reporting systems to monitor safety will fail to capture physician errors, especially errors in non-surgical fields or in areas with problematic safety culture.

Assessment of Endothelial Dysfunction in Pregnant Women with Preeclampsia or preexisting Vascular Disease. Inna Landres, Maria Small, Adesh Smjusingh, Samuel Ramsawak, and Keith P. Williams. Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut, Department of Obstetrics and Gynecology, Mount Hope Maternity Hospital, University of the West Indies, Port of Spain, Trinidad, and Department of Obstetrics and Gynecology, Hospital of St. Raphael, New Haven, Connecticut.

The purpose of this research was to investigate vascular dysfunction in pregnant women with either preeclampsia or preexisting vascular disease using non-invasive brachial artery ultrasound.

The first study is a matched case control of 12 preeclamptic vs. 24 normotensive pregnant women. The second study is a prospective cohort of 40 pregnant women with preexisting vascular disease (diabetes, chronic hypertension, thromboembolic disease, or previous preeclampsia). This group represents women at high risk for developing preeclampsia.

Main outcome measurements were brachial artery flow mediated vascular dilation (FMVD) and Doppler waveform analysis. In the prospective cohort, additional outcome measurements included the development of preeclampsia, the severity of disease and adverse maternal and fetal outcomes.

Brachial artery flow mediated vascular dilation (FMVD) was significantly reduced in women with preeclampsia (4.5 percent ± 2.7 percent) compared with matched controls (9.8 percent ± 4.0 percent; p < .002). The timing of maximum dilation was variable among subjects and represents the best measurement of the difference in FMVD between the two groups. Correlation analysis between the change in Doppler waveform parameters (acceleration, acceleration time, peak systolic velocity and pulsatility index) and change in FMVD identified only peak systolic velocity (PSV) as significant; p = .040. However, comparison of change in PSV between preeclamptic and normotensive controls was not significant (13.5 percent ± 22.7 percent vs. 20.5 percent ± 27.8 percent; p = .432).

In summary, endothelial function is impaired in women with preeclampsia as well as in women with preexisting vascular disease who are at high risk for developing preeclampsia. These findings support the central role of endothelial dysfunction in the pathogenesis of preeclampsia. Brachial artery sonography is a useful non-invasive method of detecting endothelial dysfunction in pregnant women and may have a role in predicting the development of preeclampsia in high-risk groups.

At the Root of Health Disparities: An Examination of the Social Mediators of Minority Achievement. Naudia N. Lauder, Stacey Aronson, Joshua Aronson, and Forrester A. Lee. Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

The black-white achievement gap is a historical problem in the United States. General theories support the idea that both the cultural model and the stereotypes faced by
minorities have an impact on standardized performance. Though there is extensive work documenting the negative consequences of stereotypes, a limited number of works have explored the social mediators of stereotype vulnerability and the independent effects of these factors on standardized performance levels. The goal of this study was to investigate the effect of eight social mediators (generational number, stereotype vulnerability, societal prejudice susceptibility, ethnic pride identification, self-confidence fragility, personal expectation, parental expectation, and parental expectation susceptibility) on standardized performance. Thirteen hundred pre-medical students participating in a science enrichment program at 11 institutions were surveyed. An electronic survey tool was used to as a cross-sectional measure of the postulated mediators. These measures were then correlated with the SAT math scores of each student. Bivariate analysis demonstrated the significance of four of the eight mediators (generational number, stereotype vulnerability, self-confidence fragility, and parental expectation susceptibility) in determining performance levels. In addition, hierarchical regression shows the persistence of the significance of two of the variables (self-confidence fragility and parental expectation) throughout the tiered analysis. Consistent with our predictions, there are social mediators which have significant effects on the standardized performance of underrepresented minorities. These mediators are modifiable and represent possible mechanisms for the closure of black-white achievement gap. The implication of these mediators and their effects not only on standardized performance, but in the realm of health care disparities and beyond, is discussed here.

The Role of CCAAT Displacement Protein in Neutrophil-specific Gene Expression. Aimee Lee, Arati Khanna-Gupta, and Nancy Berliner. Section of Hematology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

CCAAT displacement protein (CDP) is a highly conserved, ubiquitously expressed homeodomain protein with extensive homology to the Drosophila cut protein. CDP contains three conserved DNA-binding repeats called cut repeats, as well as a conserved homeodomain sequence. CDP is a transcriptional represser of several developmentally regulated genes including gp91-phox, CCAAT enhancer binding protein epsilon (C/EBPε), and its downstream targets the neutrophil secondary granule proteins (SGPs), including lactoferrin (LF). We have previously shown that CDP binds to and represses both the C/EBPε and LF gene promoters, thereby preventing expression of SGPs both directly and indirectly. CDP overexpression represses expression of SGPs in 32DeI3 cells, a murine myeloid cell line that undergoes differentiation in response to G-CSF stimulation. Several attempts at generating a CDP knockout mouse have been undertaken, but all have produced incomplete knockouts. I generated short hairpin RNA (shRNA) constructs to knock down CDP in 32DwtI8 cells, which contain a chimeric G-CSF receptor linking the intracellular domain of the G-CSF receptor with the extracellular component of the erythropoietin (EPO) receptor, and differentiate in response to EPO. CDP repression in clones expressing the shRNA for CDP appears to correlate with increased LF expression in uninduced cells. Control clones do not express LF until induced with EPO for several days. The knockdown of CDP does not appear to affect the expression of C/EBPε, suggesting that LF expression reflects direct modulation of CDP binding to its promoter and is not an indirect effect of increased C/EBPε expression. This suggests that CDP can function as the sole negative regulatory element for LF gene expression, and that relief of CDP repression can increase LF expression independent of positive regulatory factors.
Informed Consent and Awareness of Radiation Dose and Risks Associated with Diagnostic CT Scans. Christoph I. Lee, Andrew H. Haims, Edward P. Monaco, James A. Brink, and Howard P. Forman. Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut.

- Purpose is to determine the informed consent practices and awareness level concerning radiation dose and risks associated with CT scans among patients, ordering physicians, and radiologists.

- Adult patients seen in the emergency department (ED) of a United States academic medical center during a two-week period with mild to moderate abdominal or flank pain and who underwent CT were surveyed. Patients were asked whether or not they were informed about the risks, benefits, and radiation dose of the CT scan and if they believed that the scan increased their lifetime cancer risk. Patients were also asked to estimate the radiation dose for the CT scan compared with that for one chest radiograph. ED physicians who requested the scans and radiologists who reviewed the scans were surveyed with similar questions. The chi-square test of independence was used to compare the three respondent groups regarding perceived increased cancer risk.

- Seven percent (five of 76) of patients reported that they were told about risks and benefits of their CT scan, while 22 percent (10 of 45) of ED physicians reported that they had provided such information. Forty-seven percent (18 of 38) of radiologists believed that there was increased cancer risk, whereas only 9 percent (four of 45) of ED physicians and 3 percent (two of 76) of patients believed that there was increased risk ($\chi^2 = 41.45, p < .001$). All patients and most ED physicians and radiologists were unable to accurately estimate the dose for a CT scan compared with that for a chest radiograph.

- Patients are not given information about the risks, benefits, and radiation dose for a CT scan. Patients, ED physicians, and radiologists alike are unable to provide accurate estimates of CT doses regardless of experience level. Further education of patients and physicians regarding radiation risks from CT is required.

Bone Marrow-derived Cells Engraft as Epithelium During Wound Healing and Solid Tumor Development. Sean Lee, Neil Theise, and Diane Krause. Department of Laboratory Medicine, Yale University School of Medicine, New Haven, Connecticut.

Over the last seven years, studies of bone marrow-derived cell (BMDC) plasticity have demonstrated the ability of various bone marrow (BM) cell populations to engraft into the parenchyma of tissues in all germ layers. Following certain types of injury, this engraftment is significantly increased, but no work has yet described BMDC activity following skin trauma or in solid tumors. We therefore performed two separate projects to describe the BMDC engraftment in these two settings. Sex-mismatched BM was transplanted into lethally-irradiated female mice that were then wounded one month following transplant. Fluorescence in situ hybridization (FISH) for the Y chromosome was used to follow donor-derived cells, immunofluorescence (IF) for markers of mesenchymal and epithelial cells was used to discriminate cell type, and a Cre-lox system was used to rule out cellular fusion. Examining the wounded mice at different time points following injury with concomitant FISH and IF revealed that BMDC engraft in the epidermis within three days, and that their numbers increase until they represent up to 8 percent of keratinocytes at 21 days. By eight weeks, the number of BM-derived keratinocytes falls to background levels. IF for Ki-67 (a marker of proliferating cells) showed that the BM-derived epithe-
lial cells in the skin were capable of cycling, but lack of cytokeratin 5 (expressed in epidermal stem cells [ESC]) immunochemical staining suggested that these cycling cells were not epidermal stem cells. It is thus likely that most BMDC enter the skin as transient amplifying cells. In the second project, APCmin females, which have a nearly 100 incidence of bowel adenoma, received sex-mismatched BM transplantation. Again, FISH, IF, and IHC were used to follow donor-derived cells in the tumors and to determine whether they were epithelial or mesenchymal in nature. Although this project is not yet complete, preliminary results indicate that as many as 1.6 percent of epithelial cells within bowel adenomas are BM-derived. Together, these projects provide further evidence that the microenvironment at sites of injury enhances BMDC epithelial engraftment. Further characterization of these phenomena may provide significant insights into stem cell and cancer biology.

**Jewish Legal Aspects of Medical Tattooing.** Neil Lester (Sponsored by Morris Traube). Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this paper is to analyze the extent of the Jewish legal prohibition of tattooing, and against the backdrop of this analysis, to attempt to clarify the Jewish legal status (i.e., the permissibility or lack thereof) of various forms of medical tattooing. Ultimately, this paper uncovers a novel Jewish legal approach to nipple-areola tattooing. The methods used include examination of the current literature on techniques of modern-day tattooing, as well as of the classical Jewish sources on the subject of tattooing in order to cull the fundamental legal principles which apply in the case of nipple tattooing. Next, other principles within Jewish law which provide for leniency insituations of embarrassment and psychological trauma are considered. Literature indicating that mastectomy can result in psychological trauma and that breast reconstruction can help to relieve that trauma will be presented. Finally, this literature will be applied to the relevant Jewish legal principles in order to demonstrate the conclusion that nipple-areola tattooing may be permissible within Jewish law.

**Nonverbal Social-Communication in Institutionalized Children in Armenia.** Lorky N. Libaridian, George L. Melikian, Jim Dziura, Andrew Geier, and Carol C. Weitzman. Section of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

While it is well known that institutionalization can cause developmental delay in children, there is limited data on the effects of institutionalization on nonverbal social-communication (NVSC), which is thought to be a predictor of later cognitive and language development. The purpose of this study was to evaluate the NVSC skills of children aged nine to 24 months living in an orphanage in Armenia, and to compare their skills with a similar group of children raised in families in Armenia. Both groups were evaluated using the Bayley Infant Neurodevelopmental Screener (BINS) and the Early Social Communication Scale (ESCS). The BINS is a screener used to approximate the level of risk a child has for developmental delay, while the ESCS is designed to assess the three major domains of NVSC: behavior regulation (BR), social interaction (SI) and joint attention (JA). We hypothesized that JA, the most complex of the three dimensions, would be the most affected. Children from the institutionalized group (IG) were found to be at significantly higher risk for developmental delay than the control group (CG) children. IG children also had a significantly lower frequency of total behaviors in the ESCS, with the differences in SI and BR. However, IG children had a significantly higher proportion of JA behaviors than the CG children. A significantly higher percentage of IG children
showed no complex JA or BR behavior than CG children. The findings that the IG children were at higher risk for developmental delay and had lower number of behaviors on the ESCS are in agreement with previous studies. The differences found in the domains of JA, BR and SI highlight the need for further research in NVSC in children at risk for developmental delay.

**Trends in CA-125 Changes within the Range of Normal as a Predictor of Ovarian Cancer Recurrence.** Javier Lopez (Sponsored by Peter Schwartz). Section of Gynecology Oncology, Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut.

We conducted retrospective chart review aimed at gathering information about the trends of change in serum CA-125 levels within the range of normal in two patient populations (those who recurred after treatment and those who did not recur after treatment) and using this information to predict cancer recurrence. Charts of patients diagnosed with epithelial ovarian cancer between 1998 to 2004 and who completed their treatment regimens were reviewed for CA-125 values and additional parameters. Only CA-125 values within the range of normal (<35 U/ml) during the follow-up period were analyzed. The maximum absolute increase between any two consecutive CA-125 values was statistically significant (p = .0004) for the recurrence group. The maximum slope between two consecutive CA-125 values was significant (p = .001) in the recurrence group. Finally, the maximum sum of two consecutive slopes of CA-125 values was significant (p = .003) in the recurrence group. Our data show that, for the patient treated for epithelial ovarian cancer and found to be free of disease after treatment, serial CA-125 value analysis within the range of normal will identify patients likely to continue on to develop epithelial ovarian cancer recurrence if the patient has two or more rising values, and/or if the absolute values rise 6.62 points or more.

**Factors Associated with Late Presentation for HIV Care Among Patients in Hinche, Central Haiti.** Coeurilida Louis,a Louise Ivers,a Ken Freedberg,c Mary C. Smith Fawzi,a Arachu Castro,b,d Frank Bia,a aDepartment of Medicine and Laboratory Medicine, Yale University School of Medicine, New Haven Connecticut; bDivision of Social Medicine and Health Inequalities, Department of Internal Medicine, Brigham and Women’s Hospital, Boston, Massachusetts, and Partners In Health, Boston, Massachusetts; cMassachusetts General Hospital, Boston, Massachusetts; and dProgram in Infectious Disease and Social Change, Department of Social Medicine, Harvard Medical School.

Haiti has the highest HIV prevalence in the Caribbean and Latin America and is the poorest country in the Western Hemisphere. Many patients with HIV infection present for care late in the course of their disease, a factor which is associated with poor prognosis. Our objective was to identify factors associated with late presentation for HIV care among patients in central Haiti.

Thirty-one HIV-seropositive adults, or approximately 10 of the HIV-infected population followed at a central Haiti hospital, participated in this research study. A two-part research tool that included a structured questionnaire and an ethnographic life history interview was used to collect quantitative as well as qualitative data about demographic factors related to late presentation for HIV care.

Sixty-five percent of the patients in this study presented late for HIV care, i.e., with CD4 cell count below 350 cells/mm³. Factors associated with late presentation for HIV care included lower socioeconomic status (p < .02), older age (p < .05), greater distance from the medical clinic (p < .005), and lack of prior access to effective medical care (p <
In addition, male sex patient belief that symptoms are not caused by a medical condition and prior negative experience with local hospitals also influenced timing of patient presentation. Harsh poverty was a striking theme among all patients interviewed, and was intricately associated with many of these reported factors.

Delays in presentation for HIV care in rural Haiti are linked to demographic, socioeconomic and structural factors, many of which are rooted in poverty. These data suggest that a multifaceted approach is needed to overcome barriers to early presentation for care. An approach that includes poverty alleviation strategies; provision of effective, reliable and free medical care; patient outreach through community health workers, and collaboration with traditional healers, could improve HIV case detection and reduce morbidity and premature mortality from AIDS in Haiti and in other resource-poor countries similarly affected by the AIDS epidemic.

The Regulation of Chemokines Expression in Human Endometrial Endothelial Cells: A Potential Mechanism for the Pathogenesis of Endometriosis. Janelle Luk and Aydin Arici. Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut.

The elevation of the pro-inflammatory chemoattractant cytokine levels in the ectopic and eutopic endometrium of endometriosis implies an inflammatory basis for the disease. The main aim of this study is to describe the temporal and spatial expression of interleukin-8 (IL-8) and monocyte chemotactic protein-1 (MCP-1) in human endometrial endothelial cells (HEEC) in vivo and to compare the in vitro regulation of IL-8 and MCP-1 expression by sex steroids in HEEC from women with or without endometriosis. And in the final part of the study, we investigated the in vitro regulation of IL-8 and MCP-1 expression by sex steroids in HEEC from women without endometriosis.

Eutopic endometrial tissues and endometriosis implants were grouped according to menstrual cycle phase and were examined by immunohistochemistry for IL-8 and MCP-1 expression. Endothelial cells in ectopic implants from patients with endometriosis expressed higher immunoreactivity of IL-8 and MCP-1 compared to endothelial cells in eutopic endometrium of women with or without endometriosis (p < .02). We observed a trend for higher IL-8 immunohistochemical staining in the endothelial cells of eutopic endometrium of women with endometriosis when compared to endometrium of women without endometriosis (p < .1). For in vitro studies, the effects of estradiol (5 x 10^-8 M), progesterone (10^-7 M), or both on IL-8 and MCP-1 mRNA and protein levels were analyzed by RT-PCR and ELISA, respectively. We found that both estradiol and progesterone stimulated IL-8 and MCP-1 mRNA and protein expression in HEEC from women with endometriosis compared to HEEC from patients without endometriosis. And in the final part of the thesis research, we also found that mevastatin/simvastatin exerted an inhibitory effect on the expression of IL-8 and MCP-1 in HEEC treated with IL-1α.

We postulate that the stimulation of chemokine expression by sex steroids in the endometrial endothelial cells in women with endometriosis may play a role in the inflammatory aspect of this disease and that the statins may affect the expression of pro-inflammatory cytokines in human endometrial endothelial cells and may potentially be beneficial in the treatment of endometriosis.

Suppression of MHC Class I and II in Trophoblast Cells. Raymond J. Lynch (Sponsored by Graeme L. Hammond). Department of Surgery, Yale University School of Medicine, New Haven, Connecticut.

Investigation of the physiologic suppression of MHC class I and II in trophoblast cells may offer new strategies for tissue tolerance in future xenotransplantation. Our lab-
oratory has isolated one such suppressor in the form of a noncoding 0.5-kb trophoblast noncoding RNA (tncRNA). Stable transfectants of tncRNA were produced, and MHC expression assessed by FACS. Transient transfections of tncRNA were carried out with promoter-reporter plasmids for the class II transactivator (CIITA). RNA interference was used to knock down the protein Dicer in trophoblast cell line Jar. MHC class I suppression was studied using class I promoter-reporter constructs in Jar cells, and inhibition of DNA methylation by nucleotide analog and RNA interference techniques.

Constitutive and interferon-induced expression of MHC class II is inhibited by tncRNA. CIITA promoter IV is suppressed by tncRNA at a point outside previously described cis-acting regions. Cotransfection of small inhibitory RNAs directed against Dicer reduces tncRNA's activity. Unmethylated MHC class I promoters are active in Jar. Jar cells have high levels of the DNA methyltransferase Dnmt3b, and chemical inhibition of DNA methylation reverses MHC class I, but not class II, suppression.

Jar cells suppress MHC expression by tncRNA suppression of CIITA promoters. This downregulation is dependent on Dicer and may occur through small inhibitory RNA action. MHC class I promoters are silenced in Jar by DNA methylation.

The Business Case for Bridges to Excellence: Investigating the Link Between Effectiveness and Efficiency of Ambulatory Care. Edison A. Machado, Jr., Amita Rastogi, Carrie Beadle, and Francois DeBrantes. Bridges to Excellence, General Electric Health Advantage, Fairfield, Connecticut. (Sponsored by Howard P. Forman, Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut.)

In 2001, the Institute of Medicine (IOM) released the second in a series of publications on health care quality entitled “Crossing the Quality Chasm: A New Health Care System for the 21st Century.” In the report the IOM called on all health care players to improve the health care system, suggesting a redesign in payments for care. In response to this report a collection of purchasers, providers, plans and experts designed the Bridges to Excellence (BTE) program, a health care model that rewards quality performance, in particular for chronic care, at the provider or provider organization level.

There are countless references that have shown that performance-based incentive programs can have positive effects on motivating provider behavioral change and reducing medical errors. However, there is little information in the literature to suggest a link between incentives and increased provider efficiency. In this study we examined resource utilization levels between BTE certified PCPs and Endocrinologists and non-BTE certified PCPs and Endocrinologists in the Cincinnati and Louisville markets. We hypothesize that BTE physicians in the Diabetes Care Link (DCL) program branch are not only more effective but also more efficient than non-recognized providers.

Study results revealed a lower average annualized cost for diabetes care amongst DCL providers compared to non-DCL providers, an average cost savings of $370 for the endocrinologists group and $18 for the PCP group. Statistical significance was reached only in the Endocrinology group. The majority of the costs savings realized by DCL doctors was seen in terms of decreased inpatient costs, most prominent in the highest costing episodes. Finally, we observed a pattern of decreased cost variation amongst DCL physicians, indicative of the delivery of more consistent and higher quality diabetes care. These results provide evidence to support the Diabetes Care Link program as a viable means of promoting effective and efficient diabetes care.
Improving Medical Observational Skills: Analyzing Fine Art in a Gallery Setting Vs. a Workbook Simulation. Erin M. Mahony and Irwin M. Braverman. Department of Dermatology, Yale University School of Medicine, New Haven, CT

The purpose of this study is to evaluate the significance of student-teacher interaction vs. the medium of fine art in the conduct of the observational skills workshop at the Yale Center for British Art (YCBA). In addition, this study will assess the effectiveness of a fine arts workbook that emulates the workshop at the YCBA. Fifty-eight first-year medical students were randomized to one of three groups. The radiology group participated in an interactive observational skills workshop that utilized the traditional medium of radiographic images. The workbook group completed a fine arts workbook in an independent study environment that did not involve student-teacher interaction. The museum group participated in an interactive fine arts workshop at the YCBA. Improvement in observational skills was assessed with performance exams given before and after each intervention. The workbook group showed the most significant improvement from pre-test to post-test (p value = .007). The radiology group also showed significant improvement in observational skills (p value = .024). The museum group showed no difference between pre-test and post-test scores (p value = .308). A follow-up study showed a trend toward improvement when students in the museum group were provided with question guides during the period of independent observation. The results of this study indicate that student-teacher interaction is not integral to the success of observation skills training, and show that a fine arts workbook is, in fact, an effective tool for teaching observational skills to medical students.

Influence of Recipient Socio-demographic and Clinical Characteristics on the Distribution of Live Vs. Deceased Donor Renal Allografts. Ernest I. Mandel, Kathleen M. Lorber, and Marc I. Lorber. Department of Surgery, Section of Organ Transplantation and Immunology, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this investigation was to compare deceased and living donor kidney transplant distribution using demographic and clinical characteristics to identify possible disproportionate distribution.

Demographic and clinical characteristics of all recipients of deceased and living donor renal transplants in the United States, Puerto Rico, Virgin Islands, and Guam between 1994 and 2003 were obtained from SRTR and reviewed. Income data were obtained by merging zip code with U.S. Census 2000 data on median household income. Chi-squared statistics were used to evaluate the significance of differences in proportions. Logistic regression was used to calculate adjusted odds ratios for receipt of a living vs. deceased donor renal transplant.

Analysis revealed an association between sex, race, education level, insurance, income, blood type, and level of sensitization and receipt of a living vs. deceased donor kidney transplant. Nationally, recipients who were women (adjusted odds ratio [95 percent CI], 1.23 [1.19 to 1.27]), held some college education or more (1.17 [1.13 to 1.22]), were in the second, third, or fourth quartiles of income (1.12 [1.06 to 1.18], 1.25 [1.19 to 1.32], 1.47 [1.40 to 1.55] respectively), or who were privately insured (1.95 [1.88 to 2.02]) were more likely to receive a living vs. deceased donor transplant, while African Americans (0.51 [0.49 to 0.54]), recipients with type AB blood (0.69 [0.63 to 0.75]), and recipients with higher and highest levels of sensitization (0.70 [0.66 to 0.75] and 0.36 [0.32 to 0.39], respectively) were less likely to receive a living donor transplant after adjusting for all other independent variables. Subset analysis of recipient characteristics at the Yale-New Haven Transplant Center revealed similar patterns, though did not retain statistical significance when adjusted for independent variables.
These data identified an apparent disproportionate distribution of live donor renal transplant recipients, favoring Caucasians, the better educated, those with higher income, holders of private primary health insurance, and those who are less immunologically sensitized. Future detailed analyses are indicated to explore reasons for these associations, as well as to seek solutions to ensure equitable access to renal transplantation for all individuals in need.

**The Effectiveness of a Nursery Intervention in Altering Infant Sleep Position During Subsequent Months.** Louis P. Moreno and Eve R. Colson. Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to determine whether parents, exposed to a nursery intervention, continue to keep their infants in the supine position for sleep at two to four months of age. Semistructured interviews were conducted with two different convenience samples of parents at the Yale Pediatric Primary Care Center with one group interviewed at their infants two-week health supervision visit, and the other at the two to four-month visit. All participating infants were cared for postpartum in the well newborn nursery at Yale-New Haven Children's Hospital where nursing staff placed infants in the supine position for sleep and informed parents to place their infants to sleep in the supine position at home. Compared with parents interviewed at the two-week visit, parents at the two to four month visit continued to report receiving advice from a healthcare provider to place the infant to sleep in the supine position at home (81/100 vs. 81/105) and to report seeing the infant placed in the supine position for sleep in the nursery (88/100 vs. 89/104). Parents continued to report usually placing their infants in the supine position for sleep at home (75/100 vs. 68/105). Significantly more parents of two to four-month-old infants reported usually placing their infants in the prone position for sleep (3 percent vs. 16 percent, OR: 0.2; 95 CI: 0.04 to 0.6). Thus, two to four months after birth, parents recalled the nursery interventions to promote supine sleeping, but more reported that they sometimes placed their infants in the prone position for sleep than at the two-week visit.

**Pathogenesis of Intracranial Aneurysms.** Brian V. Nahed and Murat Gunel. Department of Neurosurgery, Yale University School of Medicine, New Haven, Connecticut.

Introduction: Intracranial aneurysms (IA) are a common neurological problem, the rupture of which frequently constitutes a catastrophic neurological event. While the pathogenesis is largely unknown, it is believed that both genetic and environmental factors work in concert to some degree within patients. Our goal was to take a comprehensive approach to understanding the pathogenesis of IA by identifying factors leading to the formation, growth, and rupture of IA.

Methods: Since 1994, we have recruited patients and families with IA into the Yale Brain Aneurysm Database. Information regarding aneurysm characteristics (size, location, number), patient characteristics (age, medical, and social history), and family history were recorded. We analyzed this database for environmental factors associated with aneurysmal rupture. Within the same database, we identified and analyzed kindreds with a high IA incidence and penetrance using genome-wide linkage analysis. Collaborations with other centers provided additional kindreds to analyze and confirm our results.

Results: Analysis of our database revealed hypertensive patients with IA ≤7mm were 2.6 times more likely to rupture (p = .01, 95 percent CI: 1.21 to 5.53) than normotensive patients. Posterior circulation aneurysms were 3.5 times more likely to rupture than anterior circulation aneurysms (p = .048, 95 percent CI: 0.95 to 19.4). Further, genome-wide linkage analysis revealed significant linkage to a single locus, with a lod score of 4.2 at lp34-36.
Conclusions: We identified hypertension, young age, and posterior circulation as significant risk factors for rupture among patients with small aneurysms (<7mm). Additionally, we are the first to map the gene responsible for IA to chromosome lp34-26.

Pelvic Embolization for Intractable Postpartum Hemorrhage: Long-term Follow-up and Fertility Implications. David A. Oman, Robert I. White, Jeffrey Pollak, and Michael G. Tal. Section of Interventional Radiology, Department of Radiology, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study was to determine the long-term sequelae of pelvic embolization for postpartum hemorrhage, and to determine the effect on fertility and menses. Twenty-eight consecutive patients who underwent pelvic embolization for postpartum hemorrhage between the years 1977 to 2002 were included in the study. Chart review and telephone interviews were conducted to gather data regarding the type of delivery, causative factors of the bleeding, pre-embolization treatments, total blood loss, length of time between delivery and embolization, complications, long-term side-effects, and subsequent pregnancies. The average time to follow-up was 11.7 ± 6.9 years. The most common causes of hemorrhage were vaginal/cervical laceration, placenta accreta, and placenta previa. In only one case was the embolization unsuccessful, during which there was an accidental perforation of an internal iliac artery resulting in a retroperitoneal hematoma and subsequent total abdominal hysterectomy (TAH). All of the interviewed patients who desired to get pregnant after embolization were able to do so. Six patients reported a total of six uncomplicated pregnancies and deliveries in the years following their embolization. Of the remaining patients interviewed, none made subsequent attempts to get pregnant. The most commonly reported long-term side effects were transient buttock numbness (n = 2) and urinary frequency (n = 2). In no patients were the side effects severe enough to seek further medical attention. Pelvic arterial embolization is a safe and effective procedure and offers patients a fertility-preserving alternative to hysterectomy for treatment of intractable postpartum hemorrhage.

Evaluating Targeted Ivermectin Distribution for Controlling River Blindness. Eric M. Poolman, Michaleen Richer, Joseph Kubofcik, Thomas Nutman, and Alison Galvani (Sponsored by Michael Cappello). Division of Pediatric Infectious Disease, Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

This study combines field and laboratory data from southern Sudan with mathematical modeling of onchocerciasis to evaluate targeting specific portions of the human population for treatment with ivermectin in the control of onchocerciasis. Skin snip, hematologic, and behavioral surveys were conducted in Tambura and Yambio counties of southwestern Sudan. Polymerase chain reaction (PCR)-based detection of *Onchocerca volvulus* DNA was conducted on the skin snips to compare the sensitivity of field and laboratory detection methods. A mathematical model of onchocerciasis was developed that incorporated heterogeneity in host exposure to the vector.

Villages treated for five years with ivermectin showed significantly decreased prevalence of microfilariarminia (52.5 percent to 14.6 percent, *p* < .001, z-test). Compared to PCR, skin snip microscopy missed six of seven infections in children (sensitivity 14.3 percent, s.e. 13.2 percent). On a per dose basis, targeted treatment with ivermectin resulted in percentage decreases of equilibrium microfilarial burdens 1.7- to 5.0-fold higher than untargeted treatment.

Our results suggest ivermectin treatment has been effective in southwestern Sudan and that PCR analysis of skin snips is substantially more sensitive than microscopy, par-
particularly in children. Our model suggests targeted distribution of ivermectin may achieve similar goals in reducing the public health burden of onchocerciasis with significantly lower risk of adverse effects and while possibly delaying the emergence and spread of ivermectin resistance.

**Evaluation of the Efficacy of rhGDF-5 in a New Zealand White Rabbit Posterolateral Lumbar Fusion Model.** Bradley S. Raphael, David P. Magit, Travis Maak, Qusai Hammouri, Nancy W Troiano, Gert Polzhofer, Inneke Drespe, Todd J. Albert, and Jonathan N. Grauer. Department of Orthopaedics, Yale University School of Medicine, New Haven, Connecticut.

The purpose of this study is to test the efficacy of recombinant growth and differentiation factor-5 ([rhGDF-5] also described as bone morphogenic protein 14 [BMP-14], or miniprep-52 [MP52]) with a Healos carrier in a New Zealand white rabbit posterolateral lumbar fusion model in several concentrations with direct comparison to autograft and carrier alone controls.

The commonly used posterolateral lumbar fusion model was used to evaluate five fusion constructs (n = 13 for each group): iliac crest autograft, Healos alone (cross-linked-type I collagen with a hydroxyapatite coating), and three doses of rhGDF-5 lyophilized to the Healos carrier. The doses studied were 0.5 mg/cc, 1.0 mg/cc, and 1.5 mg/cc, with one 1.5 cc strip used per side for each procedure. At eight weeks, the rabbits were sacrificed and evaluated by manual palpation, radiographs, and histology.

Fusion results by manual palpation were: autograft 38 percent (5/13), Healos alone 0 percent (0/13), and all doses of Healos/rhGDF-5 100 percent (13/13 for each). These were statistically significant (p < .05). Radiographs had a sensitivity of 84 percent and specificity of 86 percent. Histologic analysis yielded a sensitivity and specificity of 95 percent, as well as demonstrated abundant bone formation with numerous osteoblasts and trabecular architecture in most rhGDF-5-induced fusion masses. Using a well-established lumbar fusion model, Healos/rhGDF-5 induced fusion in 100 percent of the animals studied, significantly higher than the autograft group (38 percent). At the lower two doses, solid bone formation suggested appropriate dosing. The bone shells seen in the highest dose group suggested that this dose was too high for the application being evaluated. Overall, the results of this study were encouraging and support further ongoing studies.

**The Crisis of Uninsured Children in America: Is Lack of Health Insurance Really the Problem?** Susan E. Rushing (Sponsored by Myron Genel). Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

Insurance coverage is not the sole factor limiting access to health care for children. This thesis elucidates the barriers preventing children from accessing affordable health care in the United States and recommends solutions to increase children's access to care. A literature search was employed to determine the barriers that prevent children from accessing health care. The following mechanisms for increasing access to care are suggested and analyzed: the creation of a health insurance mandate, abandonment of the public insurance re-determination process, linking health insurance eligibility to federal income tax forms, providing equitable federal funding for S-CHIP and Medicaid enrollees, reallocation of DSH payments into a front-end payment scheme, increasing the number of FQHCs, increasing physician reimbursement, improving bias awareness among physicians, increasing incentives for physicians to work in under-served areas, and changes in clinical infrastructure. For each proposed solution, predictions are made regarding the likely impact on children's access to care, costs, political and administrative feasibility, and equity and distribution of access to care for children. Increasing children's
access to care will likely require a multi-faceted approach that employs many of the suggested solutions.

**Surveying the Protein Composition of Human Cell Membranes by Shotgun Proteomics.** Mariah C. Ruth, Katheryn A. Resing, and Natalie G. Ahn. Department of Chemistry and Biochemistry, University of Colorado at Boulder, Boulder, Colorado. (Sponsored by John Paweiek, Department of Dermatology, Yale University School of Medicine, New Haven, Connecticut).

This study developed new methods for the comprehensive surveying of cell membranes by shotgun proteomics and quantitatively compared these protocols with existing proteomic methods. Using K562 cells as a model system, published methods for the solubilization and digestion of membrane proteins using (i) mixed organic-aqueous solvents and (ii) urea for membrane solubilization were compared to newly developed methods using (iii) urea and (iv) acid labile surfactants (ALS, RapiGest™). These four methods were compared based on the efficiency of protein solubilization and proteolysis, as well as peptide recovery and membrane protein enrichment. I found that using ALS yielded the greatest enrichment of membrane proteins in terms of overall number and percentage of membrane proteins from K562 extracts, as well as offering a significantly higher yield of peptides from membrane proteins. I concluded that ALS provides a significant advantage for the recovery of membrane proteins and peptides; urea extraction provides an inexpensive (though less successful) alternative; and organic solvents are suboptimal for shotgun proteomics of membrane samples. Membrane datasets were then compared to a dataset of K562 soluble proteins to evaluate for protein enrichment. I was able to confirm successful enrichment of membrane proteins using spectral counting and also increased the number of identified proteins in the K562 database to >6,000 proteins.

**Connective Tissue Growth Factor (CTGF) in Fibrosis Associated with Intestinal Neuroendocrine Tumors.** Michael D. Shapiro, Mark Kidd, and Irvin M. Modlin. Section of Surgical Gastroenterology, Department of Surgery, Yale University School of Medicine, New Haven, Connecticut.

Carcinoid tumors of the small bowel often present with fibrosis — in the peritumoral tissues, distant in the heart or lungs, and locally in the peritoneal cavity. The mechanism of such fibrosis is unclear and its timely diagnosis impossible. There exists no test to determine the risk of fibrosis, detect its presence, or monitor its progression once discovered. Furthermore, no current therapy protects against such fibrosis. We have proposed that CTGF, a mediator of the profibrotic activities of TGFß1 (a known regulator of fibrosis) is directly involved in the genesis of ileal carcinoid-related fibrosis. The aim of this study was to assess the potential correlation of serum and tissue CTGF with the diagnosis of carcinoid-related fibrosis. Serum and tissue samples from patients with gastrointestinal (GI) carcinoids, other GI and extra-GI malignancies, and control patients were collected prospectively. A GI carcinoid tissue microarray (TMA) was stained immunohistochemically with CTGF antibodies, semi-quantitatively measured using AQUA analysis, and correlated with clinical fibrosis. Significantly higher serum CTGF levels (>2 fold) were found in patients with ileal carcinoids than in patients with gastric ECL cell carcinoids (the latter of which are not associated with fibrosis) and control patients. Our results demonstrate that CTGF protein is over-expressed in small bowel carcinoid tumors associated with fibrosis and that the secreted protein is stable and detectable in patient serum. The correlation of CTGF with TGFß1 suggests that CTGF is a co-secreted fibrotic factor. Since the relationship of CTGF to fibrosis is well defined, this cytokine may be involved
in the genesis of ileal carcinoid-related fibrosis. The detection of elevated levels may provide a diagnostic opportunity to predict fibrosis and pre-empt its local and systemic complications. Furthermore, CTGF may represent a therapeutic target for management of fibrosis-related complications in patients with carcinoid tumors.

HAART-Felt Prospects: Information, Motivation, and Behavioral Skills Regarding Incipient Highly Active Antiretroviral Therapy Among Bilingual Young Adults in Tugela Ferry, South Africa. Margo D. Simon and Gerald Friedland. AIDS Program, Department of Internal Medicine, Yale University, School of Medicine, New Haven, Connecticut.

The purpose of “HAART-Felt Prospects” is to assess information, motivation, and behavioral skills (IMB) regarding antiretroviral (ARV) therapy in a high-HIV-prevalence rural South African community, and to identify deficits and strengths in its transition to widespread ARV availability.

This study was an anonymous cross-sectional survey consisting of 120 multiple-choice questions, administered to a convenience sample of HIV-serostatus-unknown bilingual English- and Zulu-speaking young adult students of Tugela Ferry. Frequencies and measures of central tendency were determined and grouped by theme. Knowledge score was calculated as percent correct answers to select information questions. Motivation (MQ) and behavioral skills quotients (BSQ) were based on a four-point rating scale. Relationships between select independent variables, including past experience with medicines, and IMB were examined in bivariate and multivariable analyses.

The sample of 176 subjects was 98.9 percent Zulu, 58 percent women, 42 percent Christian, mean age 19.1 years, grade 10 to 12. The majority had low socioeconomic status (SES) and at least one illiterate parent.

Regarding ARV information, mean knowledge score was 45.6 percent, SD 17.6; percentage with correct answers on benefit was 38.9 percent; cure and treatment beliefs: 13.5 percent; eligibility: 42.3 percent; medicine taking: 58.5 percent; side-effects: 22.2 percent; acquired resistance: 49.2 percent; and sexually transmitted resistance: 80.7 percent. Further, 121 subjects (68.8 percent) knew that HIV was the main cause of AIDS; 114 (64.8 percent) had heard of ARVs (71.1 percent from radio); and 27 (15.3 percent) reported that traditional or government-advocated folk remedies cure or treat HIV/AIDS.

Regarding ARV motivation, MQ mean per question was 2.99, SD 0.29, out of 4; mean for perceived confidence in efficacy was 2.73; perceived social support: 3.00; perceived structural support: 3.31; medication taking demands: 2.96; acquired resistance: 3.48; and sexually transmitted resistance: 3.43. In particular, 145 (82.4 percent) believed believed that ARVs work (independently predicted by perceived structural support OR=1.56 p=0.0005, low SES OR=2.51 p = .04). Regarding ARV behavioral skills, BSQ mean per question was 2.61, SD 0.64, out of 4; mean for self-efficacy on medication taking was 2.51 and side-effects tolerance: 3.16. Two additional themes emerged: 1) HIV optimism: 130 (73.9 percent), independently predicted by knowledge of ARV benefit OR = 1.46, p = .003 and identifying as a woman OR = 2.70, p = .006; 2) disclosure of HIV status: 111 (63.1 percent) believed disclosure improves ARV outcome; 159 (90.4 percent) would disclose for assistance taking ARVs; and 83 (47.2 percent) thought disclosure would be easy.

These results suggest that this rural South African community is reasonably well poised for the introduction of ARVs. This study identified both deficits and strengths, which should inform future ARV treatment enhancement programs and contribute to the overall success of HIV/AIDS therapy in this and similar communities.
Patterns of Treatment for Ductal Carcinoma in Situ of the Breast: Rationale for a Minimum Standard. Grace L. Smith, Benjamin D. Smith, and Bruce G. Haffty. Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut.

In patients with ductal carcinoma in situ (DCIS) of the breast, radiotherapy following conservative surgery (RT+CS) decreases local recurrence, but absolute event reduction may be as low as 3 percent in lowest-risk patients. Though risk-stratification systems attempt to minimize over- and undertreatment, it is not known whether recommended treatment strategies are consistently applied nationally. This study sought to quantify and evaluate national patterns of overtreatment and undertreatment of DCIS from 1996 to 2001, using a retrospective cohort study of 14,498 DCIS patients from the population-based Surveillance, Epidemiology, and End Results (SEER) data.

Of all DCIS patients, 10 percent were overtreated and 6 to 20 percent were undertreated. While overtreatment significantly decreased with time, undertreatment increased, despite a growing incidence of DCIS diagnosed with aggressive grade and large size (p for trends < .0001). Geographic variation in treatment patterns was significant after adjusting for patient and tumor characteristics (p < .0001). A substantial proportion of undertreated patients were young (10 age < 40 years) or had comedocarcinoma (34 percent).

Annually, an estimated 3,000 to 12,000 DCIS patients are undertreated. Increasing undertreatment rates and significant geographic variation in DCIS care suggests that a lack of consensus exists regarding treatment strategies for highest-risk DCIS patients. These findings emphasize the need to define a national minimum standard for treatment of DCIS.

Home Visits for First-Time Mothers: Impact on Child Maltreatment and Health care Utilization. Martine M. Solages and John Leventhal. Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

Healthy Families America is a nationwide initiative that provides intensive home visits by paraprofessionals to first-time, high-risk mothers. The aim of this study is to examine the impact of the Yale Healthy Families Program on seven outcomes in the first two years of life: 1) the occurrence of childhood injuries due to maltreatment; 2) unintentional injuries; 3) referrals to child protective services reported in the medical record; 4) immunization status at 24 months; 5) utilization of well-child health care; 6) number of emergency department visits; and 7) repeat pregnancies. We conducted a non-randomized, retrospective medical record review. The intervention group consisted of 93 families who received Health Families services. The control group consisted of 68 families who were screened for inclusion in the Healthy Families program but who did not receive services. For each child, we reviewed the medical records and abstracted information regarding the above pediatric health outcomes. We compared each of these outcomes in the intervention group with those in the control group. We also reviewed the medical records of mothers in each group and abstracted information about subsequent pregnancies. Healthy Families children attended more well child visits in the first six months of life (3.2) than their comparison group counterparts (2.7) (p = .02). However, children in the Healthy Families group were more likely to suffer injuries (p = .004). Mothers participating in the Healthy Families program were less likely to have a subsequent pregnancy (33.7 percent) than mothers in the comparison group (55.1 percent) (p = .007). This study did not demonstrate a significant impact of the Yale Healthy Families program on immunizations, emergency department visits, or child protective services referrals. We concluded that the Yale Healthy Families Program appears to have some beneficial impact on both maternal and
child health, but larger, prospective trials of home visiting programs that examine these outcomes are needed.

A New Method for Quantification of Musician’s Dystonia: The Frequency of Abnormal Movements Scale. June T. Spector and Alice G. Brandfonbrener. Medical Program for Performing Artists, Rehabilitation Institute of Chicago, Northwestern University, Chicago, Illinois. (Sponsored by Bahman Jabbari, Department of Neurology, Yale University School of Medicine, New Haven, Connecticut.)

We developed a new scale, the Frequency of Abnormal Movements (FAM) scale, for the objective and quantitative evaluation of focal task-specific dystonia in musicians, and we assessed the FAM scale for internal consistency, intra- and inter-rater concordance, and correlation, and responsiveness to change. Eighteen instrumentalists with musician's dystonia were recruited from the Medical Program for Performing Artists Clinic and videotaped playing their instrument before, after one week, and after six months of Sensory Motor Retuning (SMR) therapy. Two raters, blinded to the order of the randomized video segments, independently counted the number of abnormal (dystonic and compensatory) movements for each segment, and the number of abnormal movements was divided by the length of the segment to give the FAM score. Video segments were also rated using the Arm Dystonia Disability Scale (ADDS) and the Burke Fahn-Marsden (BFM) scale. Internal consistency of the FAM scale was good (Cronbach's $\alpha = 0.96$), as were intra-rater concordance (relative magnitude of disparity $= 8$, weighted $\kappa = 0.76$) and correlation (Intraclass Correlation Coefficient [ICC] = 0.92, Spearman's $p = 0.87$). Inter-rater concordance and correlation were better for the FAM scale (weighted $\kappa = 0.94$, ICC = 0.96, Spearman's $p = .90$) than for the ADDS (weighted $\kappa = 0.56$, ICC = 0.81, Spearman's $p = 0.68$) and BFM scale (weighted $\kappa = 0.57$, ICC = 0.82, Spearman's $p = .76$). Decrease in the FAM scale after one week of SMR was less likely to be due to chance ($p = .06$) than decrease in the ADDS ($p = .21$) and the BFM scale ($p = .53$), as assessed by the Wilcoxon signed-rank test. The FAM scale may be useful, especially in combination with subjective scales and scales assessing musical performance, for studying the natural history and effect of interventions on patients with musician's dystonia.

The Effects of 0.08 Percent Blood Alcohol Concentration Limits on Traffic Fatalities in 31 States and Washington, D.C.: A Multiple Time-Series Analysis. Matthew D. Streckert and Linda C. Degutis. Section of Emergency Medicine, Department of Surgery, Yale University School of Medicine, New Haven, Connecticut.

Purpose: Blood Alcohol Concentration (BAC) limits for drivers have been lowered from 0.10 percent to 0.08 percent in all 50 states and District of Columbia. Our purpose was to use multiple time-series models, which can provide the same level of control over confounding factors as randomized trials, to evaluate the effects of the new limits in 31 states and Washington, D.C.

Methods: We employed time-series regression analysis to evaluate the effects of lowering BAC limits to 0.08 percent. We used the federal Fatality Analysis Reporting System database as a data source and the monthly number of alcohol-related traffic fatalities as the dependent variable. We used the X-11 algorithm to control for seasonal variability and the number of weekends in each month. We also controlled for national trends. We used ARIMA analysis to quantify the effect of the lower limit for each state.

Results: Three states had significant decreases in fatalities, and two experienced significant increases, after the passage of 0.08 percent laws. Overall, 18 states experienced decreases in fatalities, and 14 experienced increases.
Conclusions: While 0.08 percent laws reduced alcohol-related fatalities in many states, the effect was significant in only a small number of states. Other states experienced increases in fatalities, some of which were significant, however it is unclear what caused these increases.

The Relationship Between Autonomic Dysfunction and Cardiac Events in the DIAD Study. Curtis H. Weiss, Deborah Chyun, and Lawrence H. Young. Section of Cardiovascular Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Coronary artery disease has an enormous impact on patients with type 2 diabetes, and early identification of individuals at increased risk for adverse events is critical. This research examined whether autonomic dysfunction predicts cardiac outcomes in patients without angina. Autonomic function was assessed in all patients enrolled in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) Study using established methods, including analysis of the heart rate response, from lying-to-standing and during the Valsalva maneuver, and power spectral analysis of heart rate variability. Patients in the lowest quartile of heart rate response to standing were 3.4 times more likely to have an adverse cardiac event as an unadjusted predictor (p < .0001), and 2.46 times more likely (p = .0022) when adjusted for triglycerides and duration of diabetes, the only other significant risk factors identified. Patients in the lowest heart quartile of heart rate response to Valsalva were 3.23 times more likely to have an adverse cardiac event as an unadjusted predictor (p < .0001), and 2.86 times more likely when adjusted for triglycerides and duration of diabetes (p = .0003). Thus, the presence of diminished cardiac autonomic response identifies patients with type 2 diabetes without angina who are at significantly greater risk of having an adverse cardiac outcome. The results of this research should help to risk stratify patients, aid in the development of appropriate management plans, and improve outcomes in patients with diabetes.

Endothelial Progenitor Cells Display Large Vessel Endothelial Cell Characteristics and Enhance Perfusion in Ischemic Tissue. Carlos K. Wesley (Sponsored by Jeffrey S. Schechner, J. Grant Thomson, and Jordan S. Pober). Department of Pathology, Yale University School of Medicine, New Haven, Connecticut.

The discovery of endothelial progenitor cells (EPCs) promoting new blood vessel growth in adult tissue may provide promise of relief to patients suffering from various forms of tissue ischemia. The goals of this project are to 1) determine an EPC vessel caliber pattern via adhesion molecule expression, and 2) demonstrate whether direct injection of human EPCs into murine tissue undergoing ischemic injury enhances tissue reperfusion.

To address these objectives, flow cytometry analysis of human umbilical cord blood and CD34+ purified human peripheral blood was carried out. An ischemic dorsal flap model was then used in SCID mice (n = 18) undergoing study-blind direct injection of: 10^5 EPCs, 10^5 HUVECs (a control cell line), or media (negative control). Laser Doppler analysis on post-op days 1, 3, 7, 14, and 21 was followed by histologic assessment of tissue sections to complete the study.

We conclude that effective neovascularization and the resulting reperfusion and oxygenation of ischemic tissue are essential in recovery from an ischemic event. We demonstrated that: (a) cord blood and young adult peripheral blood both appear to have similar populations of EPCs; (b) cultures become progressively enriched for EPC-derived ECs with time in culture; (c) the pattern of adhesion molecule expression more closely resembles that of large vessel rather than microvessel ECs; and (d) both HUVECs and ECs derived from EPCs appear to increase perfusion I in skin flaps (p = .0055). This enhancement is so rapid that it is likely, at early times, to result from vasodilation rather than new vessel formation.
The Alpha 6 Integrin Subunit in The Developing Mouse Olfactory System.
Matthew Whitley and Charles Greer. Department of Neurosurgery, Yale University School of Medicine, New Haven, Connecticut.

Integrins are heterodimeric cell surface receptors that mediate developmental events by binding extracellular matrix (ECM) ligands. Several lines of evidence suggest a role for integrins, specifically the α6 subunit, in neuronal migration, neurite outgrowth, and axon guidance during the development of the olfactory system. Therefore, we undertook an analysis of the in vivo expression of the α6 subunit in the olfactory system of the embryonic and early postnatal mouse to better understand the role it may play during neural development. In addition, as a functional assay we examined the developmental effects of the loss of this integrin subunit on olfactory development by analyzing an α6 knockout (α6 -/-). Immunohistochemical analyses and confocal microscopy using an antibody specific to α6 to examine expression from embryonic (E) day 13 to postnatal (P) day 4 in CD-1 mice were performed. The organization of the olfactory system in the α6 -/- mouse was also characterized with these methods. In CD-1 mice from E13 to E17, α6 localizes in a radial pattern extending from the core of the olfactory bulb (OB) to the nerve layer and colocalizes with RC2, a marker for radial glia. By P0, expression is limited to the external plexiform layer (EPL) and olfactory ensheathing cells (OEC) where it colocalizes with laminin and p75. In the α6 -/- mouse, areas of ectopic granule cells were observed in the mitral cell layer (MCL) of the OB. These ectopias coincided with areas of disorganization of the associated radial glial processes and breaks in the normally continuous MCL. Together, these observations suggest a role for the α6 integrin subunit in neural migration during olfactory development, likely secondary to organization of the radial glial scaffold.

Re-emerging Fear: The 1991 Outbreak of Multi-drug Resistant Tuberculosis in the New York Prison System. Jessica Yager (Sponsored by John Harley Warner). Department of the History of Medicine, Yale University School of Medicine. New Haven, Connecticut.

In 1978, amidst the congratulatory belief that antibiotics had heralded the beginning of a post-infectious era, New York City's rates of tuberculosis began to rise for the first time since 1953. Concerned clinicians and public health officials noticed the change and began advocating for increased funds to help control the disease. Tuberculosis experts gathered to assess the situation, and all warned of a possible tuberculosis outbreak. The government, however, did not act on the recommendations made by these experts. Following nearly 25 years of declining tuberculosis rates, the city's tuberculosis infrastructure had been largely abandoned, under-funded and ignored. Tuberculosis cases continued to increase annually after 1978.

In November 1991, the New York Times reported that 13 New York prisoners and one prison guard had all recently died from multi-drug resistant tuberculosis. As the Times continued to follow the story, the government finally began to take steps towards controlling tuberculosis in the correctional system and in the city. This renovation of the city's tuberculosis infrastructure was in large part the result of the organized efforts of a small group of concerned health care workers, many of whom were working at New York's Rikers Island prison complex. This group of doctors, nurses, and public health workers succeeded in preventing a citywide epidemic of multi-drug resistant tuberculosis not by using novel technologies or medications, but by updating and enforcing many of the approaches of disease control that had been employed for decades. Having learned how to prevent and cure tuberculosis, public health officials and the general public had largely forgotten the disease. However, the events of 1991 serve as a reminder that such diseases — ignored by not eliminated — retain the potential for devastating outbreaks.