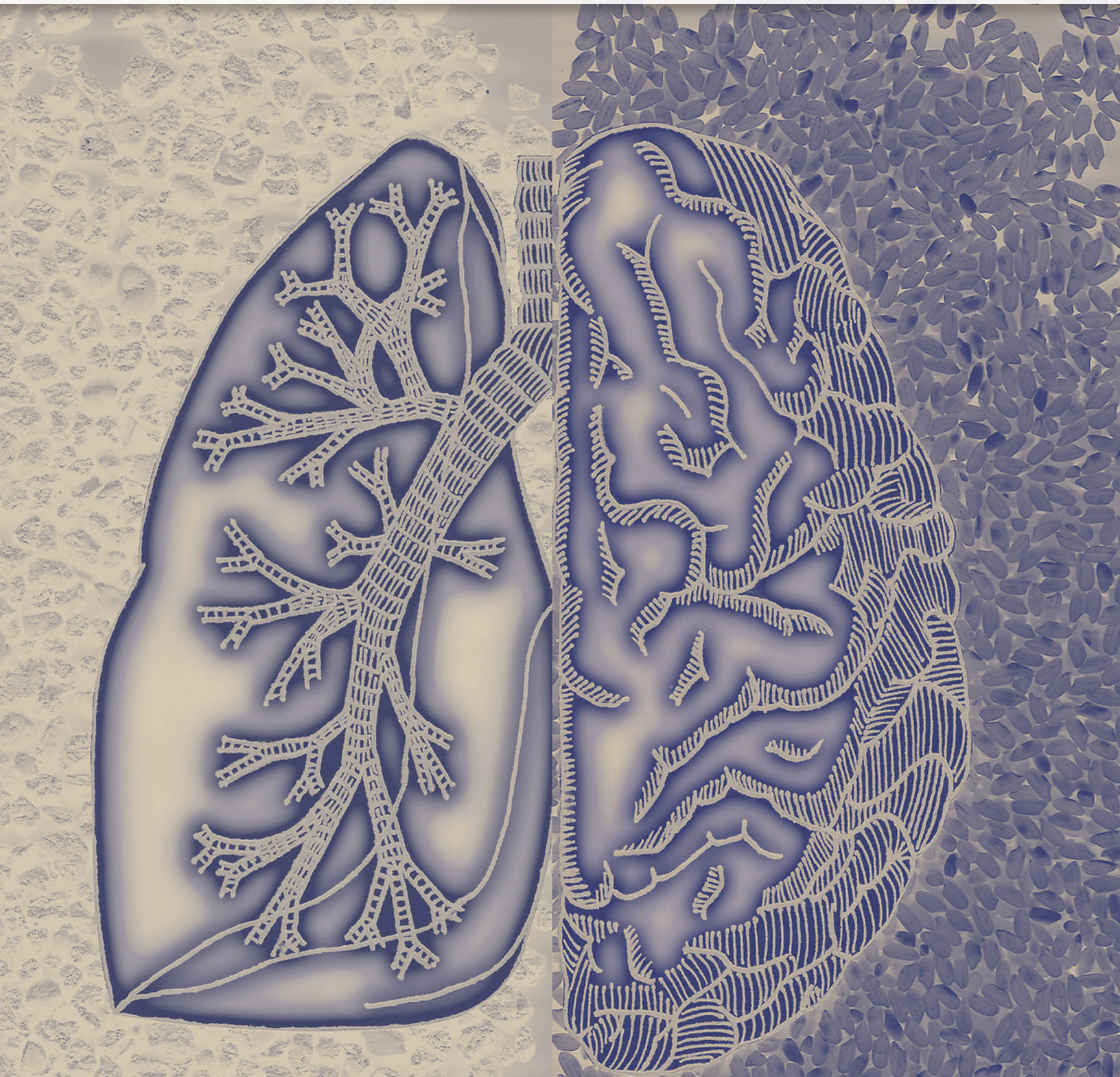
FUSION

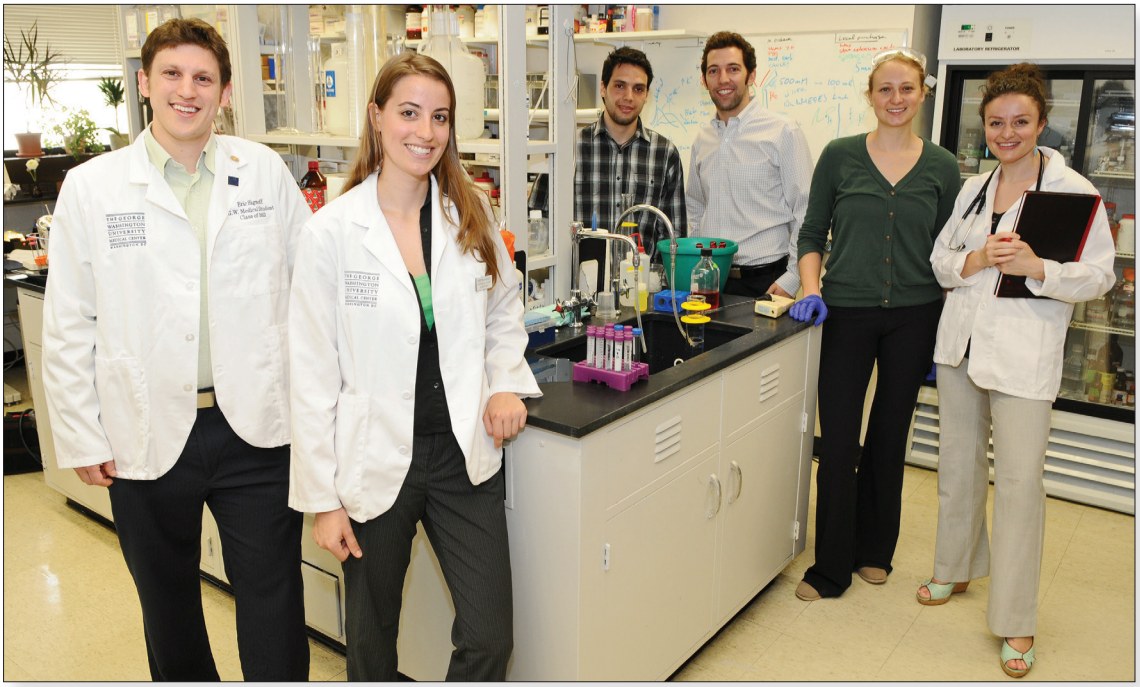
THE STUDENT-RUN SCIENTIFIC JOURNAL OF THE GEORGE WASHINGTON UNIVERSITY SCHOOL OF MEDICINE AND HEALTH SCIENCES



THE WILLIAM H. BEAUMONT MEDICAL RESEARCH HONOR SOCIETY, VOL. V, SPRING 2011

welcome to Fusion

Dear George Washington Medical Community, Faculty, and Students:



***FUSION* EDITORS:**
From left: Eric Signoff, MSII; Kristen Batich, MSII; Thomas Zaikos, MSI; Stephen Swank, MSII; Jana Freeman, MSII; and Gena Gora, MSII.

Welcome to the 2011 edition of *Fusion*, a completely student-run research journal by The George Washington University's William H. Beaumont Medical Research Honor Society at GW's School of Medicine and Health Science (SMHS). Beaumont aims to promote the value of research for students in the medical community. Among our activities, including journal clubs and Research Day, the most rewarding aspect of this society is working with our classmates and future colleagues to publish this journal.

Fusion is aptly named: the journal embodies the link between science and medicine, as articles span the gamut of scientific disciplines and clinical subspecialties both domestic and abroad. In medicine, hard science and bench research yield clinical trials, which in turn guide bedside practices and public health campaigns. Our journal features student research and perspectives in all of these phases, which is in part what makes medicine such a collaborative and exciting field. As busy medical students, it often becomes easy to approach our studies as a block of knowledge to memorize; but when we engage in research projects and discussions with classmates, we find that the process of learning can and should be a dynamic one. This is what *Fusion* is all about — student interest in research — the very thing that moves medicine forward.

The theme of GW Research Day and this magazine is advancing cancer research. Our cover image was created by Kenneth Morford, MSII. Through a multimedia piece, Morford's depiction represents the importance of interdisciplinary collaboration in medical research and highlights the art of medicine.

Finally, we would like to take this opportunity to acknowledge and thank our new faculty advisor, Vincent A. Chiappinelli, PhD, interim associate vice provost for Health Affairs, and associate dean of SMHS. His guidance and enthusiasm throughout the year has provided us with inspiration and a sense of purpose.

We are very proud of this edition of Fusion and the hard work that our colleagues put forth into creating this magazine. It is our hope that you will find as much enjoyment and inspiration flipping through the following pages as we did editing them.

Your editors,
Eric, Gena, Jana, Kristen, Stephen, and Thomas

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The Practice of Medicine: A Balance Between Art and Science

Vincent A. Chiappinelli, PhD
Interim Associate Vice Provost for Health Affairs, Associate Dean of the School of Medicine and Health Sciences, and Ralph E. Loewy Professor and Chair of Pharmacology and Physiology

It has been a pleasure to serve as the faculty advisor to the William H. Beaumont Medical Research Honor Society. The Beaumont Society is a student-run organization that brings together students with a very wide range of research interests and experiences, from basic biomedical research to clinical studies to health policy research. *Fusion* is the showcase for these students' work, and this year's edition is a fascinating window into their research world.

Medicine is both art and science, and gaining experience in both of these aspects of the field is rewarding and can lead in unexpected directions. I recommend going with what you find most interesting. An early interest in the development of the nervous system triggered my studies of nicotinic acetylcholine receptors. Finding a lack of drugs that could be used as probes for these neuronal receptors, I began to isolate proteins from snake venom and test their potencies as antagonists at these receptors. This led to the discovery of kappa-bungarotoxin. To gain more insight into how this toxin blocked nicotinic receptors I travelled to parts of China and Taiwan where these poisonous snakes live, and working with my collaborators I was able to purify additional kappa-neurotoxins. You never know where your research will take you, but it is challenging, often fun, and surprisingly social as interactions with other scientists are essential in cutting-edge research.

Medical students have a long tradition as biomedical researchers. It was a medical student who in 1846 first publicly demonstrated the remarkable value of ether as a general anesthetic. The research experiences of our GW medical students described in *Fusion* are the result of hard work, major successes and minor disasters, and above all a dedication to push the window so that science can inform decision making for both medical doctors and our society. The faculty members of SMHS congratulate the students of the Beaumont Society and express our warmest wishes for your future journeys through art and science.

***Fusion* is a publication of The George Washington University School of Medicine and Health Sciences William H. Beaumont Medical Research Honor Society.**

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advice from an expert

The Researcher's Art is First of All to Find Himself a Good Boss.

Jeremy Brown, MD, associate professor of Emergency Medicine, GW School of Medicine and Health Sciences

This issue of *Fusion* is a celebration of the vibrant research community that flourishes at The George Washington University. In any medical student's busy life it can be hard to find the time to do anything other than study and absorb pages of information; but the number of students who have not only found time to become involved with research, but also have had the patience and fortitude to see their projects through to the stage of presentation is quite remarkable. Now, where do you go from here?

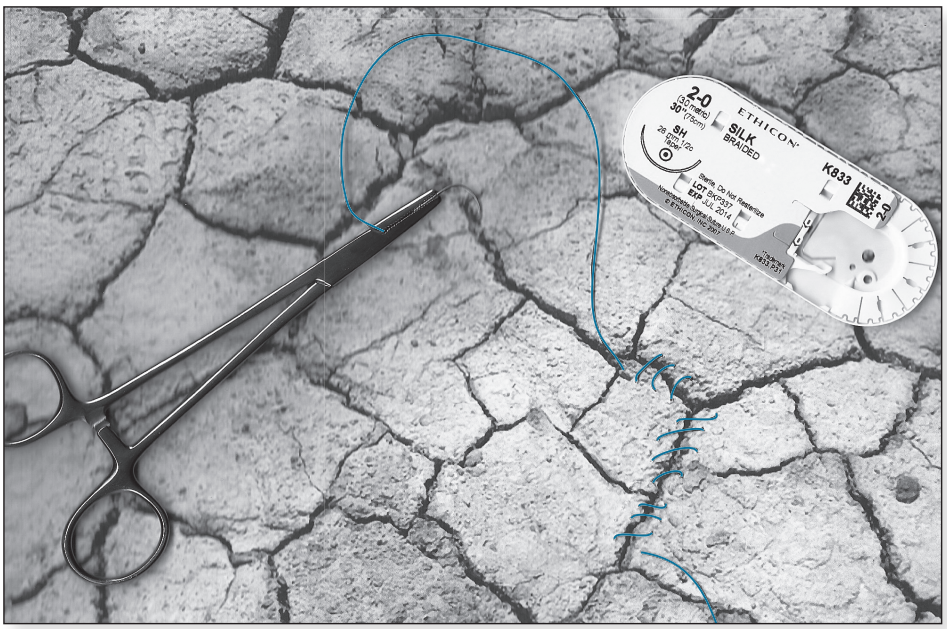
For some of you it will be enough to have participated in your project and you may have decided, upon reflection, that research is not going to be your final career choice. For others, this opportunity may have resulted in the opposite conclusion. But whether you focus on clinical practice or research, your success will likely depend on following André Lwoff's advice: find yourself a good boss. Lwoff was a French physician and microbiologist and was awarded the Nobel Prize in Medicine in 1965 for his discovery that some viruses infect bacteria. Lwoff also knew a thing or two about finding a good boss — or in the language that we use today — a good mentor; early in his career he spent a spent a year working for Otto Meyerhof — also a Nobel Prize winner — in Heidelberg. Having spent at least four years being mentored (and sometimes perhaps bossed, too) you will have seen many different styles of both teaching and treating. Your greatest ticket to success is to emulate the very best practices that you have seen and consciously shun those that you observed to be counter productive. Did your mentor use a line with a patient that seemed to work well? If so, use it yourself. And if you saw an empathetic physician reach out to a patient, copy that technique and pass it on. When it comes to research this advice is just as important. To be a great researcher you need a boss who can be a role model — someone you can both emulate and to whom you can reach out. This goal is of course a lofty one; mentors and leaders after all are only human, and they may have great skills in one area but be utterly wanting in others. That is why I suggest amending Lwoff's advice. Don't find one good boss or mentor, but rather several, and take the very best traits from each.

Many years ago, while a medical student in London, I read a long piece in the *London Times* by a distinguished Professor of Medical Ethics that outlined the reasons why research on human embryos should be banned. Rather naïvely, I wrote an equally long piece on what I considered to be the flaws in the argument, and discussed it with a mentor of mine who not only showed me the problems with my own reasoning, but encouraged me to publish the piece. Thanks to his mentorship I did precisely that. It was not perhaps a Nobel Prize winning publication, but the mentorship and advice was worth a lot more than the two lines the article took up on my resume, because it showed me how it was possible to become involved even as a young student, in the conversation and research that shapes the society in which we live. As young physicians and researchers you will have an important role in shaping the society in which you choose to make your homes. So choose your next boss wisely, for whether you will become a Nobel Prize winner or an excellent and compassionate physician, your boss — or bosses — will have a key role to play.

Cited in Max Perutz, *Is science necessary? Essays on Science and scientists*, (1991), 194.

Earth's Chief Complaint: Climate Change

Rachel Harold, MSII
Advisor: John Balbus, MD, MPH, National Institute of Environmental Health Sciences



Art by Kenneth Morford, MSII

As global climate change continues to impact the environment in which we live, human health is and will be deeply affected. Direct health impacts may take numerous forms: increased extreme heat events like the one that killed approximately 30,000, mostly elderly, people in Europe in 2003;[1] expanding geographic and seasonal ranges of vector-borne diseases such as Dengue; increased frequency of severe weather events such as hurricanes; and respiratory illnesses such as asthma due to changes in air quality. In addition, there will be health implications that result indirectly from climate change such as the morbidity and mortality associated with food and water insecurity resulting from droughts and floods. Climate change is expected to take many of the health issues we already can't control and increase their frequency, their reach, and their severity.[2]

While the issue of climate change may appear static in the halls of Congress and the summits in Copenhagen and Cancun, it is certainly moving into our exam rooms and hospitals. Clinics across the world will soon be full of patients with a chief complaint of climate change.

Unfortunately, many global leaders have been hesitant to take bold steps to mitigate the impacts of climate change by reducing greenhouse gas emissions, shifting the paradigm away from preventative policy change and focusing efforts on adaptation strategies to help global citizens handle the expected impacts of climate change. From a health perspective, inaction on climate change is especially imprudent because there are many positive health outcomes associated with reducing greenhouse gases. These "co-benefits" (and occasional "co-harms") are expected to result from changes that our global society makes to respond to climate change. For example, if communities increase public transportation infrastructure and create more systems for walking and biking in their built communities to reduce greenhouse gas emissions from cars, then the incidence of health problems such as obesity and cardiovascular disease will be reduced due to increased exercise. Another example includes replacing pervasive dirty biomass-burning indoor cook-stoves in countries such as India with low emission cook-stoves. Climate-altering emissions would be reduced, but so too would cases of chronic obstructive pulmonary disease, acute lower respiratory infections in children, and ischemic heart disease that are exacerbated and sometimes caused by indoor air pollution. In November 2009, the *Lancet* released a series that quantitatively modeled these and other predicted public health outcomes of specific strategies to reduce climate change. The results suggested significant short-term health benefits while reducing future health, economic, and ecosystem risks.

While political leaders may be responding slowly to the climate issue, the scientific and health communities are working hard to manage and prevent widespread health disasters. For example, the Group on Earth Observations is using satellite technology to monitor drought conditions in sub-Sahara Africa

which often precede major meningitis outbreaks. Meanwhile, the National Institutes of Health and the Centers for Disease Control and Prevention are working to create a cohesive national research agenda and help individual communities prepare for the health challenges of climate change, some of which may be new to American soil.

While the issue of climate change may appear static in the halls of Congress and the summits in Copenhagen and Cancun, it is certainly moving into our exam rooms and hospitals. Clinics across the world will soon be full of patients with a chief complaint of climate change.

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To Tell or Not to Tell: On Disclosing the Diagnosis of Dementia

Ayhan Yoruk, MSI
Advisor: Victoria H. Raveis, PhD, Mailman School of Public Health, Columbia University

As the number of older persons (age 65 and older) in the United States continues to rapidly rise, particularly with the imminent aging of the baby boom generation, there will be a significant increase in the incidence of age-related Alzheimer's disease. An incurable, degenerative, and terminal disease, Alzheimer's currently inflicts more than 35 million individuals worldwide and its prevalence is projected to reach approximately 107 million by the year 2050.[1] Given the major impact of the diagnosis of Alzheimer's disease on not only the patients, but also their family and caregivers, the medical practitioners' attitudes and practices regarding the disclosure of diagnosis, as related to the field of dementia, is of great concern.

Should physicians communicate a diagnosis of Alzheimer's disease to their patients? Physicians show great variation in practice, with fewer than half of clinicians regularly reporting a diagnosis of Alzheimer's to their patients.[2] Weighing the effect of the decision on patients, families, physicians, and the larger health care system as we evaluate the reasons for telling or not telling, this brief will outline the importance of straightforward communication.

The arguments that have typically been put forth against diagnostic disclosure are based largely on the principle of non-maleficence, which is the obligation to avoid harm. The emphasis on avoiding harm to patients has relied on (1) the lack of absolute diagnostic certainty without post-mortem clinical information, (2) the fact that treatment options are limited, and there is no cure, (3) the questionable ability of patients, particularly those in advanced stages of the disease, to understand the implications of the diagnosis, and (4) the potential for adverse, or even catastrophic, psychological responses to diagnostic disclosure as their justification.[3]

The arguments that have typically been put forth in support of diagnostic disclosure are based largely on the principle of providing the care that the patient deserves (justice) and patient autonomy. "Positive reasons for disclosure range from 'the patient's right to know' and facilitation of future planning to 'taking that once in a lifetime holiday.' "[2] Of particular importance is the framework within which target symptoms and symptomatic treatment options can be discussed[3] as well as opportunities to learn of and engage in therapeutic and clinical trials.[5]

It is my view that all medical professionals should adopt the practice of absolute truth-telling. There are many rational reasons for non-disclosure, but there is a lack of evidence supporting that it is more beneficial than truth-telling. Many believe that the negative outcomes anticipated by physicians and caregivers alike are worse than that evidenced in reality. In fact, literature supporting the diagnostic disclosure of Alzheimer's disease is increasing.

DEMENTIA *Continued on p. 6*

DEMENTIA

Continued from p. 5

A campaign to convince medical practitioners of the benefits of disclosing the diagnosis of dementia, particularly when compared to the disadvantages, may prove highly successful in promoting the absolute disclosure of diagnoses. This may be accomplished through advocacy via medical professional organizations or even publishing studies weighing the pros and cons of disclosing the diagnosis of dementia. Moreover, a campaign to train medical professionals on when and how to tell their patients may prove beneficial, as well as breaking common misconceptions and fears of disclosing the diagnoses. The failure to diagnose and treat persons with Alzheimer's disease is commonly attributed to the lack of physicians' knowledge about dementing illnesses, the absence of cognitive screening and the public perception that nothing can be done about the disease.[6] Further research and advancements in fields exploring the aforementioned limitations is highly recommended, particularly as our society readies itself for the rapidly growing aging-population.

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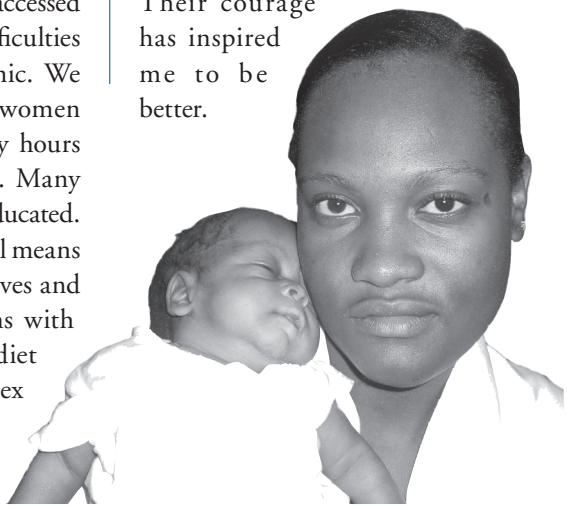
Sherley Pétion: A Resilient Spirit in the Midst of the Devastation in Haiti

Jeffanne Millein, MSII
Advisor: Melissa Curtice, RN, BSN, MSN, CNM, Truman Medical Center

Her name was Sherley Pétion. A native of Port-au-Prince, Haiti, she was a nurse working with me for the summer. The first time we met, she was in her white scrubs, carefully feeding a premature infant from a dropper. She barely looked up as I introduced myself, so absorbed in her work that an introduction was really a minimal priority. One afternoon, with all work done for the day, we remained in the delivery room waiting for labor or emergency cases. She sat in her usual seat, a white chair, near the door-less dressing room. We were talking about mundane things when she revealed how she had lost everything during the earthquake. A month prior, she was planning her wedding to the "perfect guy." She paused briefly as the painful memory overtook her. The soft lines under her eyes creased and the scar near her left eye seemed to cringe at the next few words. "He died suddenly a month before the earthquake. Just like that," she said softly. Then a couple of weeks later the earthquake hit and completely destroyed her home. She fled from the capitol and moved in with her cousin who lived in St. Louis du Nord, in northwest Haiti. Sherley described how she was despondent and barely able to function. Yet despite it all, she gradually found pieces of herself in her work. The premature infant she was caring for was able to go home, a healthy and growing little boy—all due to the time and compassion that Sherley showed in caring for him.

This clinic in St. Louis du Nord was a mere eight miles from where I grew up. My research focused on pre-eclampsia and eclampsia care in a rural setting, surveying the different stresses in patients' lives, how often they accessed care during their term and difficulties encountered getting to the clinic. We discovered that many of the women travelled long distances at early hours to secure doctor appointments. Many patients were young and barely educated. Most women lacked the financial means to properly take care of themselves and hence had underlying problems with their pregnancies. Even with diet recommendations and proper sex education, patient compliance remained low due to lack of resources. However, for many of the women who come, they receive quality care for most of their ailments and usually give birth to healthy babies.

I initially thought that I would go to Haiti having something to offer. But it was my interactions with the people I met and the relationships we built that contributed the most to my learning experience. Their resilience and refusal to stop living despite their difficult lives have muted my protests with struggles encountered in medical school and beyond. From Sherley's story to the mother who still has trouble recovering from losing a child a year ago, I have found a broader sense of purpose in my aspirations of becoming a physician. Their courage has inspired me to be better.



Sherley Pétion and her young patient

Brain Structural Evidence of Epistasis Between RGS4 and COMT Variations in Schizophrenia

Marc Lener, MSIV
Advisor: Konasale Prasad, MD, University of Pittsburgh School of Medicine

Schizophrenia is a debilitating psychiatric disorder with a worldwide prevalence of 1%. Clinically, schizophrenia is characterized by thought disorder, lack of emotional responsiveness, auditory hallucinations, and paranoid delusions. With heritability calculated at 81%, genetic association studies have identified several susceptibility loci and numerous genes linked to schizophrenia.[3,6] Among the most significant candidate risk genes for schizophrenia, polymorphisms of the Catechol-O-methyl transferase (COMT) and the Regulator of G-protein Signaling 4 (RGS4) demonstrate great potential to act interactively in schizophrenic patients.[1,4,5]

The membrane-associated isotype of COMT is responsible for catalyzing the inactivation of dopamine and is found mainly in the prefrontal cortex and hippocampus. RGS4 is a GTPase activator that acts to inhibit Gi/o and Gq, resulting in the attenuation of dopaminergic signal transduction at specific dopamine receptors. Interestingly, a reciprocal interaction occurs such that RGS4 gene expression is regulated by the increased activation of the GPCRs it modulates. Based on previously found interactions between both RGS4 and COMT[2,6,7] studies investigating functional epistasis of RGS4 and COMT in schizophrenic patients showed prefrontal cortical and hippocampal dysregulation in association with abnormal dopamine signaling[1] consistent with a dopamine hypothesis for schizophrenia. In our study, we evaluated our samples for similar associations and, in addition, examined epistatic interactions of RGS4 polymorphisms on grey matter volumes among patients and healthy subjects.

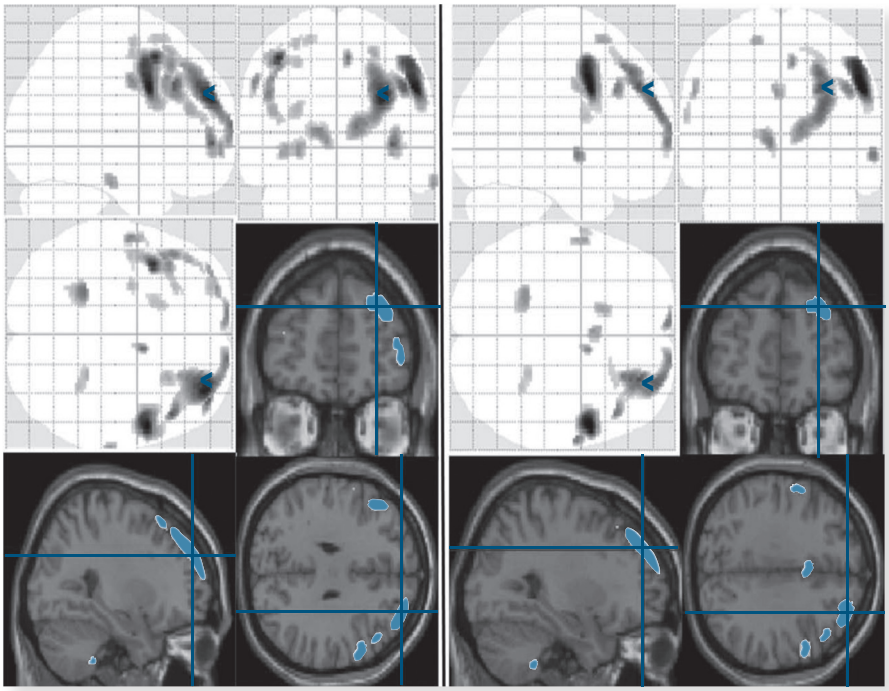


FIGURE: Glass brain pictures and rendering on to T1 image. Shaded Areas- voxels demonstrating RGS4 and COMT interaction via grey matter volumetric reduction with significance of $p < 0.01$. Blue Areas - significant voxels at $p < 0.001$.

We examined structural MRI scans from 21 first-episode, antipsychotic-naïve schizophrenia or schizoaffective disorder subjects and 19 healthy subjects using tests for interaction using voxel-based morphometry to examine grey matter alterations associated with COMT and RGS4 risk alleles both independently and interactively. We observed RGS4 and COMT interactions in the posterior cingulate, insular, occipital, and temporal regions. The most consistent finding among all interactions was grey matter reductions at the inferior and superior temporal gyri, corresponding to the heteromodal association areas (See Figure).

Our observations suggest that RGS4 and COMT variations are independently and epistatically associated with grey matter reductions at the dorsal components of heteromodal association areas, a collection of interconnected network of neural circuits that may be affected by genetically determined neurodevelopmental abnormalities in schizophrenic patients. Previous associations of functional interaction between COMT and RGS4 with altered working memory performance and Blood Oxygen-Level Dependence (BOLD) responses at the prefrontal cortex in SZ may be mediated

SCHIZOPHRENIA *Continued on p. 8*

SCHIZOPHRENIA *Continued from p. 7*

by dopamine associated neurotoxic and neurotrophic structural changes in the dorsal heteromodal association areas.

Although the exact mechanism of pathogenesis of schizophrenia has not been established, numerous underlying neurobiological mechanisms provide insight into its complex disease process. In contrast to simple Mendelian inheritance, the development of schizophrenia is determined by a complex interaction among multiple genes and environmental factors, including socioeconomic circumstances, education, family structure, life stresses, and maternal-fetal exposure to infection. Therefore, emergence of psychopathology is rooted in the interplay between genes and environment and can be seen at the level of molecular and cellular alterations resulting in dysregulations in neural circuitry. The advancement of psychiatric genetics, brain imaging, cognitive and affective neuroscience, and psychometric theory has furthered our understanding of the etiology and pathophysiology of psychiatric disorders such that new treatment interventions can be utilized.

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Identification of microRNAs Differentially Expressed in Urothelial Carcinoma

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Bladder cancer is currently the fourth most common cancer type in the United States, with over 70,000 new cases and 14,000 deaths reported in 2009.[1] Urothelial carcinoma (UC), the most common form of bladder cancer, affects the inner epithelial lining of the bladder and, in severe instances, invades the outer muscle layers. While in most cases UC presents as a noninvasive papillary tumor with good prognosis, such low-grade urothelial tumors are known for their high rate of recurrence,[2] making them difficult and expensive to treat.

MicroRNAs (miRNAs) are a recently discovered class of short, non-coding RNA molecules responsible for post-transcriptional fine-tuning of human gene regulation. Notably, miRNAs appear to demonstrate differential expression levels across various stages of cancer and thus may play a role in tumorigenesis, serving as either oncogenes or tumor-suppressor genes. Current research has shown that the expression signature of miRNAs tends to remain fairly consistent between cells of a particular type and cancer stage,[3] suggesting that a panel of miRNAs differentially expressed in malignant tissue may serve as diagnostic markers for a given cancer type.

In this study, we propose such a diagnostic panel of miRNAs that may supplement existing UC diagnostic tests. UC is traditionally diagnosed following cystoscopy accompanied by histological examination of urothelial tissue biopsy, yet these methods do not always offer a clear distinction between normal and cancer phenotypes. Analysis of miRNA expression in urothelial tissue may serve as a powerful quantitative supplement to largely qualitative cystoscopy examination, thereby improving confidence in diagnosis of UC.

RNA was extracted from 23 patient tissue samples (eight normal urothelium, eight high-grade UC, seven low-grade UC) and quantified using RT-PCR. Expression data was normalized using U6 as an endogenous control. A two-tailed t-test revealed a panel of 20 miRNAs differentially expressed in UC tissue ($p < 0.05$), with 11 down-regulated and the remaining nine up-regulated. Among these 20 miRNAs, miR-143 appears down-regulated, supporting existing research that implicates miR-143 as a tumor suppressor in bladder cancer.[4] K-Nearest Neighbors and Naive Bayes classifiers were generated using this miRNA panel and demonstrated reasonably high sensitivity (0.93 and 0.87, respectively) and specificity (0.88 and 1.00, respectively) in diagnosing UC. ROC curves for each classifier also suggested performance well above random guessing and with high accuracy. However, the majority of the miRNAs

that comprise this panel (16 out of the 20) have not been implicated in UC or any other urological cancers when queried in PubMed. Currently our collection of 20 miRNAs performs well as a diagnostic panel for UC in our patient set and may be appropriate for larger populations. Future studies will need to explore any causative role of these 20 miRNAs in UC via cell culture study and analysis of potential gene pathway targets in order to help confirm their diagnostic validity.

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miRNA	p-value	Fold Change	Expression in Cancer
hsa-miR-125a	0.026	0.227	Lower
hsa-miR-125b	0.042	0.312	Lower
hsa-miR-127	0.042	0.406	Lower
hsa-miR-138	0.014	21.859	Higher
hsa-miR-143	0.048	0.276	Lower
hsa-miR-146a	0.066*	0.305	Lower
hsa-miR-197	0.018	0.460	Lower
hsa-miR-198	0.032	0.370	Lower
hsa-miR-222	0.022	0.228	Lower
hsa-miR-23a	0.048	0.399	Lower
hsa-miR-365	0.042	26.052	Higher
hsa-miR-375	0.016	0.097	Lower
hsa-miR-376a	0.018	0.186	Lower
hsa-miR-515-5p	0.028	25.516	Higher
hsa-miR-521	0.047	6.176	Higher
hsa-miR-569	0.040	26.237	Higher
hsa-miR-587	0.020	22.454	Higher
hsa-miR-611	0.006	9.962	Higher
hsa-miR-96	0.024	5.195	Higher

TABLE: 20 miRNAs differentially expressed in urothelial carcinoma (UC) tissue as compared with normal urothelium. All miRNA fold increases/decreases are significant ($p<0.05$) with the exception of hsa-miR-146a marked with an (*).

Using a FACS-based Assay to Measure Dengue Virus Infection of DC- and L-SIGN Cells in the Presence of Neutralizing Antibodies

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Dengue virus (DENV) is a worsening arboviral disease endemic to countries in Central and South America, Africa, and South and Southeast Asia. Mechanisms of DENV infection and disease pathogenesis remain incompletely understood. Cellular receptors for DENV may impact infection dynamics and subsequent clinical disease severity.

Dendritic cell (DC) subsets express the DC-specific intracellular adhesion molecule (ICAM) 3-grabbing non-integrin (DC-SIGN) allowing direct infection of DCs by a number of pathogens. DENV has four serotypes, all of which use DC-SIGN (CD209), a C-type lectin, to infect DCs.[1] L-SIGN is largely expressed on endothelial cells in liver sinusoids.[2] In cell culture, human DCs become susceptible to DENV infection following transfection with DC- or L-SIGN. Primary human DCs naturally expressing DC-SIGN as well as monocytic cell lines transfected with DC- or L-SIGN facilitate cellular infection, release and propagation of infectious DENV virions.[1] For this reason, DC-SIGN and L-SIGN are attractive for use in assays assessing cellular infection or prevention of infection.

To better understand how cellular receptors may influence infection in the presence of pre-existing neutralizing antibodies (NAb's), we studied pre-illness serum samples from Thai subjects who subsequently experienced infection with the DENV-1 serotype. A fluorescence-activated cell sorting (FACS)-based assay was used to explore neutralizing capabilities of pre-illness serum samples mixed with DENV in the presence of B cell lymphoblastoid Raji cells transfected with either DC- or L-SIGN receptors. Antibody neutralization was performed by incubating serially diluted test and control patient sera with DENV in 96-well round-bottomed culture plates for 30 minutes.[3] Subsequent DENV infection was performed by adding serial dilutions of DC- and L-SIGN cells to the plates and incubating them overnight. This assay allowed us to quantify the antibody neutralizing capacity of infected patients

DENGUE VIRUS *Continued on p. 10*

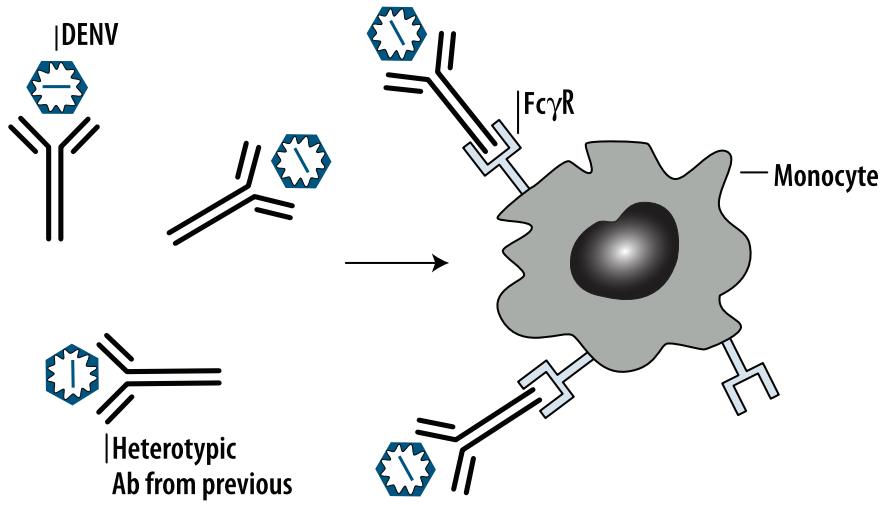

FIGURE: Neutralizing antibody (NAb) attachment to DENV blocks attachment to Fc-γR on monocytes, thereby blocking infection. The same may be true for DC- and L-SIGN lectin receptors expressed on dendritic cells (DCs).[4]

DENGUE VIRUS *Continued from p. 9*

by using flow cytometry to measure the number of DC and L-SIGN cells infected in the presence of their NAb's.

In total, we tested sera from 18 subjects who became infected with dengue and experienced a spectrum of dengue disease severities (non-hospitalized dengue fever, hospitalized dengue fever, hospitalized dengue hemorrhagic fever). The anti-DENV NAb titer in the sera was determined by calculating the dilution of sera at which point 50% of the DENV input was neutralized. Titers were determined for each sample in the presence of DC- and L-SIGN cells. A third neutralizing antibody titer was determined using the gold-standard plaque reduction neutralizing test (PRNT). The above experiments are being repeated in ongoing experiments with pre-illness sera samples from subjects who experienced DENV-2, DENV-3, or DENV-4 infections.

The FACS-based assay using DENV permissive cell lines transfected with L- and DC-SIGN cellular receptors may increase understanding of DENV-cellular interactions and host NAb immune profiles. This is especially important for quickly and effectively measuring anti-DENV NAb's of large numbers of sera from recipients of clinical trial DENV vaccines in order to measure their efficacy in stimulating host humoral immune responses. The classic PRNT requires four to seven days to complete, making it less practical for quickly generating results when compared to the FACS-based assays that takes two days to complete.

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Brain Tumor Stem Cells Isolated from a RasB8 Transgenic Murine Model Provide a Working Stem Cell Model for Malignant Glioma

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Advisor: Duane A. Mitchell, MD, PhD, Duke University Medical Center

Astrocytomas are the most common primary tumor affecting the adult CNS, with grade IV, known as Glioblastoma Multiforme (GBM), being the most lethal (12–15 month median survival).[1] Specific adjuvant therapies in various astrocytoma models have been applied in the clinical setting.[2,3] However, the development of effective targeted therapies for GBM is heavily dependent on the investigation of its pathogenesis via appropriate preclinical models that closely reproduce the clinical and histologic characteristics of human astrocytomas.

Currently there is limited understanding of the relative contribution of particular glioma cells to overall tumor growth. Recent studies have demonstrated a small fraction of cells displaying features of primitive neural progenitor cells with tumor-initiating potential, termed glioma stem cells (GSCs).[4] One current debate is that the glioma immunophenotype varies, thus additional markers for GSCs are needed to improve their isolation. One well accepted marker for GSCs is CD133, a cell surface marker expressed on progenitors of hematopoietic and endothelial cell lineages. GSCs sit at the forefront of the cancer stem cell hypothesis, which suggests that only a small fraction possesses the ability to self-renew and maintain the tumor, while most cells forego

these two abilities as they differentiate into cells that become the phenotypic signature of the neoplasm. Current treatments aim to debulk tumors but fail to target GSCs leading to treatment failure, recurrence, and ultimately mortality. Detecting these keystone cells in GBMs will provide insight into the mechanism of tumorigenesis and aid in the development of more precise treatment modalities.

We used an invasive mouse astrocytoma model generated by stem cell transgenesis of an activated *12V-Ha-RAS* gene under regulation of the human glial fibrillary acidic protein promoter.[5] This model allowed us to describe the proliferative and tumorigenic characteristics of GSCs. Astrocytoma lines contained a significant proportion of CD133$^+$ cells, the majority of which expressed CD44, a marker present on neural stem cells and human GBM cells. Furthermore, a subpopulation of lineage negative (CD133$^+$/44$^-$) cells represented ~3% of the tumor population. One requisite of detecting GSCs is that, when sorted and plated at a single cell density per well, the cell must have the capacity to generate free-floating clusters of clonally derived progeny, called tumorspheres, and its description is based on the phenomenon of neurosphere formation that occurs with non-cancerous neural stem cells. CD133$^+$ cells demonstrated greater tumorsphere formation and self-renewal via secondary tumorsphere formation after disruption of primary spheres compared to CD133$^-$ cells. CD133$^-$ cells, however, divided more extensively in culture than CD133$^+$ cells, supporting the notion that CD133$^+$ GSCs proliferate at a slower rate than differentiated CD133$^-$ cells. CD133$^+$ cells also showed enhanced tumorigenicity *in vivo* compared to CD133$^-$ cells isolated from the same tumor (Figure 2).

Here we described a subset of tumor cells derived from a transgenic model that addressed which of the morphologically diverse tumor cells could maintain tumor initiation and survival. Three findings suggest that these CD133$^+$ cells were GSCs: they (1) generated clusters of clonally derived cells resembling tumorspheres, (2) underwent self-renewal after tumorsphere dissociation, and (3) differentiated to recapitulate the phenotype of the tumor from which they originated.[6]

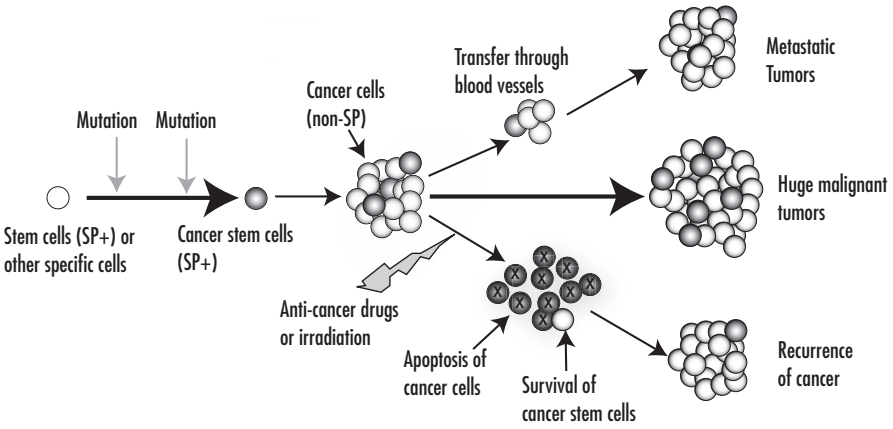

FIGURE 1: GSCs in malignant astrocytomas. GSCs comprise a fraction of tumor cells and are thought to arise from either neural stem cells or specific differentiated cells which revert to stem cells. GSCs have been shown to be resistant to chemo-radiation modalities and may be responsible for highly recurrent GBMs. [Setoguchi, T., Taga T., Kondo, T. 2004].

Because these GSCs must be targeted to eliminate the possibility of recurrence, our findings aid in the search to identify and isolate GSCs in the clinical setting. With a greater understanding of

MURINE MODEL *Continued on p. 12*

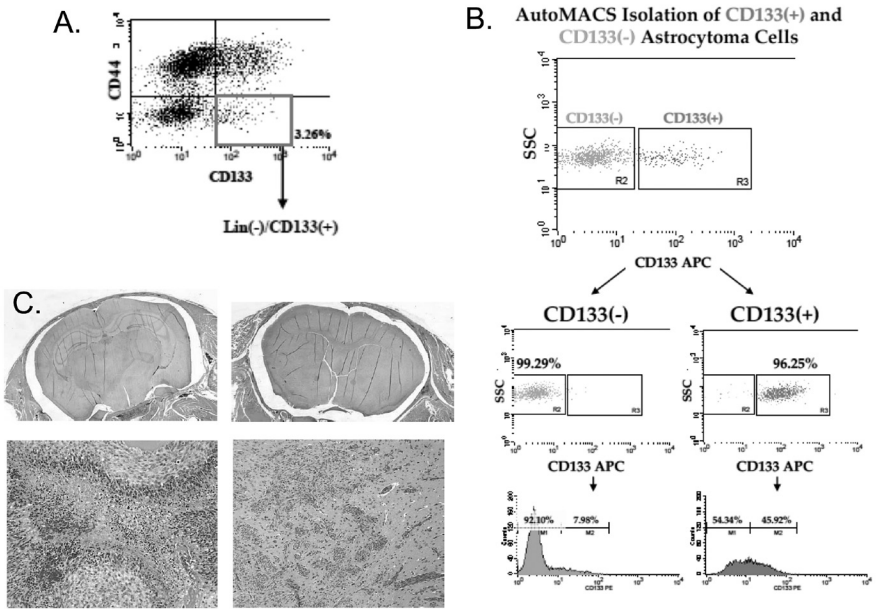

FIGURE 2: **A).** FACS analysis revealed a population of CD133$^+$ cells present in tumor lines of V12: Ha-ras-GFAP transgenic mice, in particular, a subpopulation of lineage negative CD133$^+$ cells. **B).** Astrocytoma cells were stained with anti-CD133 monoclonal antibody and separated using Miltenyi Biotech anti-biotin beads and AutoMACS. Highly purified populations of CD133$^+$ and CD133$^-$ cells were obtained (middle panel). Bottom panel shows that CD133$^+$ cells gave rise to equivalent numbers of CD133- and CD133$^+$ progeny after expansion *in vitro* while sorted CD133$^-$ cells remained CD133$^-$ (>90%). **C).** Formation of highly invasive intracranial astrocytomas by CD133$^+$ tumor cells from V12:Ha-ras-GFAP transgenic mice. Mice injected with CD133$^-$ cells exhibited no tumor growth (top panel) while 5/5 mice injected with CD133+ cells exhibited extensive growth of infiltrative tumor (bottom panel).

MURINE MODEL *Continued from p. 11*

GSC properties, including resistance to various chemo-radiation therapies, we will possess greater insight to develop novel therapies for effectively eradicating GBM.

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Cystathionine-γ-Lyase: A Target for Septic Shock

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Septic shock induced morbidity and mortality, which is a result of cardiovascular collapse and multisystem organ failure, may be attributed to vasodilation and hypotension. This leads to impaired vasoregulation, microcirculatory dysfunction, shunting, and critical organ hypo-perfusion. Hydrogen sulfide (H_2S), previously known to be produced by cystathionine-γ-lyase (CSE), and also known to be a toxic gas, has been identified as a gaseous transmitter, like nitrous oxide (NO), which promotes vasodilation.[1] This is likely done by hyperpolarization of vascular smooth muscle. Plasma H_2S levels are known to be elevated following CSE upregulation/activation in sepsis.[2] We tested the hypothesis that this excess in H_2S production contributes to vasoplegia and capillary leak due to enhanced endothelial cell permeability, and subsequent organ hypoperfusion, microcirculatory failure, hypotension, and death.

To do this, age matched wild type (WT) and CSE knockout ($CSE^{-/-}$) mice were exposed to a septic stimulus [25mg/kg intraperitoneal LPS injection or Cecal Ligation Puncture (CLP)].

PE DOSE RESPONSE CURVE

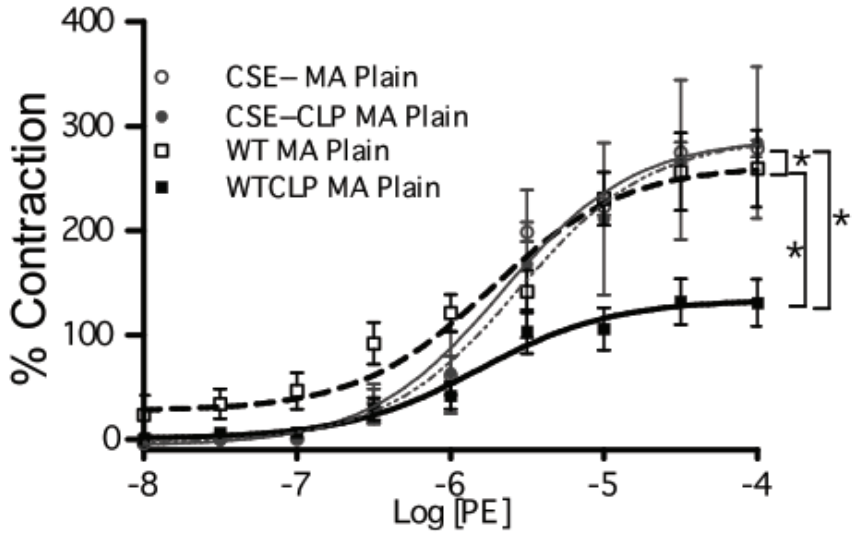

FIGURE 1. Because the degree of hyporesponsiveness to PE was significantly less attenuated in $CSE^{-/-}$+LPS (25.40% reduction) than in WT+LPS (55.60% reduction) as compared to their control counterparts, the findings supported our hypothesis that vascular hyporesponsiveness in sepsis is mediated by CSE-dependent H_2S.

The animals were sacrificed 12 hours following LPS injection or 24–36 hours after CLP, and mesenteric arteries (MAs) were dissected. Mesenteric arteries excised from WT mice that were sacrificed 24–48 hours after CLP were then placed in organ chambers, exposed to phenylephrine (PE), an α1 agonist, and vascular reactivity studies were performed. Contractile responses were measured by the changes in isometric tension of the mesenteric rings using a digital force isometric transducer connected to a data acquisition system. Vasocontractile responses showed a markedly attenuated contractile response to PE (WT CLP, Emax ~130.926% vs WT, Emax ~259.564%), with Emax measuring the maximum contractile response. In WT- CLP MAs the PE response was 50.44% compromised while totally preserved in $CSE^{-/-}$.

It was further found that there was no difference in response between $CSE^{-/-}$ and untreated WT mice in the CLP model. Phenylephrine responses (tension calibrated in mg units) were also attenuated in WT+LPS (LPS treated

WT mice) compared to WT (n = 5, Emax ~308 mg vs Emax ~694 mg). In addition, there was attenuation of the depressor response in $CSE^{-/-}$+LPS (LPS treated $CSE^{-/-}$) as compared to $CSE^{-/-}$ control mice (n = 5, Emax~789.6 vs Emax~1059).

Cell-sensing impedance substrate (ECIS) technology, a highly sensitive method quantifying permeability, further demonstrated that exposure of human lung microvascular endothelial cells to pathophysiologic levels (1mM) of H_2S (as seen in sepsis), caused a significant decrease in average barrier resistance (cell-cell and cell-matrix), but not at physiologic levels (100µM). In the first 96 hours of sepsis induction, mortality studies with CSE models of $CSE^{-/-}$ and WT mice demonstrated a 60% survival benefit in $CSE^{-/-}$.

In conclusion, genetic deletion of the H_2S forming enzyme, CSE, protects mice from vasoplegia and vascular endothelial permeability and more importantly has survival benefits in sepsis. Accordingly, CSE inhibitors may have therapeutic potential in sepsis therapy.

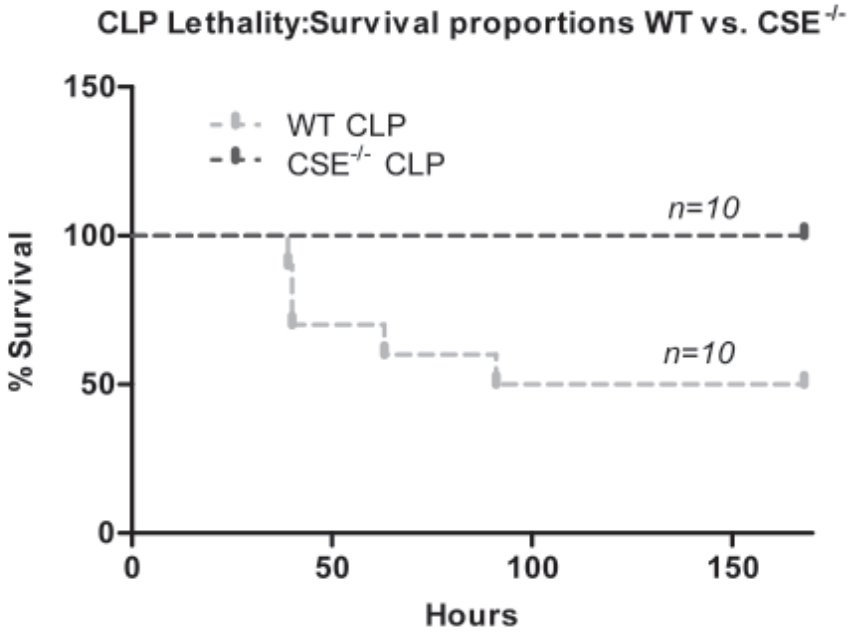

FIGURE 2. $CSE^{-/-}$ mice are shown to be protected from vasoplegia and have increased survival in sepsis.

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In Vivo Persistence of Redirected T Cells Transduced at Decreased Oxygen Concentrations

Gena Gora, MSII, Advisors: Valerie Dardalhon, PhD, Institut National de la Santé et de la Recherche Médicale, and Naomi Taylor, MD, PhD, Institut de Genetique Moleculaire de Montpellier, Montpellier, France

Adoptive T cell therapy (ACT) has emerged as an important strategy to mediate anti-tumor immunity. As demonstrated by numerous clinical trials to treat malignancies such as melanoma, this promising therapeutic approach employs T cells redirected against a target tumor antigen via introduction of a chimeric antigen receptor (CAR) or an ectopic TCR. Importantly, successful ACT requires that the transduced lymphocytes expand, persist and function *in vivo*.[1] It has been hypothesized that this therapeutic strategy is often compromised by the *ex vivo* transduction protocol. Specifically, to date, donor T cells have always been transduced at 20% oxygen, although physiological O_2 concentrations in lymphoid organs range from 2–5%.[2] High oxygen concentrations could potentially alter multiple parameters including T cell differentiation, gene expression, as well as *in vivo* expansion and function.

Here we address the above concerns by comparing the *in vivo* fate of cells transduced *ex vivo* under physiological (2%) and atmospheric (20%) oxygen conditions. Toward this goal, we engineered lymph-node (LN) T Cells from a congenic strain of donor mice ($Thy1.1^+$) to express a CAR specific for the human CD19 antigen fused to a T-cell receptor CD3-zeta signaling chain.[3] Expression of the CAR was done using mouse leukemia virus (MLV)-mediated transduction in either 20% or 2% oxygen culture conditions.

To assess the *in vivo* efficacy of ACT-mediated tumor prevention, host mice were injected subcutaneously with $4x10^5$ mouse lymphoma cells (EL-4 cell line) expressing the huCD19 antigen. On the same day, CAR-transduced donor T Cells were labeled with Carboxyfluorescein succinimidyl ester (CFSE), a cytosolic dye used to

T CELLS *Continued on p. 14*

 Continued from p. 13

monitor lymphocyte proliferation *in vivo*, and $7x10^6$ cells were injected intravenously into host mice. Following ACT, tumor growth was assessed on days 10, 13, 17, and 21 and mice were sacrificed at days seven and 21. Lymph nodes and spleens were harvested and the cell suspensions were analyzed by flow cytometry. Factors assessed included transduction efficiency, donor T-cell survival, proliferation, and differentiation.

We demonstrate that *ex vivo* gene transfer efficiency was comparable at 2% and 20% O_2 in engrafted donor cells recovered from hosts' LNs (Figure 2a). Donor huCD19-specific T cells transduced at both 2% and 20% O_2 prevented tumor development as compared to hosts that received non-transduced (NT) cells cultured at similar conditions (Figure 1). Interestingly, the phenotype of the redirected T cells was altered. Cells transduced at physiologic oxygen resulted in modified CD4:CD8 ratios (Figure 2b), associated with a decreased proliferation (data not shown) and percentage of $CD4^+$ T Cells with an effector phenotype ($CD44^+$, $CD62L^-$) (Figure 2c). While the overall persistence and differentiation of the transduced cells was markedly modified by the oxygen concentration to which cells were exposed during the transduction period, it is notable that these phenotypic differences had little effect on the recovery of transduced T cells following adoptive transfer into pre-conditioned mice (data not shown).

Our studies demonstrate that oxygen concentration during ex vivo transduction protocols has a significant effect on transduced donor lymphocytes. These findings can potentially be of therapeutic value in ACT for malignancies as transducing T cells at a more physiological concentration improves their persistence and functionality.

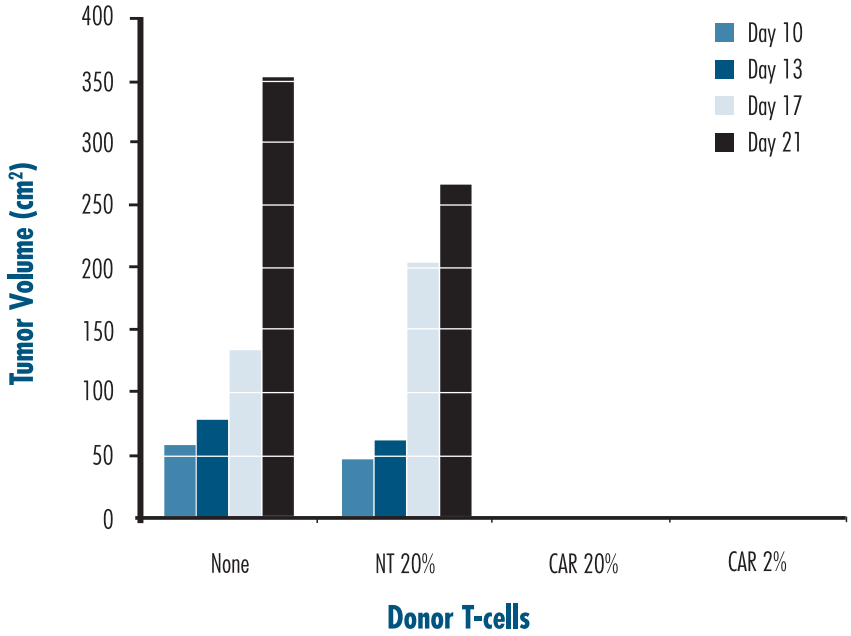

FIGURE 1: Adoptive transfer of CAR-transduced T cells specifically prevents tumor growth in lymphodepleted hosts. Prior to adoptive transfer, donor LN T-cells were transduced with a huCD19-specific CAR at 20% O_2 (CAR 20%), 2% O_2 (CAR 2%) or not transduced, but cultured under similar conditions at 20% O_2 (NT 20%).

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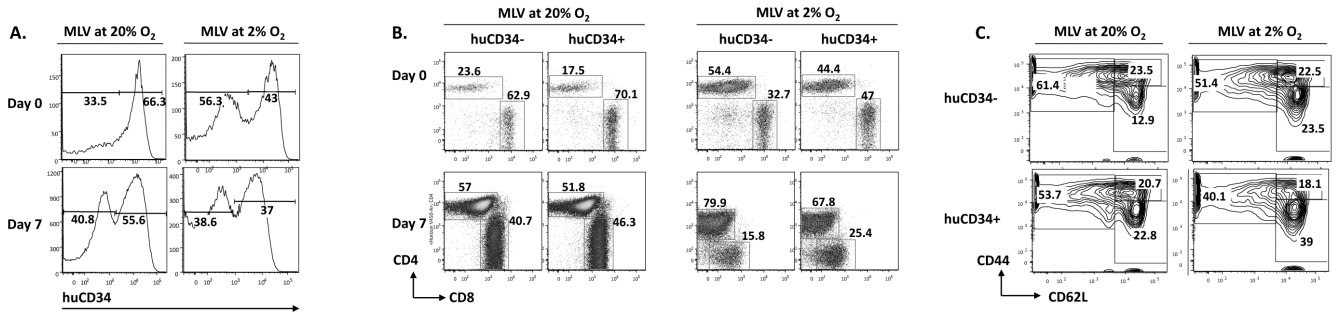

FIGURE 2: Phenotype of engrafted ($Thy1.1^+$) donor cells recovered from hosts LN. Donor T cells were stimulated for 48 hours by anti-CD3/anti-CD28 mAbs, under either 20% or 2% oxygen culture conditions. MLV-mediated transductions were performed on fibronectin-coated plates. **(A)** Gene transfer efficiency was assessed by monitoring huCD34 gene expression-marker by FACS. **(B)** CD4 and CD8 expression of transduced ($huCD34^+$) and non-transduced ($huCD34^-$) recovered cells. **(C)** CD44 and CD62L expression of $CD4^+$-gated cells on day seven post-transfer.

In vivo Imaging of the Cannabinoid CB1 Receptor Using Positron Emission Tomography

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Advisors: Robert Innis, MD, PhD, National Institute of Mental Health, and Christer Halldin, PhD, Karolinska Institute, Stockholm, Sweden

The actions of marijuana (cannabis) are mediated by receptors (primarily the cannabinoid CB_1 receptor) that have unusually high density and wide distribution in the brain.[1] In addition to mediating the effects of exogenous drugs like cannabis, these receptors also receive signals from endogenous cannabinoids (endocannabinoids), which modulate the release of several other neurotransmitters. Since abnormalities of cannabinoid receptors and endocannabinoid transmission have been hypothesized to underlie disorders of the brain (e.g., memory impairment, schizophrenia, and seizures), this neurotransmitter system has been an active target for development of drug therapies and of biomarkers to measure its *in vivo* function. Positron emission tomography (PET), which can image the distribution of receptors in the body, is a powerful tool for drug development, and can quantify the receptor as a biomarker to assess pathophysiology.[2] The purpose of these studies was to evaluate several candidate PET radioligands for their relative ability to quantify CB_1 receptors in the living brain of animals and humans.

We first assessed [^{11}C]MePPEP as a PET radioligand through studies in rodents.[3] Wild-type and genetically modified mice were used to determine that [^{11}C]MePPEP is not a substrate for the P-glycoprotein efflux transporter and that the majority (about two-thirds) of its binding in brain is specific to the CB1 receptor. Pharmacologically active doses of CB_1 agonists had no effect on [^{11}C]MePPEP in rats, which suggests a large CB_1 receptor reserve (Figure 1). Pharmacokinetic modeling of CB_1 receptors using brain radioactivity and measurements of radioligand in arterial plasma yielded stable measures after 70 minutes of scanning. The results suggest that [^{11}C]MePPEP might be successful in humans, although competition studies with endocannabinoids would not be possible, and radiometabolites might cause consistent overestimation of CB_1 receptor density.

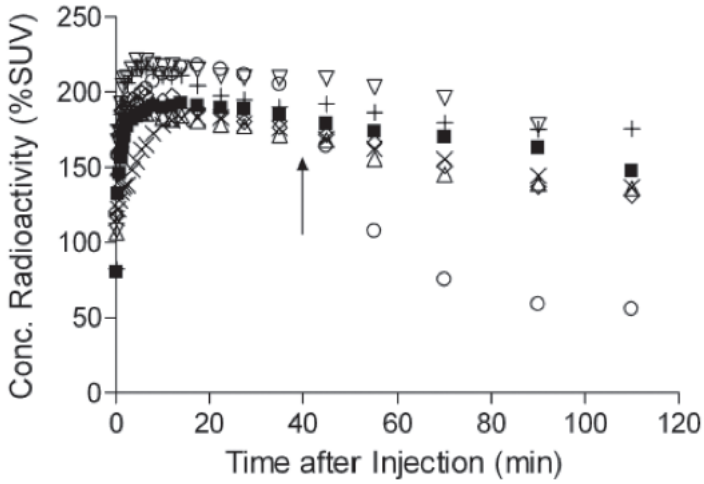

FIGURE 1: [^{11}C]MePPEP can be displaced by antagonist, and not by agonist, in rodent brain. Drugs were administered IV to rats 40 min after [^{11}C]MePPEP. Compared to the baseline curve (■) inverse agonist rimonabant (❍) displaced the majority of radioligand, whereas agonists anandamide (Δ), methanandamide (∇), CP 55,940 (◊), URB597 (anandamide reuptake inhibitor, ×), and URB597 with anandamide (+) were unable to displace the radioligand.

Second, we examined [^{11}C]MePPEP in healthy human subjects using the "gold standard" of compartmental modeling to quantify receptor density in brain.[4] [^{11}C]MePPEP had high uptake in brain, could be imaged for 210 minutes, and could quantify CB_1 receptors within about 60 minutes of scanning. However, the accuracy and precision of the pharmacokinetic modeling hinged upon the accuracy of radioligand measurements in arterial plasma. A radioligand with a longer radioactive half-life, such as from ^{18}F, would be expected to provide superior measurements in arterial plasma.

We then evaluated several ^{18}F-radiolabeled analogues of MePPEP in monkeys. [^{18}F]FMPEP-d_2 was selected for study in humans due to its superior uptake in brain compared to [^{18}F]FEPEP, and reduced uptake of radioactivity in bone compared to [18F]FMPEP.[5] In humans, [^{18}F]FMPEP-d_2 could image and quantify CB_1 receptors with better accuracy and precision compared to that of [^{11}C]MePPEP. As suspected, the accuracy in measuring radioligand in arterial plasma was the critical improvement needed in the pharmacokinetic modeling.

Finally, we examined the biodistribution and estimated the dose of radiation that would be received in human studies using [^{11}C]MePPEP and [^{18}F]FMPEP-d_2.[6] Both radioligands had high uptake in the brain, liver, and lungs, and both had significant uptake of radioactivity in the bone marrow, but not in bone (Figure 2). Regardless, both radioligands have an effective dose similar to that of other clinically used PET radioligands.

CB1 RECEPTOR *Continued on p. 16*

In conclusion, we have shown that both [^{11}C]MePPEP and [^{18}F]FMPEP-d_2 can quantify CB_1 receptors in brain. However, [^{18}F]FMPEP-d_2 is superior to [^{11}C]MePPEP because it has greater precision and accuracy. Thus, [^{18}F]FMPEP-d_2 is a promising PET radioligand to measure CB_1 receptors in vivo, and can now be used to explore the role of this receptor in human health and disease.

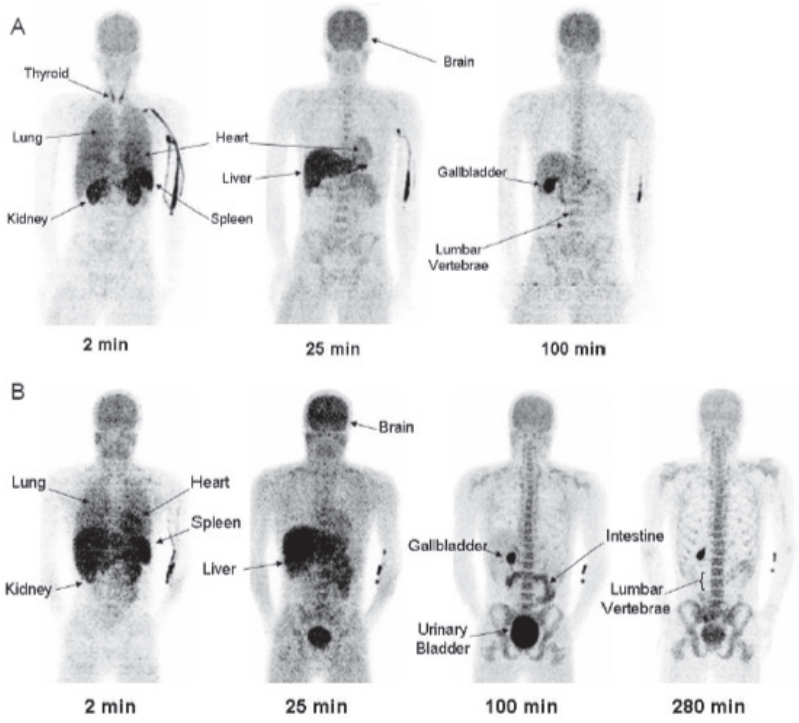

FIGURE 2: Biodistribution of A) [^{11}C]MePPEP and B) [^{18}F]FMPEP-d_2 in human at several times after injection of radioligand.

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Spontaneous Uveitis in the Absence of IFN-g in Transgenic Mice Expressing a Retina-specific T cell Receptor

Neena Passi, MSII
Advisor: Reiko Horai, PhD,
National Eye Institute

Experimental autoimmune uveitis (EAU) serves as an animal model of human uveitis. In mice, the classical EAU model is induced by immunization with retinal antigens such as interphotoreceptor retinoid binding protein (IRBP) in complete Freund's adjuvant and in many cases with injection of pertussis toxin as an additional adjuvant. A new transgenic mouse strain expressing a T cell receptor specific for $IRBP_{161-180}$ (IRBP TCR Tg) has recently been developed in our laboratory.[1] The IRBP TCR Tg mouse spontaneously develops EAU-like ocular inflammation with early onset, providing a useful model to study the basic mechanisms of uveitis.

Interferon-gamma (IFN-g) and interleuken-17 (IL-17) are two major cytokines involved in T cell effector functions and autoimmunity. Our previous studies showed that systemic neutralization of IFN-g exacerbated EAU,[2] and IFN-g deficient (GKO) mice developed EAU comparable to their wild-type counterparts.[3] A more recent study showed increased production of IL-17 in lymph nodes and in uveitic eyes of GKO mice.[4] These results suggest that IL-17-producing Th17 cells might serve as pathogenic effector cells in GKO mice.

In this study, to further investigate the roles of IFN-g and IL-17 in the development of uveitis, we sought to evaluate the development of spontaneous uveitis in the absence of IFN-g. GKO mice were crossed

with the IRBP TCR Tg mice and their disease progression and cellular responses were examined. Fundospic and histopathologic analysis were used to monitor retinal inflammation and disease progression. $IRBP_{161-180}$-specific lymphocyte proliferation was assessed with [^{3}H]-Thymidine staining. IFN-g and IL-17 production in culture supernatants were analyzed by ELISA.

Our study revealed that IRBP TCR Tg-GKO mice develop spontaneous uveitis with similar incidence, but less severity than their heterozygous (IRBP TCR Tg-GHet) and wild-type (IRBP TCR Tg) littermates, suggesting that IFN-g is dispensable for disease onset but may have a role in disease progression (Figure 1). Lymph node cells and splenocytes from the IRBP TCR Tg GKO mice exhibited comparable proliferation responses to $IRBP_{161-180}$ as compared to their wild type controls, supporting previous findings that IFN-g is not required for priming pathogenic T cells (Figure not shown). Lymphocytes from IRBP TCR Tg-GKO mice produced more IL-17 than those from the IRBP TCR Tg mice, suggesting that IL-17-producing T cells may play a role in the development of uveitis in IRBP TCR Tg-GKO mice (Figure 2). Further studies are needed to elucidate the roles of IFN-g and IL-17 in the development of autoimmune uvietis.

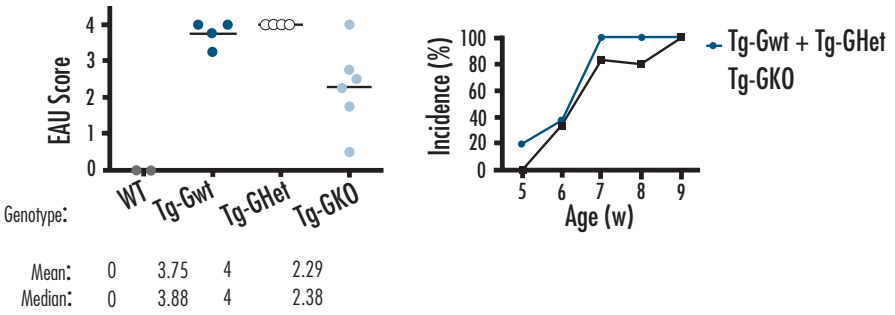

FIGURE 1: IRBP TCR Tg-GKO mice spontaneously develop EAU-like uveitis with less severity than IRBP TCR Tg mice. **Left**, EAU scores of wild-type (Non-Tg), IRBP TCR Tg (Tg-Gwt), IRBP TCR Tg-GHet and IRBP TCR Tg-GKO mice between four and seven months old determined by histopathology. Scores were assigned on a scale of 0 to 4, according to the extent of inflammation and tissue damage. Each point represents one mouse (average of both eyes). ($p<0.05$). **Right**, Kinetics of disease onset in Tg-Gwt, Tg-GHet and Tg-GKO mice based on weekly fundoscopy readings. Tg-GKO mice showed similar disease incidence as their heterozygous and wild-type counterparts.

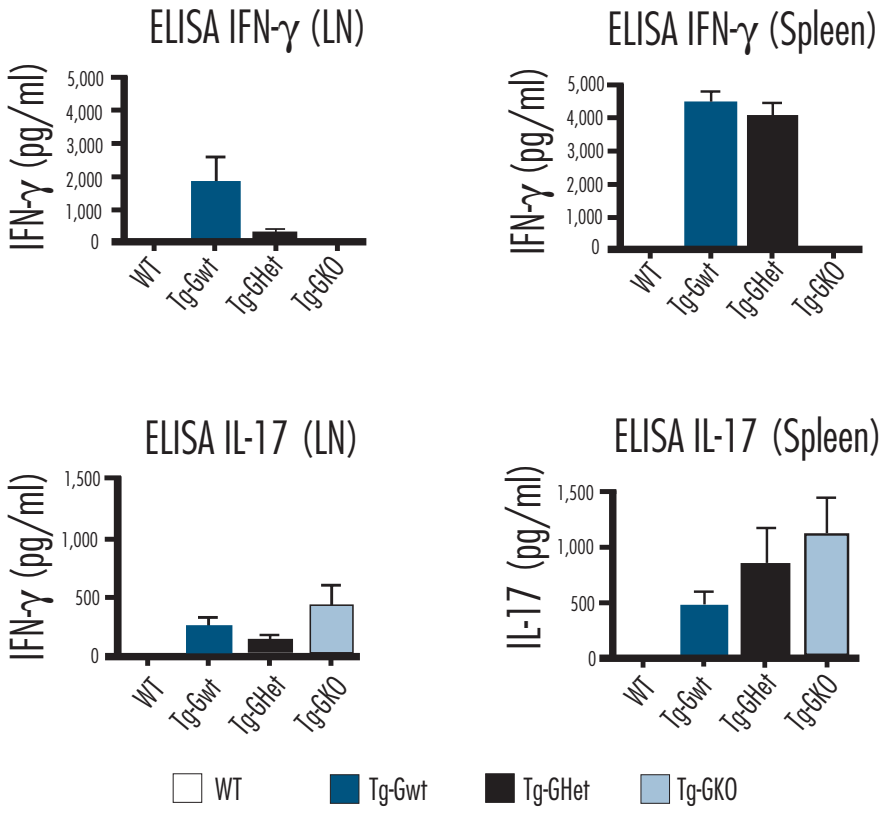

FIGURE 2: TCR Tg-GKO mice produce IL-17. Culture supernatants of lymph node cells and splenocytes were stimulated with IRBP peptide (1μg/mL) were collected and measured for IFN-g (left) and IL-17 (right) by ELISA. Tg-GKO cells produced no detectable IFN-g as expected, whereas parallel supernatants for the other TCR Tg genotypes contained significant amounts of IFN-g. There was no significant difference in the amount of IFN-g produced by Tg-Gwt and Tg-GHet mice. Measurements of IL-17 in the same supernatants showed that Tg-GKO mice produced more IL-17 than the wild-type controls and Tg-GHet mice; however, these differences were not statistically significant.

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Appropriate Role of Aprotinin in Thoracic Aortic Surgery: Should We Have it Back?

Andrew Zhang, MSII
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Outcomes	Aprotinin (n=183)	Control (n=183)	P-value
24 Hr Drainage	590.4¬±290.9	763.4¬±470.8	0.0001*
RBC transfusion	1.84¬±2.36	2.5¬±2.97	0.01*
FFP transfusion	1.75¬±2.36	2.26¬±3.64	0.11
Platelet transfusion	0.78¬±1.36	1.54¬±2.07	0.0001*
Total ventilation (min)	1403¬±1834	1992¬±3210	0.03*

FIGURE: Unpaired analysis for continuous clinical variables.
* denotes statistical significance

Thoracic aortic surgery, with or without deep hypothermic arrest, is an inherently precarious cardiac operation characterized by aberrations in the normal properties of blood. These alterations in hemostasis and thrombogenesis are associated with particularly increased rates of stroke and mortality, and consequently, there is a need to finely control postoperative bleeding in this subset of surgeries.[1,2] The safety of aprotinin use in cardiac surgery has been heavily debated, both before and after its withdrawal by the FDA in 2007. Concerns have centered on putative excess thrombosis, embolism, and renal failure.[3,4,5,6] A pilot study at our institution suggested that in thoracic aortic surgery, aprotinin, an antifibrinolytic serine protease inhibitor, was safe and effective for conventional use in these operations.[7] The aim of this investigation was to determine if a larger cohort would confirm safety and efficacy of aprotinin in thoracic aortic surgery. In this case-control study, we demonstrate that the use of aprotinin offers all benefit and no liability in thoracic aortic surgery. Patients undergoing surgery for thoracic aneurysm or dissection at Yale-New Haven Hospital between 1995 and 2010 were considered for inclusion in this study. 183 patients receiving aprotinin during this time period were each matched with 183 controls based on preoperative criteria (age, gender, urgency of surgery, location of aneurysm) for a total enrollment of 366 patients. Pre- and post-operative data were collected from the medical records of aprotinin patients and their matched controls. Success of matching was assessed by bivariate analysis and then clinical outcomes analyzed. Among the 366 subjects enrolled in this study, aprotinin patients showed significant benefits compared to controls in 24-hour chest tube drainage, RBC transfusion, platelet transfusion, and total ventilation time (see figure). There were three cases of renal failure in aprotinin patients and one in controls while there were also seven embolic events in aprotinin patients and seven in the controls. There were no Myocardial Infarctions (MI) in the aprotinin patients and three in the controls. Additionally, (in paired analysis for dichotomous clinical outcomes) aprotinin patients showed an odds ratio of 0.48 (p-value 0.02) for any complication (embolism, MI, stroke, renal failure, pulmonary complication, arrhythmia, or death). Our findings demonstrate that clinical outcomes and complications were significantly reduced in patients receiving aprotinin as compared to those that did not. The results of this study lead us to believe that aortic surgery and aprotinin may be especially suited to each other. We simply did not find the purported deleterious effects associated with this drug. Thoracic aortic surgical patients are likely suffering from aprotinin withdrawal, and its reinstatement for this specific indication should be considered.

The results of this study lead us to believe that aortic surgery and aprotinin may be especially suited to each other.

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Use of Musculoskeletal Ultrasound to Diagnose and Treat Symptomatic Sacral Bursitis: a Case Report

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We report a case of a man in his forties presenting with radiating leg pain. Radiculopathy was diagnosed by a previous physician based on Magnetic Resonance Imaging (MRI) findings and physical examination. Epidural injections were ineffective in relieving pain. Upon referral to this practice, an ultrasound examination demonstrated a large sacral bursa compressing the sciatic nerve, which was not apparent on pelvic MRI. This bursa was drained and injected with cortisone, resulting in pain resolution.

The United States Agency for Health Care Research and Quality guideline specifies MRI as the modality of choice for suspected spinal soft tissue damage, such as radiculopathy.[1]

The United States Agency for Health Care Research and Quality guideline specifies MRI as the modality of choice for suspected spinal soft tissue damage, such as radiculopathy.[1] A review article on lumbosacral radiculopathy states that diagnosis should be confirmed with MRI or electromyography (EMG).[2] If a disc herniation is found, it should be treated with a pain treatment plan or an epidural injection. For pain refractory to treatment after four weeks, surgical evaluation is indicated.[2]

Bursitis has been shown to mimic lumbosacral radiculopathy at multiple locations including the piriformis bursa,[3] trochanteric bursa,[5] and iliopsoas bursa.[4] Swezey et al suggests that this is common in an elderly population, with thirty-one out of seventy patients having bursitis versus radiculitis.

In the United States, MRI is the imaging study of choice for diagnosis of bursitis.[7,8] Ultrasound has also been shown to be effective in diagnosis of bursitis compared with MRI but less detailed.[6,9] In Europe, ultrasound is the study of choice for the identification of iliopsoas bursitis due to its lower cost versus MRI.[9]

To our knowledge, this is the first case reported in the literature where MRI failed to identify bursitis. As morbidity, mortality, and cost associated with surgery are high, it may be reasonable to rule out bursitis prior to proceeding with surgical intervention. In addition, due to the lower cost and in this case report greater accuracy, ultrasound may be preferable over MRI as an initial diagnostic modality for bursitis as is done in Europe.

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Robotic Radiosurgery for Inoperable Patients with Peripheral Stage IA Non-Small Cell Lung Cancer: Local Control and Survival Using 5-mm Margins

Beant Gill, MSIV
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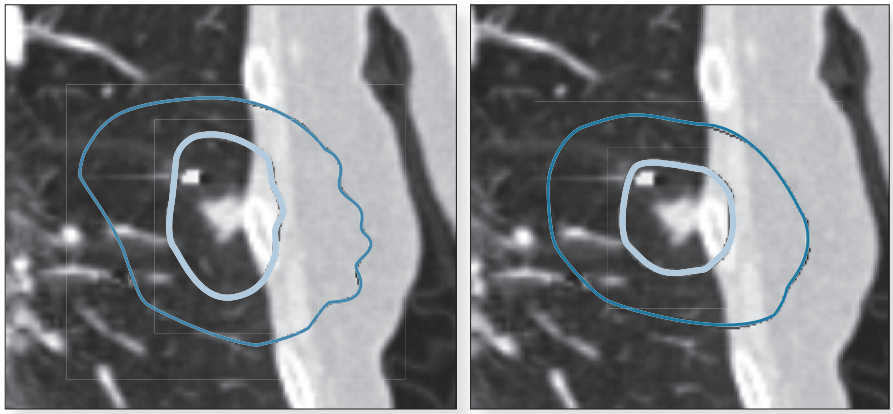

FIGURE 1: CyberKnife treatment planning with RTOG standard margins (left) and 5 mm margins (right). The V15 is 76 cc and 53 cc, respectively.

Due to its typical late clinical presentation and aggressive course, lung cancer continues to be the leading cause of cancer mortality worldwide. Lobectomy has been established as the primary curative option for early-stage non-small cell lung cancer (NSCLC) with five-year overall survival rates between 60–80% and local control rates ranging from 5–11%, based on historical data.[1] Nonetheless, many newly diagnosed patients are older with multiple medical co-morbidities, precluding them from surgical management. Prior studies have attempted to establish external beam radiotherapy as a treatment modality in early-stage, medically inoperable NSCLC; however, survival rates and toxicity associated with such treatment have been discouraging.[1]

Robotic radiosurgery with image guidance offers a precise and effective treatment for inoperable peripheral stage IA non-small cell lung cancer.

The relatively new technique of stereotactic body radiotherapy (SBRT) enables the delivery of high doses in few fractions. Several studies have now been conducted, providing evidence of excellent local control rates and improved overall survival with SBRT; toxicity remains a concern, however, due to normal lung tissue exposure to radiation.[2–4] Of note, in a majority of these studies, RTOG standard margins were adopted for the clinical treatment volume, which includes 1.0 cm longitudinally and 0.5 cm axially. Our study aims to narrow these margins and thus decrease normal lung tissue damage, measured by the volume receiving 15 Gray (V15), while maintaining local control and overall survival rates.

Inoperable patients with biopsy-proven peripheral clinical stage IA NSCLC were enrolled in this single institution study. Three to five gold fiducial markers were implanted in or near tumors under computed tomography (CT) guidance to serve as targeting references. Gross tumor volumes (GTVs) were contoured using lung windows and margins were expanded 5 mm circumferentially to establish the planning treatment volume (PTV). Non-isocentric treatment plans were designed using hundreds of pencil beams with a median collimator diameter of 25 mm. All treatments were delivered utilizing the CyberKnife system with Synchrony. Gross tumor doses ranged from 42–60 Gray (Gy) in three equal fractions (BED Gy10 >100).[4] Clinical examination and PET/CT imaging were completed at six-month intervals following treatment. The V15 was calculated using standard RTOG margins and 5 mm margins (Figure 1).

Twenty-four patients with a mean maximum tumor diameter of 2.2-cm and a mean GTV of 10 cc were treated over a four-year period. The mean calculated V15 was 202 cc with a 5 mm margin and 236 cc with the RTOG margins. At a mean follow-up of 36 months, the three-year Kaplan-Meier local control and overall survival estimates were 95% and 79%, respectively (Figure 2). Five patients with severe emphysema (baseline post-bronchodilator FEV_1 < 40% predicted) died of progressive lung dysfunction following treatment.

Robotic radiosurgery with image guidance offers a precise and effective treatment for inoperable peripheral stage IA NSCLC. Limiting the margin to 5 mm decreased the V15 by an average of 35 cc (range, 15–60 cc) while preserving local control rates comparable to published studies using larger margins.[3,4] The ability to spare lung tissue is of great importance since

progressive lung dysfunction was the sole cause of death among this group of patients.

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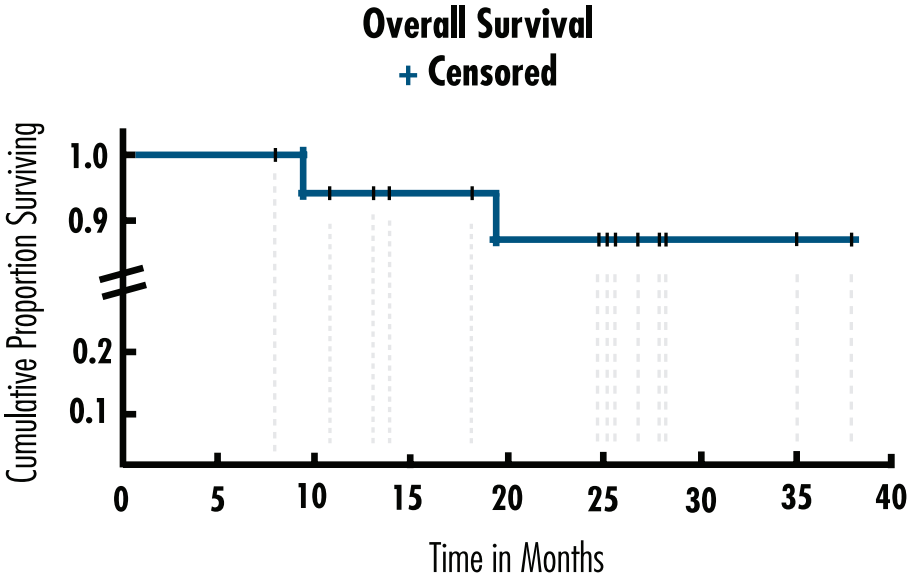

FIGURE 2: Kaplan-Meier curve demonstrating improved overall survival up to three years following treatment.

Demographics of Pulmonary Complications in Sickle Cell Disease

Kathy Chyjek, MSII
Advisors: Suzanne van Meer, MD, University Medical Center Utrecht, Utrecht, Netherlands, and Lewis L. Hsu, MD, PhD, Children's National Medical Center

Sickle cell disease (SCD) is an inherited blood disorder that affects multiple organ systems, with both acute and chronic manifestations. Pulmonary complications are of particular importance in patients with SCD as they are commonly associated with high morbidity and mortality.[1,2] Research suggests that children with both SCD and asthma have higher morbidity as measured by more frequent hospitalizations for vaso-occlusive crises and acute chest syndrome (ACS) episodes, and as much as double the risk of mortality when compared to pediatric SCD patients without asthma.[3] Therefore, the diagnosis of reactive airway disease in pediatric SCD patients is clearly a poor prognostic factor. However, it is currently not known whether there is any degree of modifiable risk associated with aggressive empirical treatment of asthma in the pediatric SCD population. Although SCD disproportionately affects people of African and Latino ancestry, the association between socioeconomic status and prevalence of SCD is unknown.

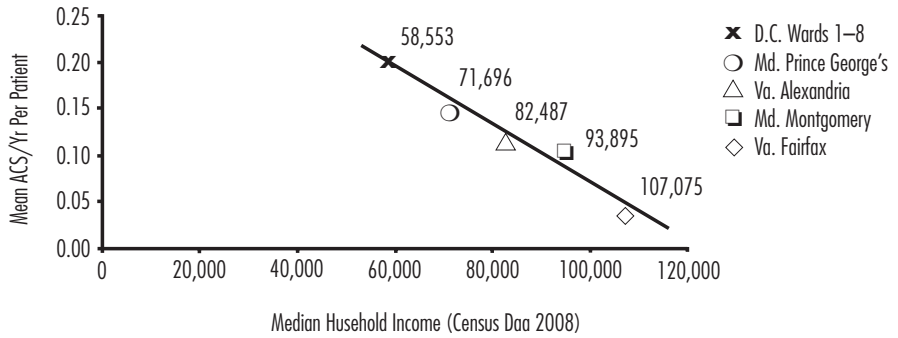

FIGURE: Washington, D.C., Metropolitan Area Distribution of Acute Chest Syndrome Episodes in Sickle Cell Disease Patients by Socioeconomic Status.

This study investigated whether socioeconomic status, as determined by zip code distribution in the Washington Metropolitan Area, correlates with reactive airway disease in pediatric SCD patients as it does in asthmatic children without SCD. A five-year retrospective study examined randomly sampled 400 out of 950 total pediatric SCD patients seen at Children's National Medical Center between 2008 and 2010. We extracted hematological, pulmonary as well as demographic patient information from electronic medical records (Cerner PowerChart system). Median household incomes from 2008 were linked to zip codes in various regions of the Washington Metropolitan Area and results were then analyzed using non-parametric statistical methods. The Mann Whitney U test was used to determine differences in the characteristics between pediatric SCD patients with a diagnosis of reactive airway disease

SICKLE CELL *Continued on p. 22*

 Continued from p. 21

versus those without a diagnosis of reactive airway disease.

Among the 400 pediatric SCD patients, there was a strong inverse relationship between socioeconomic status and the rate of acute chest syndrome episodes (mean number of episodes per patient per year). The rate of acute chest syndrome episodes was 0.20 for all of Washington DC (n=56), 0.15 for Prince George's County (n=147), 0.10 for Montgomery County (n=81), and 0.04 for Fairfax County (n=33), which had median household incomes of $58k, $72k, $94k, and $107k, respectively.

Acute chest syndrome episodes were also significantly more prevalent in children diagnosed with reactive airway disease (18.75%) compared to those with no history of asthma ($p < 0.05$).

Socioeconomic status as marked by geographical distribution appears to be a strong source of diversity in pulmonary complications of pediatric SCD patients in the Washington Metropolitan Area. Our data is subject to the limitations of a retrospective chart review, but it effectively sets the stage for future prospective studies. Also, further analysis of this data could account for differences in the rate of acute chest syndrome episodes in SCD patients on hydroxyurea or chronic transfusions, as opposed to those not undergoing any treatment for SCD. Lastly, the data can be useful in planning service delivery, such as evaluating whether a satellite pulmonary-hematology clinic might enhance convenience of service for pediatric SCD patients in the Washington, D.C., Metropolitan Area.

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Flat Blood Pressure Response to Exercise in Patients with the Total Artificial Heart: The Feasibility of Cardiac Rehabilitation

Harajeshwar Singh Kohli, MSII
Advisor: Keyur B. Shah, MD, Virginia Commonwealth University

The total artificial heart (TAH) is a mechanical circulatory support device that orthotopically replaces a recipient's native ventricles and all four cardiac valves (Figure 2). Total heart replacement is an effective bridge to transplant for patients with bi-ventricular heart failure and is an alternative to implantation of concomitant right and left ventricular assist devices. The TAH consists of two implantable pneumatic pumps operating at a fixed ejection rate and ejection pressure.[1] Increases in cardiac output during activity with TAH are thought to be dependent on increased venous return. The blood pressure (BP) response to and safety of exercise in patients with a TAH have not been reported. We hypothesized that blood pressure does not augment in response to exercise in patients with a TAH.

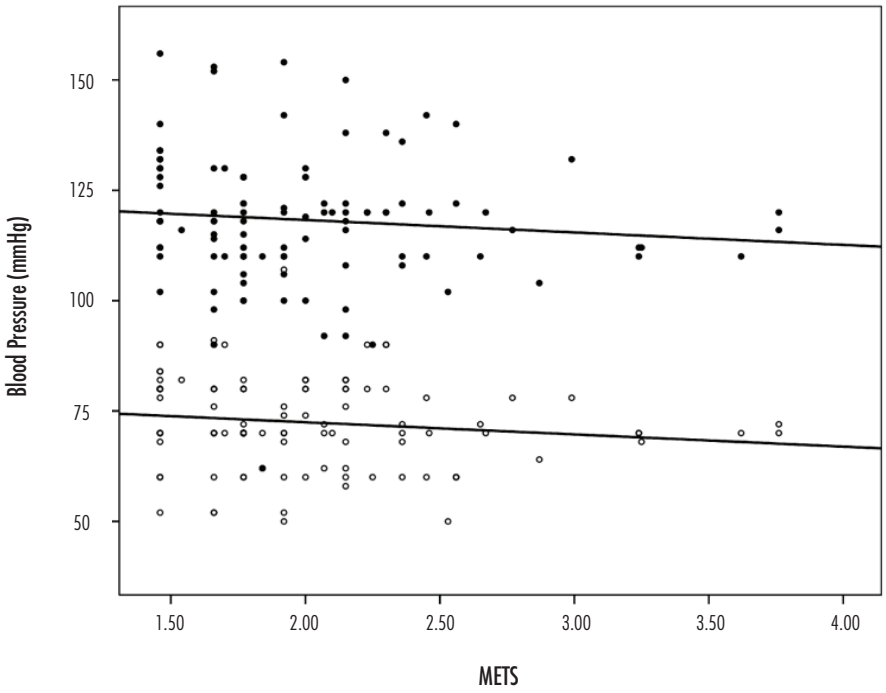

FIGURE 1: Scatter plots for blood pressure versus Metabolic Equivalents (METs) achieved. Solid black circle = systolic blood pressure, Hollow circle = diastolic blood pressure.

Here we show that during circulatory support with a TAH, there was a flat BP response to exercise, meaning BP did not significantly increase or decrease. However, aerobic exercise training early after device implant was safe and feasible in a supervised setting. In this study, 30 patients participated in physical

therapy and 22 of these patients proceeded to participate in treadmill rehabilitation. After TAH implant, patients initiated physical therapy at a median of five days (IQR: four – seven days) and 22 patients began treadmill exercise at a median of 19 days (IQR: 13 – 35 days). The duration of treadmill exercise (week 1: 8.35 ± 3.29 minutes vs. week 4: 18.62 ± 9.07 minutes, $p < 0.001$; week 1: 8.70 ± 3.80 minutes vs. week 8: 25.95 ± 15.06 minutes, $p = 0.006$) and the Metabolic Equivalents (METs)[6] achieved increased over the course of rehabilitation (week 1: 1.53 ± 0.13 METs vs. week 4: 1.85 ± 0.24 METs, $p < 0.001$; week 1: 1.53 ± 0.13 METs vs. week 8: 2.30 ± 0.52 METs, $p = 0.001$). The BP's before, during and post-exercise were similar (120/69 ± 13/13 vs. 118/72 ± 15/10 vs. 120/72 ± 14/12 mmHg; systolic: $p = 0.3$, diastolic: $p = 0.1$). The BP's weakly negatively correlated with METs achieved during exercise and the association was not statistically significantly (systolic: $\beta = -0.09$, $p = 0.3$, diastolic: $\beta = -0.14$, $p = 0.2$) (Figure 1). The maintenance of systemic blood pressure with activity is possibly related to increased venous return (preload), which in turn increases the stroke volume of the right and left TAH pumps. Venous return during exercise is facilitated by the skeletal muscle contraction, neurally mediated venoconstriction and respiratory pumps.[2,3,4] Additionally, concomitant regional vasoconstriction in the splanchnic and renal beds helps maintain and augment systemic blood pressure during exercise.[5]

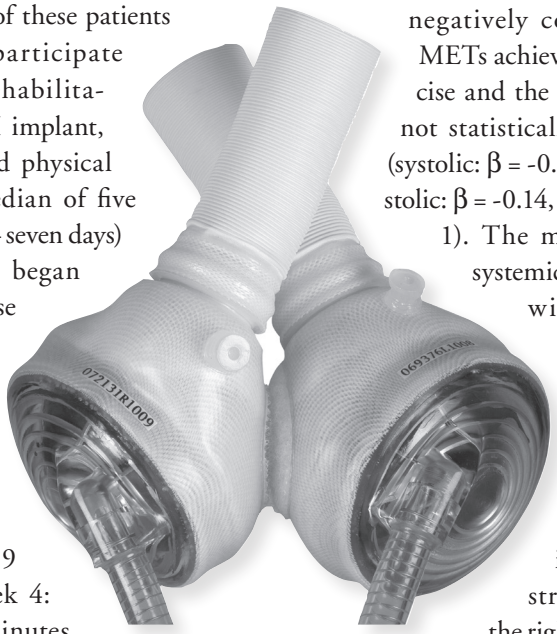

FIGURE 2: Total artificial heart (courtesy of *www.syncardia.com*).

The results of this study are pertinent as patient rehabilitation and mobility will be of increasing concern as TAH patients will be free to go home in the near future.

This study demonstrates that patients with a TAH (1) have a flat blood pressure response to exercise, (2) can safely participate in a physical rehabilitation program early after device implantation, and (3) exhibit improvement in exercise performance over the course of a rehabilitation program. These are the first data to describe the safety, implementation and efficacy of a regimented physical rehabilitation program for patients supported with an artificial heart.

Currently in the United States, patients with a TAH are bound to inpatient wards of hospitals, as the size and weight of the device prohibit patient discharge. However, utilization of a portable console is currently under investigation. The results of this study are pertinent as patient rehabilitation and mobility will be of increasing concern as TAH patients will be free to go home in the near future. Future patient studies measuring multiple exercise metrics with more intense exercise in a prospective manner will provide further guidance on rehabilitation for patients with the device.

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Enoxaparin Treatment for Cerebral Venous Thrombosis in a Pediatric Patient

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Advisors: Richard Young, MD, GW Hospital, and John F Hamilton, MD, Inova Regional Neurosurgery Service

Cerebral venous sinus thrombosis (CVST) is a rare but life threatening disorder in children that has been more readily diagnosed and managed due to enhanced neuroimaging modalities, improved identification of risk factors, and increased coverage in the literature. Some risk factors include head or neck infections, acute systemic illness, hematologic disorders and prothrombotic states including homocysteinemia.[1–2] Multiple studies have shown that the most common sites for thrombosis were the superior sagittal sinus (55%), lateral or transverse sinuses (51%), and the straight sinus (24%).[1] Of the numerous presentations of thrombosis, headache is reported in 90% of cases.[2] Following clinical suspicion of sinus thrombosis, MRI and MRV (Magnetic Resonance Venography) are the gold standard diagnostic tools.[2] After the diagnosis has been established, the majority of existing data supports systemic anticoagulation as the initial step in treatment. Patients with more serious presentations or those with clinical deterioration require direct thrombolysis or surgical intervention and anticoagulation.[3–5] Anticoagulation is typically achieved with heparin and this is the medication of choice for the majority of stable patients.[6]

Our case highlights a 14-year-old right-hand-dominant female that presented for evaluation of a cerebellar lesion. She had a recent history of headache and vomiting and positive dysmetria in her right upper extremity on exam. Past medical history was pertinent for premature birth and colectomy secondary to necrotizing enterocolitis. Upon admission, she was noted to have a decline in mental status. The patient was initially following commands but this function diminished soon thereafter. A head CT showed a large right cerebellar hemisphere infarct with right-to-left shift and tonsillar herniation secondary to mass effect from the infarct. Right suboccipital craniotomy with right cerebellar partial lobectomy of necrotic brain with placement of a twist drill right frontal ventriculostomy was performed by neurosurgery. No complications from surgery were observed upon discharge. The patient was sent home on colace, enoxaparin, glycerin suppository, and vitamin B complex therapy. She presented at follow-up without complaints of headache, nausea, vomiting or other complications. Subsequent evaluation showed elevated homocysteine levels.

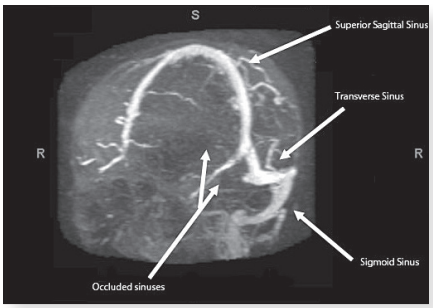

FIGURE 1A: Pre-Treatment. MR Venogram consistent with thrombosis of the straight, right transverse, sigmoid dural venous sinuses, the vein of Galen, and the internal stable veins and the basal veins of Rosenthal as well as the inferior sagittal sinus.

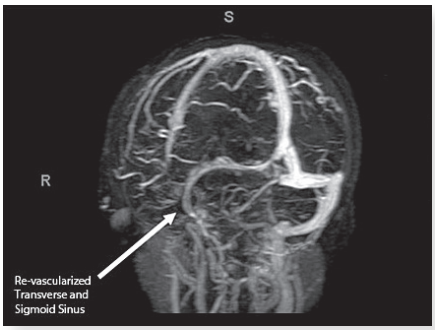

FIGURE 1B: Post-Treatment. There has been interval partial recanalization of the right sigmoid, transverse sinuses. There is also questionable minimal signal in the vein of Galen with persistent thrombosis of the straight sinus and the internal cerebral veins.

This case illustrates the most evidenced-based management for a patient with suspected venous sinus thrombosis. The patient's history of infantile gastrointestinal disease and homocysteinemia are known risk factors for CVST.[2,9] Exam findings including headache and vomiting prompted ordering a brain CT, a valid initial imaging tool for cerebral venous sinus thrombosis.[7] Interestingly, the team caring for this patient decided to use enoxaparin prophylaxis after surgery. Although enoxaparin is more expensive than heparin, its once daily dosing, and lower heparin induced thrombocytopenia risk for patients with good renal function made it a better option in this case. Based on a literature review and the outcome of our case, diagnosis and treatment of CVST remains very difficult due to rarity of cases and clinical variability.[8–9] Further research must be undertaken to determine the effectiveness of treatment choices such as enoxaparin as the best possible management for these patients.

Although enoxaparin is more expensive than heparin, its once daily dosing, and lower heparin induced thrombocytopenia risk for patients with good renal function made it a better option in this case.

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CyberKnife Radiosurgery for Previously Irradiated Vaginal Tumors

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Vaginal recurrences and the subsequent development of metastatic disease is a well known pattern of gynecological cancers. Therefore, the primary goal of initial radiotherapy should be to prevent these vaginal failures.

Patient	Age	Performance Status (ECOG)	Symptom	Primary Cancer	Histology	GTV (cc)
1	45	0	Bleeding	Uterine	Papillary serous	18.56
2	89	2	Bleeding	Uterine	Adenocarcinoma	43.24
3	57	0	Bleeding	Uterine	Adenocarcinoma	52.48
4	65	2	Dysuria	Urethral	Adenocarcinoma	14.35
5	68	0	Bleeding	Uterine	Adenocarcinoma	80.83
6	56	0	Dysuria	Vaginal	Squamous cell	44.46

TABLE 1: Patient and Tumor Characteristics

GTV = Gross Tumor Volume; ECOG = Eastern Cooperative Oncology Group Performance Status reflects effect of disease on patient's daily life.[9]

Patients presenting with primary and recurrent vaginal tumors have historically been successfully treated with several weeks of conventionally fractionated radiation therapy followed by several days of inpatient low-dose rate (LDR) intracavitary or interstitial brachytherapy. To improve patient tolerance of the therapy, researchers in the past decade have developed effective outpatient high-dose rate (HDR) brachytherapy protocols.[5]

Regardless of the method, brachytherapy is an invasive procedure associated with physical and psychological discomfort and anxiety[1-4] and chronic bowel, bladder and vaginal toxicity.

The current standard treatment for primary or recurrent vaginal carcinoma usually involves external beam radiation therapy (EBRT) and/or brachytherapy (BT).[5] EBRT generally decreases the initial tumor size, and BT is used subsequently. BT is used for a small cancer volume (i.e. less than 3 to 4 cm in diameter) and requires inserting a radioactive source (or radioisotopes) directly into or around the cancer. The highest radiation doses are delivered closest to the radioactive source. BT may be either intracavitary (sealed radioactive source within a body cavity, i.e. the vagina) or interstitial BT, a procedure that delivers radiation using needles inserted into the cancer and the surrounding tissues prior to salvage therapy.[6]

The CyberKnife is a novel minimally invasive means of delivering brachytherapy-like radiation dose distributions to vaginal tumors (Figure 1). We report the clinical efficacy and toxicity of salvage CyberKnife radiosurgery for six patients with previously irradiated vaginal tumors not amenable to brachytherapy.

Six consecutive women were treated over a five-year period (Table 1). Two patients presented with primary vaginal tumors (vaginal squamous cell carcinoma and urethral adenocarcinoma) and four with vaginal recurrences (uterine endometriod adenocarcinoma three and ovarian papillary serous carcinoma). We found that four of the six patients receiving > 30 Grays (Gy) with the CyberKnife procedure had a complete clinical response at three months post-therapy. Cancers found in two different patients (a primary vaginal adenocarcinoma and a recurrent papillary serous uterine cancer) persisted at three months and ultimately progressed despite receiving 25 Gy of radiation. At a median follow-up of 23 months, the two-year Kaplan-Meier local control of tumor growth and overall survival estimates were 56% and 100%, respectively. No severe (> grade 3) toxicities, defined as late gastrointestinal complications, life-threatening complications, or complications requiring surgery,[8] were attributed to CyberKnife treatment.[7]

Our results demonstrate that patients with vaginal tumors, which were previously unresponsive to conventional radiotherapy, may be successfully treated with the CyberKnife radiosurgery system. Further studies are needed to investigate this novel therapy among newly diagnosed patients. We believe such studies may adapt the current radiation treatment regimen of primary

CYBERKNIFE *Continued on p. 26*

and recurrent vaginal tumors to include CyberKnife as a first line treatment modality.

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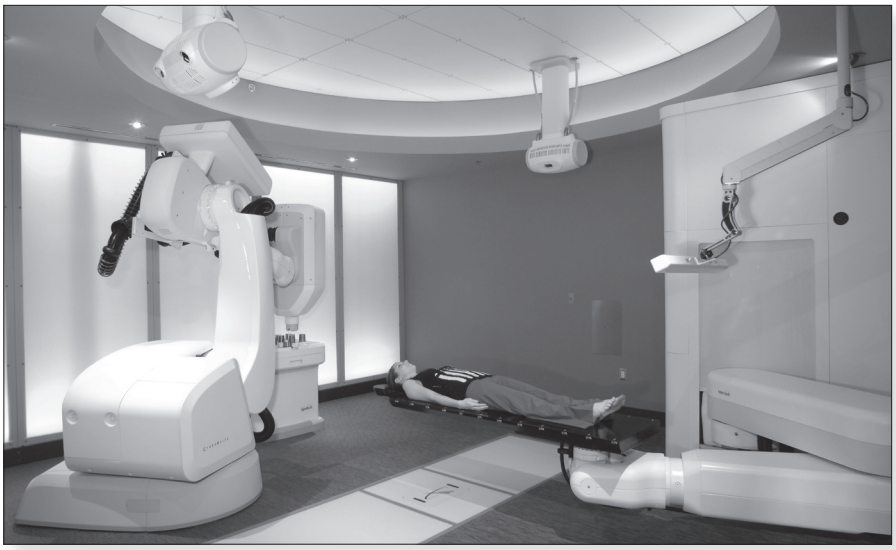

FIGURE 1: The CyberKnife LINAC is mounted on a robotic arm with six joints. One of the flat-panel amorphous silicon detectors can be seen on the side of the treatment table. (Courtesy of *Accuray.com*)

Bi-Rads Subcategorization as a Useful Predictor of Malignancy

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Advisors: Laura Liberman, MD, and Kimberly Feigin, MD, Memorial Sloan-Kettering Cancer Center

In the late 1980s, the American College of Radiology (ACR) began an initiative to create the Breast Imaging Reporting and Data System (BI-RADS) lexicon for mammography interpretation in order to standardize how to classify breast lesions and quantify their likelihood of being cancerous. Despite acceptance of this lexicon, interobserver variability was still high regarding the specific lesion classifications.

In 2003, the ACR further clarified each lesion by providing illustrations and representative photographs of each example. In addition to introducing a lexicon for sonography and MRI, the latest BI-RADS also further organized the category 4 lesions in three subgroups — 4a, 4b, and 4c.[1] Lazarus et al. and Sanders et al. conducted retrospective studies of these subcategories focusing on microcalcifications which both showed that the subcategories were useful predictors of malignancy.

One of the goals of this study was to look at the positive predictive value (PPV) of each subgroup to determine whether there is statistically significant correlation between the categories and the occurrence of cancer for masses. This HIPAA compliant and IRB approved retrospective study reviewed reports of 73,760 mammograms at the New York Memorial Sloan-Kettering facility from Dec. 1, 2003–April 30, 2007 to identify all lesions referred for biopsy (n=1575). Patients were 23–95 years old at the time of their diagnostic mammogram (mean age 56.9 [± 13.3 years]). In all cases, a core needle biopsy, stereotactic core needle biopsy, or fine needle aspiration was performed to determine pathology for the presence or absence of malignancy. Synchronous suspicious lesions (n = 261) were excluded to rule out multiple findings with different levels of suspicion. Film mammographic examinations were performed at either the Guttman Diagnostic Center or the Breast Examination Center of Harlem. Diagnostic evaluation included lateral and magnification views for all patients included in the study. Final assessment categories were independently assigned to each mammogram by one of five interpreting radiologists as follows: BI-RADS category 4a for lesions with low likelihood of malignancy; category 4b for lesions with an intermediate likelihood of malignancy; category 4c

for lesions with moderate likelihood of malignancy; and category 5 lesions for highly suggestive of malignancy (> 95%).[1] Statistical analysis was performed using chi-square and Fisher's exact tests.

Among 1,314 lesions, 382 (29%) were assigned BI-RADS category 4 without subcategorization, 451 (34%) 4a, 241 (18%) 4b, 88 (7%) 4c, and 152 (12%).[5] Histopathology results were available for 1,233 lesions in 1,216 women (92.3% follow-up). The cancer rate in these 1,233 lesions was 36% (441/1,233). The cancer rate did not differ significantly between lesions classified as BI-RADS category 4 without subcategorization (104/341 = 30%) vs. the sum of all lesions classified as BI-RADS 4a, 4b, and 4c (194/744 = 26%) (p = 0.2). As expected, the cancer rate increased significantly (p<0.001) with increasing BI-RADS subcategory: the cancer rate for subcategory 4a was 13% (58/433); 4b, 29% (64/223); 4c, 82% (72/88); and 5, 97% (143/148). There was also a statistically significant increase in the cancer rate among masses (Table).

BI-RADS Category	Total Lesions	Cancerous Lesions	PPV
4	118	37	37/118 (31%)
4a	205	16	16/205 (8%)
4b	72	22	22/72 (31%)
4c	43	38	38/43 (88%)
5	69	68	68/69 (99%)
Total	507	181	181/507 (36%)

TABLE: Frequency of Cancer and PPV as a Function of BI-RADS Category. Bolded and unbolded PPV values were found to be statistically significant with p-values<0.02 and p<0.001, respectively.

BI-RADS 4 subcategories 4a/b/c may be useful predictors of malignancy for mass lesions. Further investigation, including analysis of specific lesion features, will assist radiologists in making evidence-based recommendations for use of BI-RADS subcategories 4a/b/c, enhancing communication, practice, and research.

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Occupational Radiation Exposure of Interventional Radiologists and Staff During Performance of Biopsies Guided by CT Fluoroscopy

Sagine Berry-Tony, MSII
Advisor: Raymond Thornton, MD, Memorial Sloan-Kettering Cancer Center

The National Council on Radiation Protection and Measurements reports that exposure to potentially harmful ionizing radiation from medical procedures has seen a more than seven fold increase between the early 1980s and 2006.[1,2] "The total number of CT examinations performed annually in the US has risen from approximately 3 million in 1980 to nearly 70 million in 2007 … greater use of CT has resulted in a concurrent increase in the medical exposure to ionizing radiation."[3] "During conventional CT guided interventions, operation of the CT scanner is performed at the operating console outside the CT imaging room."[4] Images are captured while all personnel step out of the imaging room to the control area- a protected location behind leaded glass, thus greatly reducing if not eliminating the risk of exposure to ionizing radiation.

During CT fluoroscopy however, connection of a footswitch and control panel directly to the gantry of the CT scanner, require the physician operator to stand in the CT suite while images are acquired, imposing the risk of occupational radiation exposure.[4] Personnel who work in fluoroscopy suites routinely wear leaded gowns to minimize their occupational exposure to radiation. Other dose mitigating strategies include staying as far away as possible from the X-ray source-inverse square law. Some studies have shown substantial radiation exposure to operators who use CT fluoroscopy. Our objective was to study the amount of radiation reaching the physician and nurse when they stand in positions typical of daily work.

With an anthropomorphic operator phantom positioned 80cm from the gantry (Close), 160 cm from the gantry (Far), and at the side of the CT unit (Side), CT fluoroscopy was performed at the patient phantom's upper abdomen using typical machine settings of 60 mA and 120 kV. Radiation dose was recorded at the operator's: lens (with and without leaded 0.75 mm lead equivalent eyeglasses), neck (with and without thyroid shield), left chest wall (with and without leaded apron), and left side (to simulate extremity dose) using a solid-state dosimeter. Measurements were then repeated with the operator phantom in the position typical of a nurse in a fluoroscopy

RADIATION EXPOSURE

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suite, approximately 350cm from the gantry (Nurse). Measurements were repeated with disposable tungsten-antimony drapes (0.25 mm lead equivalent) on the patient phantom, and suspended transparent leaded shields (0.5 mm lead equivalent) positioned at the gantry, and at 10 cm from the operator lens.

Results were expressed as the ratio of scattered dose received by the operator phantom (μR) to the radiation dose delivered to the patient phantom (mGy cm). The shielding efficacy of each strategy is expressed graphically.

Our findings show that operator dose was minimized by stepping to the side of the CT scanner when CT images were being obtained. The profile of scattered radiation from the CT scanner and the shielding effect of the machine housing are the best explanations for this observation. Nurse doses at 350 cm from the midpoint of the gantry were similar to maximally protected physician doses, and likely due to the mechanism predicted by the inverse square law.

Ratio Exposure to DLP (μR / mGy cm)				
Locations	80 cm	160 cm	350 cm	Side
Eye Unprotected	22.15	6.81	1.30	0.85
Eye Protected (Glasses)	2.97	0.75	0.00	0.00
Eye Protected (Shield close to CT)	1.17	4.04		
Eye Protected (Shield 10 cm from face)	0.40	0.00		
Eye Unprotected (Rad Pad)	21.13	4.32	1.04	0.76
Eye Protected (Glasses and Rad Pad)		0.57		
Neck Unprotected	9.66	5.44	1.24	0.55
Neck Protected	0.94	0.40	0.00	0.00
Neck Protected (Shield close to CT)	0.00	0.00		
Neck Protected (Shield close to face)		0.00		
Left Breast Protected (Apron)	0.69	0.00	0.00	0.00
Left Arm Unprotected	17.94	3.97	0.83	0.00
Left Arm Protected (Shield close to CT)	6.82	3.57		
Left Arm Protected (Shield close to body)		0.33		
Left Arm Unprotected (Rad Pad)	14.16	2.94		

TABLE: **CT Dose Index (CTDI):** A characterization of absorbed dose, measured in a homogenous phantom by a diagnostic medical physicist during quality assurance, quality control experiments; units are mGy.

Dose Length Product (DLP): An approximation of the total energy a patient absorbs from the scan; units are mGy cm.

microRoentgen (μR): A unit of radiation exposure, obtained by measuring the amount of radiation required to liberate a certain amount of charge in a known volume of air.

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High Levels of Intra-tumoral Tumor-infiltrating Lymphocytes and No Angiolymphatic Invasion Increase Recurrence-free Survival in Stage 1A NSCLC.

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The presence of tumor infiltrating lymphocytes (TILs), specifically $CD8^+$ cytotoxic T-lymphocytes, have been found to increase survival in many forms of cancer, including NSCLC, endometrial, bile ductal, colonic, esophageal, and urothelial cancers, as well as melanoma and follicular lymphoma.[1–8]

The relevance of TILs in the prognosis of NSCLC, however, still remains controversial. In this study, we compared the outcomes of stage 1A NSCLC with and without tumor infiltrating lymphocytes to evaluate the effects of TILs on recurrence and survival patterns.

From 2000 to 2009, 273 anatomic segmentectomies and lobectomies were performed on stage 1A NSCLC. Patients were stratified into TIL^- and TIL^+ cohorts based on pathological evaluation. Further investigation was conducted on the effects of TILs in patients with and without angiolymphatic invasion. Variables analyzed include overall survival, recurrence-free survival, and type of recurrence (locoregional vs. systemic).

Five-year recurrence-free survival (RFS) was significantly increased in the TIL^+ group vs. the TIL^- group (87% vs. 73%, p = .011) [Figure 1], more so in women (p = .016). The presence of angiolymphatic invasion (ALI) was associated with decreased five-year RFS versus patients without ALI (61% vs.

85%, p<.001). Significantly, in the ALI negative group, TIL+ patients experienced a significantly increased five-year recurrence-free survival vs. TIL- patients (93% vs. 80%, p = .036). Furthermore, in TIL+ patients who did experience recurrence, locoregional recurrences rates were similar to those in the TIL- group, at 3.5% and 5.4%, respectively. Systemic recurrences, however, occurred in 16.4% of the TIL- patients and only 6.4% of the TIL+ patients (p = .0295). Results are summarized in Table 1.

High levels of intratumoral TILs are associated with improved recurrence-free survival in stage 1A NSCLC patients as well as a reduced likelihood of systemic recurrence. When angiolymphatic invasion is not present, the beneficial effects of TILs become even more profound.

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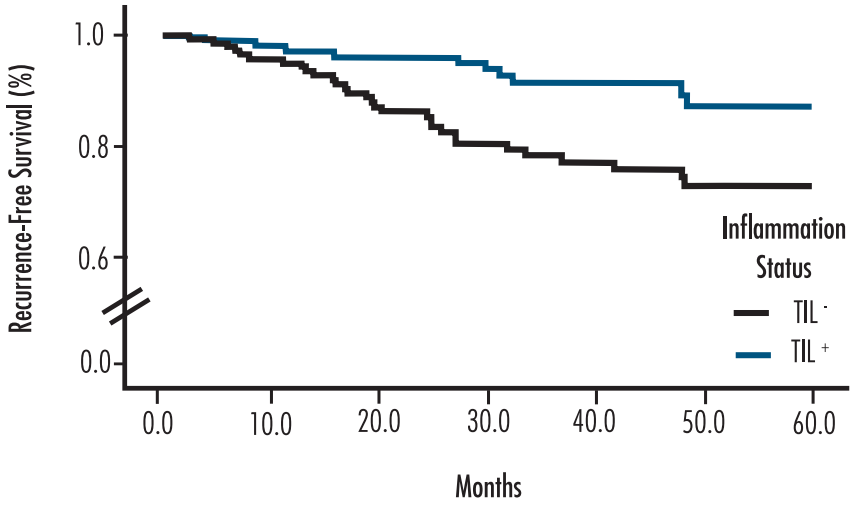

FIGURE: Increased 5-year recurrence-free survival in TIL+ NSCLC.

	TIL+	TIL-	p
Overall Population	87%	73%	.011
Gender			
Male	83%	76%	.219
Female	90%	69%	.016
Age, mean years (range)	68 (40-86)	68 (46-79)	—
Procedure			
Lobectomy	86%	74%	.049
Segmentectomy	92%	72%	.133
Histology			
Adenocarcinoma	85%	69%	.074
Squamous Cell	90%	78%	.147
Adenosquamous	—	—	.114
Large Cell	—	—	.355
Other	—	—	.808
Differentiation			
Undifferentiated/Poor	92%	76%	.341
Moderate	87%	63%	.003
Well	—	—	—
Size			
<2cm	93%	73%	.004
2-3cm	79%	73%	.571
Angiolymphatic Invasion			
ALI+ 93%	79%	.126	
ALI-	68%	56%	.036
Recurrence Location (frequencies)			
Distant/Systemic	6.36%	16.42%	.030
Locoregional	3.5%	5.4%	.555

TABLE: Five-year Recurrence Free Survival Characteristics

Functional and Structural Connectivity of Language and Working Memory in Children with Epilepsy

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Epilepsy is one of the most common serious neurological conditions affecting pediatric populations.[1] Seizure foci play an important role in terms of resulting cognitive impairments or changes that can occur in these patients.[2] Recent studies have found that white matter tracts have shown immature myelination patterns in children with developmental and cognitive delays.[3] DTI has been used to measure white matter tract integrity by measuring directionality and degree of water molecule movement in the brain.[4]

In epileptic patients with a localized seizure focus, functions of the affected hemisphere may lateralize to the contralateral hemisphere. Subsequent higher FA values (implying white matter tracts with a greater degree of myelination) are observed in the contralateral hemisphere.[5] Our cross-sectional study compared 15 controls to 16 pediatric epilepsy patients with left hemisphere focal seizures. We hypothesized that these patients would have decreased FA values in the left frontal lobe.

Scanned images were rated for quality and FSL software was used; images were pre-processed and the "most representative" FA image was identified. All subjects' FA images were aligned to this target image. TBSS was used to generate a standard-space images for all subjects and then merge these into a single 4D image from which a mean FA skeleton was constructed. Voxelwise statistics were performed and using the Johns Hopkins white matter atlas in FSL, our data showed increased FA values for patients in the following R hemisphere structures:

- Anterior internal capsule: connections implicated in working memory, learning, fine motor skills
- Retrolenticular internal capsule: optic tract connections
- Corona radiata (anterior, superior): associated with reading ability
- Posterior thalamic radiation: connections between thalamus and parietal, occipital lobes

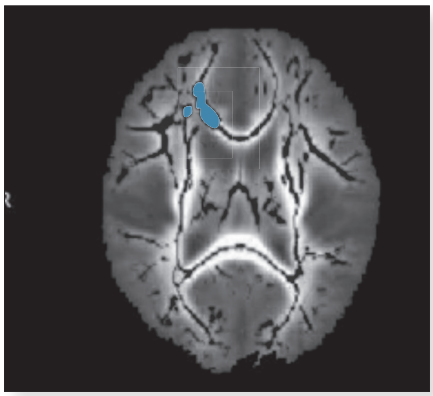

FIGURE 1: Blue: patient FA > control FA

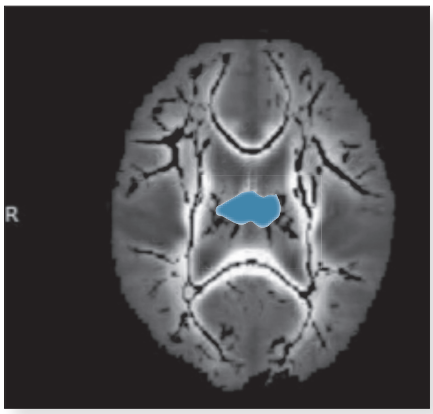

FIGURE 2: Blue: control FA > patient FA

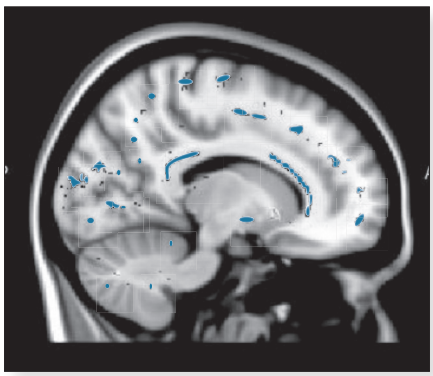

FIGURE 3: Blue: patient FA > control, in right hemisphere

These structures for which patients have higher R side FA values are implicated in reading, working memory, etc., supporting the hypothesis that patients with L sided lesions are more likely to rely on R side white matter to perform cognitive functions, which become increasingly organized throughout childhood. However, there was no accompanying decrease in the FA values of the corresponding L side structures. Patients showed bilateral increased FA in the genu of corpus callosum and superior cerebellar peduncles, as well as a bilateral increased FA in the fornix — which has been previously reported in other studies.[6]

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25-OH Vitamin D Levels in Patients with Retinal Pathology: A Retrospective Study

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Vitamin D deficiency has now been recognized as a pandemic and low serum levels have been associated with a multitude of diverse adverse health effects.[1] In addition to its well-established role in calcium regulation, Vitamin D also has antioxidant, immunomodulatory, anti-inflammatory, and anti-angiogenic properties,[2,3] all of which are mediated by the Vitamin D receptor.[4] Although the Vitamin D receptor has been demonstrated to be highly expressed in the human retina,[5] the association between serum vitamin D levels and retinal health has not been established. In regard to retinal disease, two studies have shown Vitamin D serum levels to be inversely correlated with diabetic retinopathy and a possible protective role in age related macular degeneration.[6,7] However, the association between serum Vitamin D levels and retinal occlusive diseases has not been demonstrated.

Our retrospective study looked at 565 patients diagnosed with either diabetic retinopathy, age related macular degeneration or retinal vascular occlusive disease over the past five years and compared 25-OH vitamin D levels drawn during the same time period. These patients were subcategorized by disease type and severity, and 25-OH vitamin D levels were compared with an age- and gender-matched control group of patients seen in our ophthalmology department without the aforementioned diagnoses. In patients with multiple levels taken, the earliest level was used in an attempt to use levels taken before Vitamin D supplementation therapy was initiated. Exclusion criteria included patients on 1000 IU or greater daily dose Vitamin D. Results were compared using student t-tests.

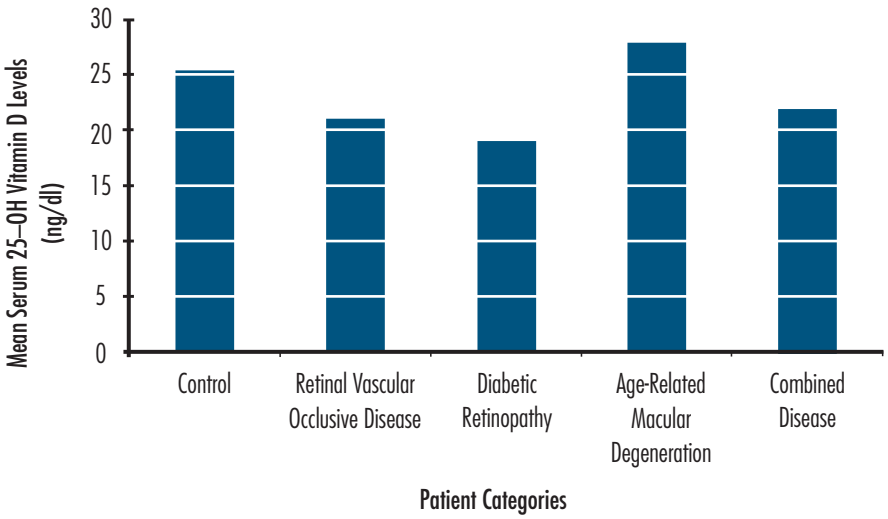

FIGURE: Mean Serum 25 — OH Vitamin D Levels Among Retinal Disease Groups.

Our study showed that patients with diabetic retinopathy ($p<0.0001$), retinal vascular occlusive disease ($p<0.035$) and the combined disease group ($p<0.004$) had significantly lower serum 25-OH vitamin D levels when compared to patients without retinal pathology (Figure). To the best of our knowledge, this is the first report comparing Vitamin D levels and retinal vascular occlusive disease. No statistically significant difference in serum 25-OH vitamin D levels was observed in patients with dry versus wet age related macular degeneration ($p<0.41$) or nonproliferating diabetic retinopathy versus proliferating diabetic retinopathy ($p<0.66$). There was also no significant difference in levels of patients with age related macular degeneration as a whole compared to patients without retinopathy. Further study is needed to identify whether vitamin D can be used as a marker for these conditions and if supplementation has any role in altering disease development or progress.

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Strengthening the Safety Net: Evaluating Access to Primary Care in the Emergency Department

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Uninsured and low-income patients often rely on the "safety net" for their medical care which includes local community health centers or low cost clinics, health department services, and local emergency departments (ED).[1] In Prince George's County the safety net system is particularly limited because of a lack of adequate primary care providers and facilities to serve the counties' 80,000 uninsured patients.[2] Many of these patients resort to using the ED for routine medical care or conditions that are preventable with consistent outpatient primary care.[3] Although patients can receive treatment in the ED for any health issue, the long term benefit of care delivered in the ED is limited by the lack of appropriate follow-up for patients without a primary medical physician.[4] This is particularly important in our low income chronically ill population where access to regular care could significantly improve health status and reduce avoidable ED visits.

"Strengthening the Safety Net" was proposed to determine if direct primary care referral and appointment scheduling from the emergency department at point of service would increase rates of primary care follow up from the Prince George's County ED. Furthermore, the study sought to assess the self described perceived barriers to primary care in the uninsured ED population.

	Complaints With No Follow-up			Complaints With Follow-up			
	Intervention	Control	Total %	Intervention	Control	Total %	p value
Acute	19	20	39 (88.64)	7	11	18 (66.67)	0.03
Chronic	4	0	4 (9.09)	4	4	8 (29.63)	0.03

TABLE 1: Follow up results of patients with either chronic or acute medical conditions.

A randomized prospective pilot study of ED adult patients was conducted. A direct scheduler was placed in the ED from 9 a.m to 5 p.m., Monday through Friday to coordinate discharge follow up for intervention patients. English speaking patients without a primary care physician who required follow up with a PCP within a three-week time frame were invited to participate. At discharge, the intervention group had a follow-up appointment made with either of two participating low-cost clinics and the control group was given the routine discharge contact information and instructions to schedule a follow-up appointment. All participants were called one month after their ED visit to ascertain if they followed-up and to discuss barriers to follow-up. Clinics were also called to verify appointment attendance. A proportional t-test was used for comparison of data.

Sixty-six patients were enrolled in this study over a period of one month. Demographic characteristics and disease severity were similar between the intervention and control groups. Follow-up rates were 29% for the intervention group and 40% for the control group (P = 0.25); there was no difference in follow up between the two clinics in the intervention group. The most common reason for not following up for both groups was a lack of transportation (13%), resolution of symptoms (13 percent), and work conflict (13%). Interestingly, patients with chronic medical complaints were more likely (30% vs. 9%, p = 0.03) to follow up with an outpatient clinic. Overall results indicated that while providing a scheduled appointment upon discharge from the ED did not improve compliance with outpatient follow up, patients with chronic medical complaints were more likely to obtain follow up.

The limitations of this study included a small study population, and differences in the services offered between the two community clinics. The implications of this study promote further collaboration between emergency medicine and the community health center network in Prince George's County, and there are currently policy discussions at the administrative level of the ED and the community clinics to the benefits and drawbacks of the results of this pilot study. Furthermore, the study warrants further investigation into efficacious program development and implementation in targeting the uninsured population that utilized the ED for ambulatory primary care visits. Subsidized transportation options and flexibility of appointment hours may contribute to higher compliance with outpatient follow-up among this at risk population. Also, the development of

SAFTEY NET *Continued on p. 33*

urgent care centers or services within the community health network is a perceived need, as many patients didn't follow up with a PCP due to absolving symptoms at time of follow-up. It is possible that there was higher follow up rate in those patients with chronic conditions because of the ongoing need for affordable continuity of care.

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	Intervention %	Control %	Total %
Forgot Appointment	2 (16.67)	1 (5.26)	3 (9.68)
Lack of Transportation	4 (33.33)	0 (0.00)	4 (12.90)
Lack of Childcare	0 (0.00)	0 (0.00)	0 (0.00)
Lack of Eldercare	1 (8.33)	0 (0.00)	1 (3.23)
Work Conflict	4 (33.33)	0 (0.00)	4 (12.90)
Language Barrier	1 (8.33)	1 (5.26)	2 (6.45)
Symptoms Better	3 (25.00)	1 (5.26)	4 (12.90)
Inconvenient Hours	—	2 (10.53)	2 (6.45)
Cost	—	1 (5.26)	1 (3.23)
Location	—	2 (10.53)	2 (6.45)
Other	0 (0.00)	5 (26.32)	5 (16.13)

TABLE 2: Reasons for lack of follow-up.

Head Injury and Posttraumatic Stress Disorder Among Those Present South of Chambers Street in Manhattan During the Sept. 11, 2001 Terrorist Attacks

Sarah Mohajeri, MSI
Advisor: Steven D. Stellman, PhD, Columbia University Mailman School of Public Health, World Trade Center Health Registry

Man-made disasters leave significant levels of stress on the exposed population, and studies have shown that the mental health effects go beyond short-term stress and affect the population on multiple dimensions. The terrorist attacks of Sept. 11, 2001, have been associated with a variety of adverse health outcomes in the exposed population such as asthma and other respiratory conditions. The World Trade Center Health Registry, a Bureau of the New York City Department of Health and Mental Hygiene, was created to investigate the long-term health effects of the Sept. 11 attacks and has conducted multiple research projects following its inception. The baseline survey of 71,437 individuals exposed to the disaster, conducted between 2003 and 2004, reveals a prevalence of Posttraumatic Stress Disorder (PTSD) of 15.5% among lower Manhattan residents.[4] PTSD has been associated with multiple exposures resulting from the attacks,[3] with head injuries being of special interest, as the physical and cognitive consequences of such an injury may be related to later development of PTSD.

The relationship between PTSD and head injury has been a subject of great debate within the literature, both empirically and theoretically. Many studies have reported associations between head injury and PTSD, including a study of Oklahoma City bombing survivors.[8] Other studies have concluded PTSD cannot develop following a Traumatic Brain Injury (TBI),[7] and some have even

SEPT. 11 *Continued on p. 34*

 Continued from p. 33

concluded that severe TBI is protective against PTSD.[5] None of these involved World Trade Center survivors. To examine this issue we investigated the relationship between head injury and PTSD outcome.

This study focused on a sub-sample of registry enrollees who were physically present in the eligible area south of Chambers Street in Manhattan, between the time of the first plane impact and noon (n=43,487) [The two plane crashes occurred about a half-hour apart.]. The baseline survey collected information on head injury and several measures of mental health, including the PTSD Check-list (PCL) Civilian Version.[1,6] Exposure to head injury was measured by asking respondents if they experienced a concussion. Head injury was one of seven specified categories of physical injury.

Our study found that head injury was a significant and strong predictor of PTSD (Adjusted OR=5.2, 3.8-7.1) within the population that was present south of Chambers Street during the terrorist attacks. Based on previous research on this population,[3] we controlled for the witnessing of horrific events, dust cloud exposure, age, income, ethnicity, and gender as possible confounding variables. Our findings were consistent with literature that supports the association between TBI and PTSD.

Findings from this study may help future investigators to further examine the relationship between head injury and stress disorders, and to focus on possible mechanistic processes that may be responsible for the observed association. The persistence of mental illness[2] among the population exposed to the terrorist attack on Sept. 11 highlights the need to provide treatment options and access to medical resources to those who have experienced traumatic events.

	Model 1	Model 2	Model 3	Model 4†	Model 5††
	Crude OR (95% CI)	Crude OR (95%t CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Head Injury	8.2 (6.3–10.8)	–	7.4 (5.6–9.7)	5.2 (3.8–7.1)	N/A*
Witnessing Horrific Events	–	3.0 (2.7–3.5)	3.0 (2.7–3.3)	2.3 (2.0–2.5)	2.3 (2.0–2.5)
Dust Cloud	–			1.8 (1.7–2.0)	1.8 (1.7–2.0)
Age	0–17			1.0	1.0
	18–24			1.8 (1.2–2.8)**	1.8 (1.2–2.8)**
	25–44			3.7 (2.5–5.6)	3.7 (2.5–5.6)
	45–64			4.4 (2.9–6.7)	4.4 (2.9–6.6)
	65+			2.2 (1.4–3.4)***	2.2 (1.4–3.4)***
Gender	Male			1.0	1.0
	Female			1.4 (1.3–1.5)	1.4 (1.3–1.5)
Ethnicity	White			1.0	1.0
	African American			1.5 (1.4–1.6)	1.5 (1.4–1.6)
	Hispanic			2.2 (2.0–2.4)	2.2 (2.0–2.4)
	Asian			1.0 (0.9–1.1)*	1.0 (0.9–1.1)*
	Multiracial			1.8 (1.4–2.1)	1.8 (1.4–2.1)
	Other			2.1(1.6–2.7)	2.1 (1.6–2.7)
Income	less than $25,000			4.8 (4.2–5.4)	4.8 (4.2–5.4)
	$25,000–$75,000			2.3 (2.1–2.6)	2.3 (2.1–2.6)
	$75,000–$150,000			1.4 (1.2–1.5)	1.4 (1.2–1.5)
	$150,000 or more			1.0	1.0
Witnessing Horrific Events* Head Injury					N/A*

P<0.0001 except *(p>0.05), **p<0.01, ***p<0.001.
Model 1: univariate logistic model, head injury as single predictor variable, PTSD as outcome.
Model 2: univariate logistic model, witnessing horrific events as single predictor variable, PTSD as outcome.
Model 3: bivariate logistic model, head injury and witnessing horrific events as predictor variable, PTSD as outcome.
† Hosmer and Lemeshow Goodness of Fit Test statistics: Chis-quare=16.1 DF=8 p<0.041.
†† Hosmer and Lemeshow Goodness of Fit Test statistics: Chis-quare=16.2 DF=8 p<0.040.

TABLE: Crude and adjusted odds ratios for association between head injury and PTSD in World Trade Center Health Registry enrollees using univariate and multivariate logistic regression Analysis, with terms for interaction between head injury and witnessing horrific events.

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Traditional Birth Attendants: A Non-Traditional Way to Improve Access to Prevention of Mother-to-Child HIV Transmission Efforts among Women in Rural Southern India

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Advisor: Purnima Madhivanan, MBBS, MPH, PhD, Public Health Research Institute, Mysore, India

Interview with a traditional birth attendant (TBA) in a rural village of Mysore, India. Public Health Research Institute.

Comprising approximately one-sixth of the world's total population, India has faced a host of medical and socioeconomic issues, including access to maternal health care and a rising human immunodeficiency virus (HIV) epidemic. The prevalence of HIV/AIDS among the total adult population is 0.36%, with an estimated 2.5 million people currently living with HIV/AIDS.[1] In the State of Karnataka in Southern India, the primary mode of HIV transmission is heterosexual contact, and HIV prevalence is estimated to be 0.69% among the general population. Notably, HIV prevalence at antenatal care (ANC) clinics in Karnataka State has exceeded 1% in recent years.[2]

A particular challenge to the HIV epidemic in India has been access to maternal care for HIV-infected women of reproductive age. In many rural areas of Karnataka State, less than 10% of all HIV-infected women receive ANC services, including access to antiretroviral medication during pregnancy and delivery to decrease the risk of mother-to-child transmission of HIV. Traditional birth attendants (TBA) attend many home deliveries in these rural communities, yet TBA do not receive training for prevention of mother-to-child transmission of HIV (PMTCT).

In this study, we examined the prevalence of TBA-assisted births and the provision of ANC in a large village-based population sample in the subdistrict of Mysore, India. Using enumerated data on village households, we conducted a population based door-to-door survey of a random sample of rural villages from August to September 2008. Sociodemographic data were collected from each household, including the mother's age at first childbirth, number of children below six years of age in the household, place of delivery, who assisted each delivery, and whether antenatal care was received. Multivariable logistic regression was used to assess factors associated with receiving ANC. The study was conducted by Public Health Research Institute (PHRI) in Mysore, India and received funding from the Elizabeth Glaser Pediatric AIDS Foundation.

Among 16 villages, we surveyed 1,342 households (94.4% response rate). The median age of women at first delivery was 19.5 years (range 11–46 years). Among all children under six years of age, 39.3% were delivered at home versus 60.7% in a hospital/clinic. Deliveries were assisted by a doctor or nurse (62.7%), TBA (31.1%), relative (5.8%), and other (0.4%). In multivariable analysis, factors independently associated with receiving ANC included institutional delivery (odds ratio [OR] 13.0, 95% confidence interval [CI]: 8.4–20.1) and high socioeconomic status (OR 2.7, 95% CI: 1.8–3.9).

Our data showed that a substantial proportion of women delivering at home were less likely to receive antenatal care and HIV prevention services. As we continue to confront the HIV epidemic in India with a multipronged and open-minded approach, particularly in rural areas, TBA performing home deliveries might serve as key community members to increase access to ANC services for women who do not receive care in hospitals. Identifying and training TBA in HIV prevention strategies might allow for an alternative means to improve access to health care in these hard-to-reach populations.

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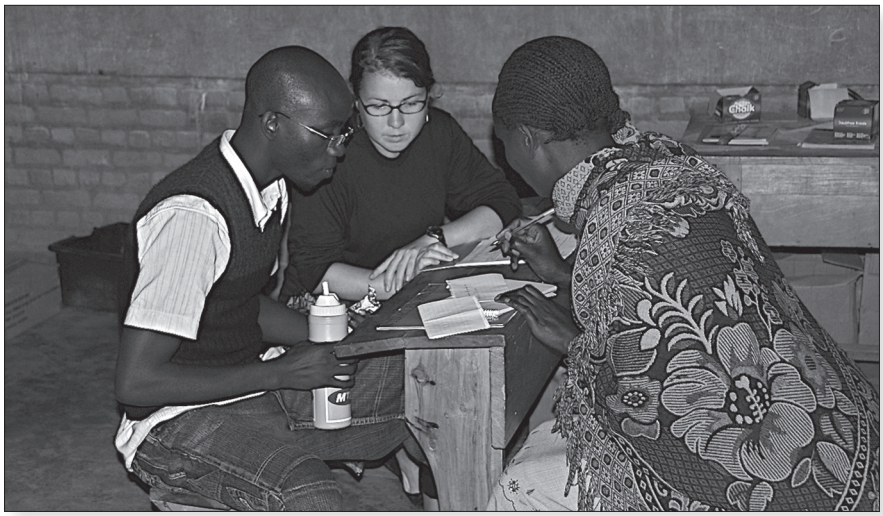
A Sociocultural Evaluation of Neglected Tropical Diseases (NTDs) and Deworming Campaign Efforts in Northern Rwanda

Lindsay Wheeler, MSII
Advisor: Peter Hotez, MD, PhD, FAAP, The George Washington University School of Medicine and Health Sciences



Working with a translator to interview the mother of a child at risk for soil transmitted helminths in the Bureau District of northern Rwanda.

Neglected tropical diseases (NTDs) represent one of the greatest economic and health burdens experienced by the people of Rwanda. Data from 2008 found that 66% of the school-aged population was infected with soil-transmitted helminthes (STHs), including ascariasis, trichuriasis, and hookworm. In some districts in the Northern Province, the prevalence among school children surpassed 90%.[1] Parasitic infections are reported by health centers to be the second most frequent reason for outpatient visits.[2]

With support from Legatum, an international investment group, and in collaboration with the Global Network for Neglected Tropical Diseases, the Access Project and Ministry of Health joined forces to develop an integrated NTD education and treatment campaign to lower the burden of STHs and schistosomiasis. The purpose of this community-based research was to evaluate community perceptions of the current control efforts as well as knowledge of STHs and schistosomiasis.

We conducted 122 interviews in the districts of Musanze and Burera, two regions of northern Rwanda that received recent mass drug administration (MDA) against STHs and schistosomiasis. The interviews consisted predominantly of open-ended questions and specific multiple-choice questions. The total sample size included 60 children and 62 adult volunteers, including community health workers, health center staff, teachers and parents.

Results indicated that both children and adults regard infection with STHs and schistosomiasis as a significant issue. Over 75% of health center staff and community health workers identified intestinal worms as their first or second priority medical concern, compared to HIV/AIDS, tuberculosis, malaria and pneumonia. Adults identified several consequences of worms, including delayed physical development, promotion of poverty and absence from school.

Poverty was cited as the most common barrier to prevention. Additionally, community health workers reported many people not following advice on NTD prevention because it was impractical or not considered important. These results suggest that strengthening the message of behavior change and reinforcing the deleterious effects of worm infections is critical to the future of the campaign. Larger issues, such as access to clean water and resources must be confronted in order to achieve a long-term impact in NTD control.

Nearly all the children interviewed believed they had been infected and treated. They understood the causes of infection and symptoms, which they had learned primarily through school. The vast majority of the children were "very worried" about infection and reported that they were practicing the recommended behaviors to prevent infection. Most (73%) reported hand washing before eating, but far fewer (45%) reported hand washing after using the toilet, indicating a need for a targeted education campaign.

Overall, our data suggest that among a sample of adults and children in Northern Rwanda there is a basic knowledge of the risks of NTDs and that current control efforts are accepted. Although this study has several limitations, including reporting bias and small sample size, we believe it highlights the major attitudes expressed by the community. Further research is needed to better understand the direct impact of NTDs on school attendance, economy, and child health and development in Rwanda.

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about the beaumont society

The William H. Beaumont Medical Research Honor Society is a research society of medical students that was established in 1935 to honor Dr. William H. Beaumont (1785–1853), a U.S. Army surgeon known as the "father of gastric physiology" for his groundbreaking research on human digestion. The organization seeks to foster a continuing interest in research and to promote the value of research in the practice of medicine. As a part of this mission, the Society integrates current research topics into the curriculum; publishes Fusion, a scientific journal showcasing GW School of Medicine and Health Sciences student research; makes available information on research opportunities throughout the area, including the William T. Gill Summer Fellowship for GW medical students; and highlights student and faculty research accomplishments at the annual GW Medical Center Research Day.

How It was Made

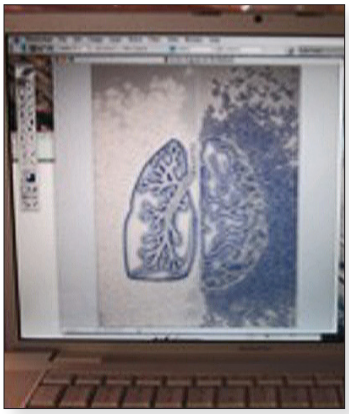
Second–year medical student Kenneth Morford relied on drawing ability, ordinary office equipment, and a little bit on ingenuity to produce the cover Illustration for this edition of *Fusion*. Step 1 in the process was to draw the brain and lung illustrations. For step 2, he cut out the sketches. In step 3, Morford assembled the sketches, adding colored construction paper, rice, and gravel. Using a flat-bed scanner he created a digital image of the construction in step 4. And finally in step five, Morford adjusted the image using Adobe Photoshop.

STEP 1: Draw it

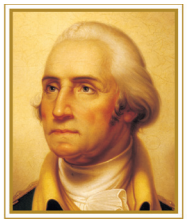
STEP 2: Cut it out

STEP 3: Assemble it

STEP 4: Scan it



STEP 5: Photoshop it



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Fusion **is the annual student-run scientific journal of The George Washington University's William H. Beaumont Medical Research Honor Society. It was created to showcase student achievements in basic science and clinical research, public health, medical education, and international health-related travel experiences.**

Submissions from the classes of 2012, 2013, and 2014, as well as the incoming class of 2015, for next year's edition of the journal will be accepted beginning September 2011. More information about the submission process will be provided during the summer of 2011. If students have any questions or comments, please contact the Beaumont Society at *gwbeaumont@gmail.com*.