

Kids Connection

a monthly newsletter from MUSC Children's Hospital



November 2007

Letter from the Chair

Dear faculty, Children's Hospital staff and friends,

What Do You Value?

It appears that we value our time, our money, and service to our fellow man. Physicians should feel the need to help their patients and those who do not have the resources to obtain adequate medical care. While there are many free clinics in the United States, many still go without adequate care, without adequate nutrition and shelter, and without hope.

In addition to wanting to serve patients directly, it is also important to develop improved treatments for disease and injury. In this way, the physician scientist provides for future cures and improved public health. Among a dwindling number of individuals who have the creative drive to discover, the MD/PHD programs have provided an element of scholarly pursuit that will help to spearhead future discoveries and new cures.



L. Lyndon Key, MD
Professor and Chairman
Department of Pediatrics

We are also seeing a changing demographic with women assuming a greater and greater role in pediatrics and medicine. In the US, about 75-80 percent of the physicians going into pediatrics are women. This leads to the need to provide the services that allow well-trained doctors and care personnel to work. In our program, we have been looking for ways to improve the ability for young female and male physicians to be able to be at work without having to worry about their children's care or their pocketbook. We now offer a program that pays for up to 26 weeks of daycare that can pay for or supplement child care (*if you wish to engage a in home caretaker*).

The world keeps turning. The discoveries continue to improve lives. The service-oriented physicians help others without regard to time or money. Values are not about time, money, and possessions, but they are all about helping your fellow woman or man.

Sincerely,

L. Lyndon Key, MD
Chair, Department of Pediatrics



FEATURE STORY

What do new pediatricians value?
See page 2.

What do new pediatricians value?

Recent study shows emerging pediatricians want to be of service without engaging in research

A new study, the results of which have just been published in the *Journal of Pediatrics*, surveyed nearly 3,500 medical school graduates and found that while future pediatricians -- particularly females -- ranked caring for others at the top, they put research, academic and teaching pursuits at the bottom.



The Hervey Allen Oak that stands at the southwest corner of Colcock Hall (www.musc.edu/colcockhall) has witnessed many things over the last 200 years. Today, four generations of health professionals, Dr. Ken Holden (Silent Generation), Dr. Bernie Maria (Baby Boomer), Dr. Michelle Hudspeth (Generation X), and MD/PhD student Amena Smith (Generation Y) stand under the Porter Oak to discuss the professional values of future pediatricians.

Titled “What do future (female) pediatricians value?,” the article polled recent medical school graduates registered with the Careers in Medicine website, an online career planning program operated by the Association of American Medical Colleges (AAMC). Only participants in residency two years or less were included.

First author and MD/PhD student Amena Smith, who is enrolled in MUSC’s Medical Scientist Training Program, says the first concern was the shortage of academic pediatric neurologists and other pediatric sub-specialists. “We wanted to know why there was a deficit. And we hoped to determine how to address it.”

Using a 35-value inventory called Physician Values in Practice Scale (PVIPS), the survey measured six values that help identify what’s most important and satisfying about being a physician: prestige – being recognized by others as a top physician; service – caring for others regardless of financial gains or other rewards; autonomy – the importance of freedom, independence and control over clinical decision

making; lifestyle – having a predictable and stable work schedule, management – supervising and having responsibility for others; and scholarly pursuits – engaging in clinical or basic research, academic medicine and teaching.

It found that pediatric students scored much higher than others on service, placing it above autonomy, management and prestige.

“Regrettably, across all specialties, scholarship has lower value, and in people choosing pediatrics, scholarship was the lowest,” notes Dr. Bernie Maria, the senior author and principal investigator of the ongoing study.

What this indicates, explains Smith, is that pediatricians entering the field are very interested in caring for people, but are not as interested in research. “And that is problematic for institutes like the DCRI, and ultimately for the advancement of children’s medical care.”

“We’re making important discoveries in science, yet if we don’t create proper incentives, we may not have the medical professionals to carry this work forward,” adds Dr. Maria. “We won’t be able to make optimal use of this information without new generations of academicians.”

The survey also looked at differences between the sexes, finding significant differences between men and women on all professional values except management issues in practice.

Among the findings: women in both the pediatrics group and the “all other” group valued service to a greater extent than their male counterparts, and both placed significantly lower emphasis on the value of scholarly pursuits. Overall, men in both groups valued autonomy, prestige and scholarly pursuits, while women placed higher value on lifestyle and service.

Second year MUSC medical student and co-investigator Robbie Hendry, agrees with the findings. “My classmates seem more focused on recognition and prestige,” he offers.

He believes part of the problem is they’re not familiar with academic medicine. “They don’t understand the benefits of it, that it offers opportunities to be effective participants in a patient’s quality of life. The rewards are more related to direct patient contact and to being part of a rewarding care team.”

There were also differences between future female and male pediatricians. Of 350 participants, 27 percent were men and 73 percent were women. "Pediatrics is the first specialty with a female majority," explains Dr. Maria, "Nationwide, over 80 percent of interns are women, and these numbers reflect that."

"Since scholarly pursuits are less appealing overall and particularly among women, who make up the majority of the pediatric field, pediatrics really stands to lose in the research world," notes Smith.

This survey was a first step, she continues. The next is to determine the differences between generations, find out how to acknowledge them and foster career development for the next generation.

"The strategy is for current mentors in the field to link the scholarly aspect more closely to the highly valued autonomy, lifestyle, and service, to make it more attractive," concludes Smith. "That's where the appeal of translational research comes in."

The questions are: What does my generation think is important, what do our mentors/teachers think is important and how can they be linked? How can the previous generation of predominantly male pediatricians make academics exciting, and show new, primarily female investigators how to marry the two interests so their careers are fulfilling?"

Stay tuned: In their next paper, the authors will report values differences by generation and findings from focus groups of Generation Y students (born 1980-) that probe the dichotomy between prestige and scholarly pursuits.

This is the first time there's been data that addresses these issues, notes Dr. Maria. "It's a snapshot that shows us that people in their 40s to 60s are mentoring young physicians in their 20s and 30s who have very different priorities. To attract more of the new generation to medicine, to pediatrics, to academics – to move the field forward – we need to pay attention more than ever to generational and individual differences."

He hopes Generation Y pediatricians will see that one of the best ways to serve many children is to move the field forward with novel treatments through translational research.

Message from our Medical Director

This month's newsletter addresses "professional values", a term that can have many different meanings to various individuals and groups. Dr. Key's letter focus's on "service" as a value for physicians and others, while this note will address a combination of goals and behaviors. Three questions come to mind when I consider the professional values of the medical staff:



J. Philip Saul, MD
Medical Director
Pediatric Cardiology

- **What do you believe is important?**
- **What do you aspire to?**
- **How do you plan to act to implement the first two questions?**

Certainly, there should be some common answer to these questions for all physicians. We should all believe the health and wellbeing of our patients is important. As pediatric care providers, we should all aspire to effectively manage the psycho-social and physical components of our patients health, and we should all practice in a manner that accomplishes that. Further, we should treat our colleagues and patients/families with respect and good communication. However, the more detailed answers to these questions will almost certainly vary among us as function of numerous factors, including our backgrounds, career stage, personal ambitions and personality. The dictum "do unto others as you would have them do unto you" may be a great starting place for all of us. The critical issue for me then comes down to each member of the medical staff consciously considering these or similar questions and abiding by their answers until they consciously change them. Follow your hearts and keep up the good work.

Children's Research Institute News Brief



Bernard L. Maria, MD, MBA
Executive Director
Darby Children's
Research Inst.



Inderjit Singh, PhD
Scientific Director
Darby Children's
Research Inst.

MSTP students discover the human side of research

A unique program makes it possible for MUSC MD/PhD students to take what's captivated them during hands-on clinical work, and then apply that knowledge to discoveries in the lab.

"These are our future scientists, the people we're counting on to be the future faculty of medical schools," says Dr. Perry Halushka, director of MUSC's Medical Scientists Training program, or MSTP. "These are young people who want to make a difference. They'll be the ones who will make discoveries and then translate them into therapies and medical improvements."

By combining clinical and research opportunities, the program offers MD/PhD students the chance to become physicians as well as scientists. The NIH-funded program at MUSC is one of about 40 in the country, and is highly competitive. Dr. Halushka says the number of applicants rose 10 percent this year, to 96 for about seven positions.

The curriculum includes basic science courses and clinical rotations, plus graduate education and sufficient time to conduct a significant research project leading to a Ph.D. Students are encouraged to enroll the summer before the first year of medical school; most complete the program in seven to eight years.

"We're encouraged to go to clinic, identify a problem and then address it with our research," explains third year student Amena Smith. "Because we've met patients with the disease and have seen the consequences of the disease, we're able to come into the lab and research something we have a passion for. It's motivating, basically."

Currently the 55 MSTP students at MUSC are investigating issues ranging from aging and cancer, to cardiovascular disease and the neurobiology of addiction.

Eleven are collaborating within the DCRI to tackle child-related diseases. First year student Anthony Leonard is analyzing the expression patterns of the breast cancer resistance protein in human glioblastoma.

"This is the most malignant and deadly brain tumor we've classified," says Leonard. He hopes his research will help clarify the protein's role in enhancing tumor cell resistance, particularly tumor regrowth in children.

DeAnna Baker is also working in the DCRI, researching the removal of sphingosine kinase, one of the sphingolipids, which she believes could lead to a decrease in inflammation related to rheumatoid arthritis.

Relating her medical background to her current research gives her a more concrete perspective on her goal, says Baker.

"The MSTP provides a great infrastructure for research, even before I start work on my PhD," agrees Leonard. "Working in the DCRI puts me within easy access to collaborators, and it's full of investigators who emphasize the importance of translational research."

Third-year student Joe Palatinus is collaborating with researchers in the DCRI to develop an ACT1 peptide to increase the rate of diabetic wound healing.

"The program has allowed me to work on the human, animal model and cellular levels," adds Smith. She says her experiences as a medical student – such as drawing blood and talking to patients – give her an advantage.

"The nice thing about being both a clinician and a researcher is that you get to see problems up-close, and then you get to take that information and do something about it in the lab."

It's definitely a unique opportunity, agrees Dr. Halushka. "I always remind these students that they're doing research and collaborating on studies that could have an impact on potentially thousands of people."

2007 MD/PhD Projects:



DeAnna A. Baker

Mentor: Dr. Gary Gilkeson

Role of Sphingosine Kinase I in a Mouse Model of Chronic Inflammation

DeAnna Baker, Lina Obeid, MD, Gary Gilkeson, MD

Ralph H. Johnson VA Medical Center, Charles P. Darby Children's Research Institute, Medical University of South Carolina, Charleston, SC

Sphingosine kinase I (SphK1) is one of the two enzymes that phosphorylates sphingosine to create sphingosine 1 phosphate (S1P) and has an established relationship with cell signaling molecules such as ERK and p38 MAPK. Abnormalities in sphingolipids are implicated in a variety of disease states, especially in the pathogenesis of certain cancers. However, their role in other disease states is poorly understood. Based on previous in vitro

results, SIP has an apparent role in inflammation. Recent data demonstrated a relationship between TNF alpha, a contributor to inflammation, and SIP produced by SphK1. Fibroblast cell lines stimulated with TNF alpha lead to an increase in SIP following SphK1 activation. Removal of SphK1 by siRNA in fibroblast cell lines stimulated with human TNF alpha (hTNF) lead to a decrease in the formation of the inflammatory mediator prostaglandin E2 (PGE2) (Pettus et al., 2003). This in vitro data lead us to further experiment in an in vivo model. We have obtained transgenic mice that constitutively express a modified copy of the hTNF alpha gene leading to chronic, progressive synovitis detectable as swelling and deformity in the fore and hind paws at around 20 weeks of age. These mice were crossed with mice lacking functional copies of the SphK1 gene (SphK1 KO). Thus, the absence of the SphK1 gene will allow us to study its direct effects on hTNF-induced chronic synovial inflammation. The mice were genotyped to determine the presence/absence of SphK1 and the transgene and monitored weekly for evidence of inflammation. In preliminary observations of a limited number of mice, hTNF transgenic SphK1 KO mice develop less joint swelling and deformity than hTNF transgenic mice with functioning copies of SphK1 and transgenic mice heterozygous for SphK1 of comparable age. Also, TNF transgenic, SphK1 KO mice had less detectable activated ERK than transgenic mice heterozygous for SphK1 or SphK1 heterozygous mice. These preliminary data suggest that SphK1 induced SIP production is a key factor in the inflammatory arthritis present in hTNF mice.

Pettus, B.J., Bielawski, J., Porcelli, A.M., Reames, D.L., Johnson, K.R., Morrow, J., Chalfant, C.E., Obeid, L.M., and Hannun, Y.A. (2003). The sphingosine kinase 1/sphingosine-1-phosphate pathway mediates COX-2 induction and PGE2 production in response to TNF-alpha. *FASEB J* 17, 1411-1421.



Loretta L. Hoover

Mentor: Dr. Steve Kubalak

Regulation of TGF-beta signaling by retinoid receptor ligands occurs in a time frame that is independent of transcriptional events

Loretta L. Hoover, M. Elizabeth G. Burton, Bonnie A. Brooks, and Steven W. Kubalak

Department of Cell Biology and Anatomy, Cardiovascular Developmental Biology Center, Charles P. Darby Children's Research Institute, Medical University of South Carolina, Charleston, SC

The molecular events responsible for most congenital heart defects are poorly understood. We have previously reported increased transforming growth factor beta 2 (TGF-beta-2) as well as increased apoptosis in the developing heart of the midgestational (E11.5-13.5) retinoid x receptor alpha knockout (RXR alpha -/-) mouse model of congenital heart disease. Interestingly, Smad2, a signaling factor downstream of TGF-beta-2, is perturbed in the E12.5 RXR alpha -/- such that outflow tract mesenchymal cells show less nuclear-localized activated (i.e. phosphorylated) Smad2 (pSmad2) when compared to similar cells in the wild type. This finding led us to investigate the temporal expression

of pSmad2, and preliminary evidence suggests a futile negative feedback mechanism is at work in this mouse. Our in vitro work is focused on whether activation of retinoic acid signaling affects pSmad2 accumulation. We treated wild type E12.5 dispersed heart cells with combinations of TGF-beta-2 and the RXR alpha agonist, 9-cis-retinoic acid (9-cis-RA) and evaluated activation of Smad2, which occurs within minutes of treatment. As expected, treating cells with TGF-beta-2 for 1 hour resulted in an increase in pSmad2 as detected by Western blot when compared to treating with 9-cis-RA. When cells were treated with the combination of TGF-beta-2 and 9-cis-RA, we detected a statistically significant increase in the amount of pSmad2 when compared to treating with TGF-beta-2 alone. In our characterization of this molecular event, we have expanded our studies to include evaluation of normal epithelial and mesenchymal cell lines as well as several cancer cell lines. Our studies are aimed at determining the mechanism of how retinoids can potentiate canonical TGF-beta signaling in an acute timeframe independent of transcriptional events. Results suggest important components of TGF-beta signaling affecting Smad2 activation and nuclear accumulation are regulated by retinoids in a manner that has been unappreciated until now. We have evidence supporting that these interactions may be responsible for the congenital heart defects seen in the RXR alpha -/-.



Anthony P. Leonard

Mentor: Dr. Bernie Maria

Hyaluronan-CD44 interactions and regulation of BCRP/ABCG2 in human spinal and cerebral gliomas

Leonard, AP; Gilg, AG; Toole, BP; Maria, BL.

Departments of Pediatrics and Cell Biology and Anatomy, Charles P. Darby Children's Research Institute, Medical University of South Carolina.

Malignant human spinal cord gliomas are extremely rare tumors which are associated with a dismal prognosis for survival and high spinal neurological morbidity. Hyaluronan oligomers (o-HA) that inhibit HA interactions with cell surface receptors (e.g. CD44, RHAMM) inhibit tumor growth and invasiveness in a highly malignant C6 rodent spinal cord glioma model. In vitro, o-HA reverse malignant properties of C6 cells including the expression of breast cancer resistance protein (BCRP/ABCG2), an ATP-drug effluxer abundant in highly tumorigenic CD133+ glioma progenitors. Interestingly, o-HA treatment in vivo also abrogates recruitment of non-C6 (host-derived) BCRP+ progenitors which primarily express neural (vs. bone marrow) markers. Because little is known of the biology of human spinal cord gliomas and there is limited evidence whether highly chemoresistant BCRP+ cells are relevant in human cerebral or spinal gliomas, we undertook immunohistochemical analyses of rare human spinal cord gliomas to determine the presence of BCRP, CD133 (glioma progenitor marker), matrix metalloproteinase inducer EMMPRIN (which regulates HA synthesis), and multi-lineage stem/progenitor marker nestin. Twelve paraffin-embedded human spinal cord gliomas ranging from WHO grade 1 to 4 obtained from the MUSC Tumor Bank were used in this analysis. Most tumors exhibited an increased expression of the above antigens, including both grade IV spinal cord glioblastomas. It is not known if abundant

BCRP+ cells in high grade human spinal cord gliomas are tumor cells, tumor progenitor cells, or recruited non-glioma progenitors (as observed in our rat spinal model). High levels of expression of CD133 and BCRP in subcutaneous xenografts of human cerebral glioblastomas in nude mice suggest BCRP could well be expressed at high levels in tumor cells and not just in recruited progenitors. Taken together, these data suggest that BCRP+ cells present in our animal model are present in both cerebral and spinal cord human gliomas, which is indeed confirmed via confocal microscopy of human brain GBM staining for BCRP, CD133, and CD44. Imaging confirms tumor-wide presence of a subpopulation of cells with BCRP+/CD133+ phenotype both adjacent and distal to BCRP+ vessels. Further studies are needed to determine the origin(s) and function of BCRP+ cells in gliomas now that their presence has been confirmed in the human disease.



Michael P. O'Quinn

Mentor: Dr. Rob Gourdie

A Peptide Incorporating a Carboxy-Terminal Domain of Cx43 Improves Recovery of Cardiac Function Following Injury

Michael P. O'Quinn (1), Brett S. Harris (1), Tim C. McQuinn (2,1), Richard P. Visconti (1), Kyu-Ho Lee (2,1), Carol A. Eisenberg (1), Leonard M. Eisenberg (1), and Robert G. Gourdie (1)

(1) Department of Cell Biology and Anatomy, (2) Department of Pediatrics, Medical University of South Carolina, Charles P. Darby Children's Research Institute, Charleston, South Carolina, USA

Disease-associated remodeling of Cx43 gap junctions (GJ) has been linked to increased incidence of cardiac arrhythmias. We have previously shown that dynamic changes in interaction between Cx43 and the actin-binding protein ZO-1 are an important determinant of GJ size and distribution in cardiomyocytes (Hunter et al., 2006). As part of this work we developed a membrane-permeant peptide incorporating a carboxy-terminal domain of Cx43, designed to competitively inhibit the interaction between Cx43 and ZO-1. Subsequent investigations demonstrated that treatment of cutaneous wounds with the Cx43 peptide, in a pluronic gel, enhanced wound healing; decreasing inflammation and accelerating closure, as well as improving mechanical properties and decreasing granulation tissue deposition. Based on these results, we initiated studies of the effects of the peptide in cardiac wound healing. Since coronary artery ligation produces injuries of variable size and geometry, we developed a novel epicardial cryoinjury model that enabled production of a discrete wound displaying minimal variation. Additionally, we re-formulated peptide delivery for cardiac application from pluronic gel to an adherent methylcellulose patch to provide timed, localized release. Echocardiographic studies of cryoinjured hearts treated with the Cx43-based peptide exhibited significantly improved ventricular function (as evidenced by reduced dilation) compared to groups exposed to a control peptide. Interestingly, this change was most pronounced at seven days, though it persisted throughout the 8-week time course of the experiment. Quantitative

histological analysis of these hearts showed that treated scars have more uniform collagen organization, which may explain decreased dilation occurring in response to the peptide. Cryoinjury of transgenic mice expressing a LacZ reporter under the control of a GATA-6 enhancer indicates upregulation of a fetal gene program in association with injury. In preliminary observations, the level of LacZ expression is increased in cryoinjuries treated with the Cx43 based peptide. In conclusion, our data suggest a Cx43 carboxy-terminal sequence may upregulate an adaptive response to cardiac injury that results in an inhibition of dilation.



Joseph A. Palatinus

Mentor: Dr. Rob Gourdie

The effects of a gap junction derived peptide on diabetic skin wounds

Joseph A. Palatinus, Gautam Ghatnekar, and Robert G. Gourdie

Department of Cell Biology and Anatomy, Children's Research Institute, Medical University of South Carolina, Charleston, SC 29403, USA

Diabetes is the 6th leading cause of death in the United States and over 20 million people currently suffer from this metabolic disease. One of the most devastating complications of the diabetic condition is the decreased ability to heal. Chronic wounds are a hallmark of diabetic patients. These wounds frequently appear in the distal limbs and are refractory to standard wound care measures. Diabetic wounds frequently become gangrenous and require limb amputation presumably because of microvascular occlusion resulting in decreased tissue perfusion and intercellular communication. There is a need for new interventions to increase the rate of diabetic wound healing. Our lab has developed a peptide (dubbed ACT1) composed of the carboxyl terminus of the gap junction protein Connexin 43. This peptide has been shown to increase the rate of wound repair and decrease scar tissue formation in skin wounds of normal CD1 mice. Currently studies are underway to determine the efficacy of the peptide in diabetic models of injury.



Juan C. Varela

Mentor: Dr. Steve Tomlinson

Downregulation of Crry on tumor cells leads to the induction of an anti-tumor T-cell response in a metastatic model of bladder cancer

Juan Carlos Varela, Masaki Imai, Carl Atkinson and Stephen Tomlinson

Department of Microbiology and Immunology, Children's Research Institute, Medical University of South Carolina, Charleston, SC 29403, USA

It is believed that many types of tumors protect themselves from the effects of the complement system by upregulating the expression of membrane-bound

complement inhibitors on their cell surface. Complement inhibitory proteins expressed on cancer cells can provide protection from anti-tumor antibodies and may modulate the induction of an immune response to tumor-associated antigens. In the current set of studies we investigated: (1) the mechanisms leading to the upregulation of complement inhibitors on tumors from bladder cancer patients, and (2) the consequences of complement inhibitor downregulation on the effector and inductive phases of an immune response to bladder cancer in a syngeneic model of mouse bladder cancer.

Paired samples of tumor and normal tissue from 22 bladder cancer patients were analyzed for expression of MUC1, CD46, CD55 and CD59, and matched serum samples analyzed for anti-MUC1 IgM and IgG levels. MUC1 was upregulated in 86% of tumor samples. CD46 was upregulated in 77%, CD55 in 55% and CD59 in 59% of tumors. Analysis of the relationship between anti-MUC1 antibody levels and complement inhibitor expression revealed a significant correlation between the expression of the complement inhibitors CD46 and CD55 on tumor cells and the presence of IgM and IgG anti-MUC1 antibodies in the serum of bladder cancer patients. Hence, we propose a mechanism where selection of tumor cells with higher expression of complement inhibitors is mediated by antibodies against the tumor antigen MUC1.

In a separate set of studies, stable siRNA-mediated downregulation of the complement inhibitor Crry led to an increase in C3 deposition and complement-mediated lysis of bladder cancer cells in vitro. In vivo studies determined that mice injected i.v. with bladder cancer cells expressing lower levels of Crry had a significant decrease in tumor burden and a significant increase in survival compared to mice inoculated with bladder cancer cells expressing normal levels of Crry. While anti-tumor antibody responses were detected in the mice injected with Crry low tumor cells, the decreased tumor burden and improved survival was determined to be caused by the enhancement of an anti-tumor T cell response and was dependent, at least in part, on a functional complement system. The current data indicates that the complement system and complement inhibitors play a significant role in the induction and/or enhancement of T cell responses against tumors in a syngeneic model of mouse bladder cancer.



Khaled Moussawi

Mentor: Dr. Peter Kalivas

Rewiring Cocaine Addiction: The Role of N-Acetylcysteine in Reversing Impaired Plasticity after Chronic Cocaine

Department of Neurosciences, Children's Research Institute, Medical University of South Carolina, Charleston, SC 29403, USA

A major feature of cocaine addiction is the vulnerability to relapse. This vulnerability is thought to be rooted in the long term neuroadaptations in the neurocircuitry comprising the cognitive-motor interface. While some electrophysiological studies have tried to assess neuroplasticity in the ventral striatum after chronic withdrawal in brain slices, we looked into the prefrontal-

accumbal changes after prolonged withdrawal from cocaine self administration in vivo. To address this question, we measured the ability of this pathway to undergo long term potentiation (LTP) and long term depression (LTD) in vivo. Rats were trained to self-administer cocaine for 10 days, followed by 21 days withdrawal (2 weeks extinction and 1 week abstinence). Field potentials in the dorsomedial nucleus accumbens were recorded after ventral prefrontal cortex stimulation. LTP induction (2 trains of 50 Hz, 2 seconds each) resulted in around 50% potentiation in the yoked saline animals, and was severely impaired in the cocaine group (<10% potentiation). LTD (3 trains of 5 Hz, 3 minutes each) was also blunted (~20% depression) after chronic withdrawal as compared to the control (~55% depression). Interestingly, systemic injection of N-acetylcysteine (100mg/kg), an antioxidant related to glutamate homeostasis, restored both LTP and LTD in the chronic cocaine animals. Together, these results indicate that previous hypotheses suggesting that addiction is associated with an enduring LTD state at the excitatory synapses in the accumbens are incomplete. Rather, a loss of both LTD and LTP indicates that cocaine addiction shifts the accumbens into a pathological state that is deficient in physiological adaptation to the new, important changes in afferent stimulation embodied in LTP and LTD. It is possible that this state may underlie decreased reinforcement of natural rewards and increased vulnerability to relapse observed in cocaine addiction.

Evidence-Based Tip

Report from AAMC: Our Changing Values

I write our EBM Tip this month from Washington, DC, where I am attending the AAMC Annual Meeting. What better place to see modeled the professional values exposed and modeled than from those to whom we entrust the education of our future physician? If you will allow me, I would like to depart from my usual subject area to share with you some of what I am hearing here.



Laura Cousineau, MLS

MUSC Library
Dept. of Pediatrics
EBM Faculty

The theme of this year's meeting is "Health in the Balance," and many of our leaders speak of a change in our healthcare landscape, in our cultural values, and in our ability to provide what is needed for our patients. The common thread, the underlying connection, is the need to balance the needs of our individual patient with the health needs of all of our citizens.

Dr. Darrell Kirch, AAMC President, spoke of the change in our culture. Where competition, hierarchy, individual excellence and the respect for expert opinion may still be the dominating values, we are moving towards a different way of achieving excellence. Transparency—where how decisions are made and how dollars are obtained and spent—is our new value. Specialized teams are replacing the individual caregiver, where continuity of care replaces becomes the new value. Patient-centered care, outcome focused care, and collaborative care become our new institutional values. Our reward system shifts from

recognizing personal achievement to recognizing the ability to network, to collaborate, to create and work in healthcare teams.

Our values in the research arena are shifting as well. AHRQ Director, Dr. Carolyn Clancy, spoke on the need to focus on reliability instead of achievability. Where as we now pride ourselves at the incredible medical miracles we are able to provide for the few, we need to balance that with the time, effort and funding we put towards "getting it right" for the all the patients all of the time. She spoke of systematic reviews conducted by her agency to set standards for quality of care, and the need to build clinical information systems that access these standards at the point of care.

Perhaps most evocative was Dr. Daniel Federman, a senior dean at the Harvard Medical School, and the only speaker to receive a standing ovation. He described the need for medical education that is "intellectually dazzling, emotionally gratifying, and morally transcendent." He demanded a curriculum that invokes disgust, outrage and shame at the inequities and lack of care for so many of our citizens. He was asked by a reporter what would happen if his students could not practice the way they were taught, when his way of teaching did not match the world that his students faced. "Then," he replied, "they will have to change the world."

A special thanks to the following individuals for their efforts in putting together Kids Connection each month.

Editor: Bernard L. Maria, MD, MBA, Jennifer Cherock, Trio Solutions Inc.

Publisher: Brian Cendrowski, Trio Solutions Inc.,
Roxanne Hicks, Trio Solutions, Inc.

Feature Writer: Mary Sue Lawrence, Trio Solutions Inc

Contributing Writers: Lyndon Key, Bernard Maria, John Sanders,
Inderjit Singh, Philip Saul