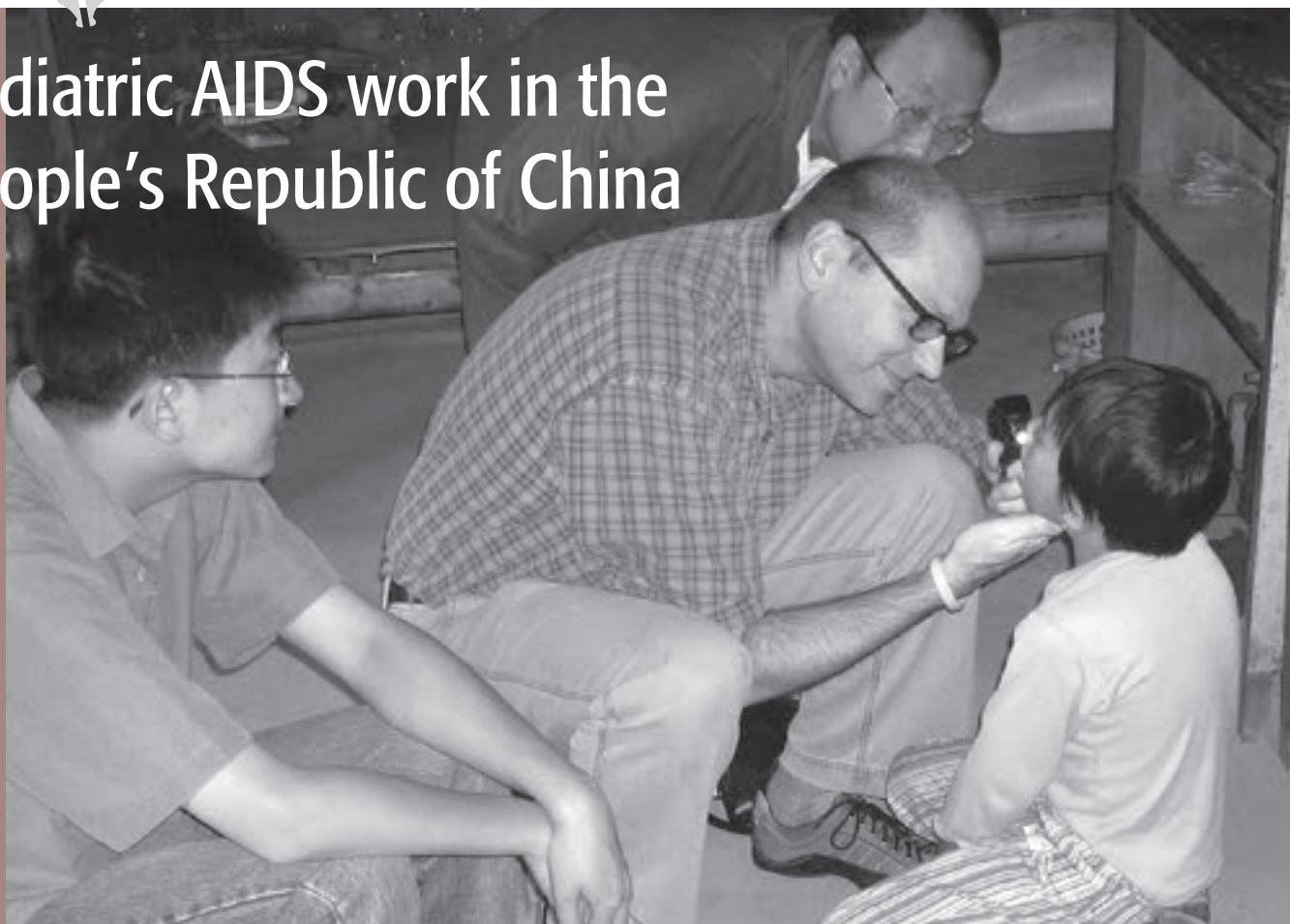


Pediatric AIDS work in the People's Republic of China



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It is impossible to work in infectious diseases and not have a global perspective. Recent avian influenza concerns highlight the interconnectedness of infectious disease transmission patterns. Migratory birds seem to have a complete disregard for national borders. Weak public health infrastructures in the world's most populous nations are a threat to an increasingly integrated global community.

The Brown Department of Medicine has historically recognized the importance of an international focus on infectious diseases, and particularly HIV. We have developed strong collaborations across Asia, Africa, and the Caribbean. Brown's focus on research and training has bolstered clinical care in a number of settings, particularly in Kenya,



Chairman's Message

Edward J. Wing, MD

At this time of year, it is always exciting to interview prospective house staff for the Brown training programs in medicine. At Lifespan, there are a total of approximately 150 residents in four different tracks, categorical (89), primary care (26), preliminary (11), and med/peds (16) plus 5 chief residents. In addition, there are a total of 75 fellows in 8 separate fellowships. At Memorial Hospital of Rhode Island, there is a vigorous primary care internal medicine program with a total of 30 residents. Our programs are attracting applicants from all sections of the country with an upsurge recently from some of the best programs in the South and West. The quality of the house staff by all measures has increased each year. The Department is on the map nationally and the "buzz" on the street and on the Internet is that Brown has some of the most dynamic and exciting training programs in the country. Credit goes to the entire faculty who teach and interact with our house staff as well as the outstanding program directors, Drs. Michele Cyr, Kelly McGarry, Fred Schiffman, and Dominick Tammaro (Lifespan) and Dr. Eleanor Summerhill at Memorial.

One of the attractions of the Brown Training programs is the opportunity for international experiences in Kenya, India, Cambodia, China, and the Dominican Republic. Dr. Herb Harwell in this edition of the Newsletter describes his truly remarkable experiences in Asia. Dr. Carter's work on tuberculosis in this country provides a direct link with her research and clinical work in Kenya. Rotations with Dr. Carter are available for students and residents both in Providence and in Eldoret Kenya.

Drs. Mark Fagan and Joe Diaz, either of who can be contacted for further information, head the growing program in the Dominican Republic.

Finally, I wish to point out the burgeoning research programs in basic and translational investigation in the Department. Dr. Gideon Koren and Dr. Ulrike Mende, both recently recruited from the Brigham and Woman's Hospital in Boston, and have hit the ground running in establishing the Cardiovascular Research Center. Their work, centered on biochemical and cellular mechanisms in cardiovascular disease are supported by four NIH RO1 grants. Similarly, outstanding research is ongoing in the Liver Research Center under Dr. Jack Wands. Two investigators who have made important observations in the cellular pathophysiology and immunology of the hepatitis virus are Drs. Jisu Li and Shuping Tong. Their work, supported by RO1 grants from the NIH and a recent award (Dr. Tong) from the American Cancer Society, has become internationally recognized in the past few years. Many other investigators are growing their programs successfully as well.

The Department at all levels, clinical care, education, and research continues to improve each year, and I am sure that 2006 will be no exception.

Full Time and (Research) Faculty Appointments

Rhode Island Hospital *Cardiology*

Gong Xin Liu, MD
Assistant Professor (Res.)

Memorial Hospital *Hematology/Oncology*

Humera Khurshid, MD
Assistant Professor

The Miriam Hospital *Infectious Diseases*

Leonard Moise, MD
Instructor (Research)



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Dr. Jerome Larkin joins the Division of Infectious Disease



JEROME LARKIN, MD, recently joined the Department of Medicine as an assistant professor of medicine in the Division of Infectious Disease. Dr. Larkin received his MD from the Robert Wood Johnson Medical School of the University of Medicine and Dentistry of New Jersey in 1993. He completed a combined Internal Medicine/Pediatrics residency at Baystate Medical Center in Springfield, MA, serving as Chief Resident for the Combined Medicine Pediatrics Residency Program during his fourth year. After residency he worked as the Associate Program Director of the med/peds program for three years. After a brief sojourn in private practice in central Vermont, he reentered training, completing a fellowship in Infectious Disease at Dartmouth Hitchcock Medical Center in September, 2005. Prior to medical school Dr. Larkin was in the Peace Corps in Liberia and worked for a non-profit AIDS service organization in New Jersey. His wife, Sara Farley, is also a pediatrician.

Dr. Larkin's clinical interests include hospital consult medicine, mycobacterial disease, malaria (in part based on personal experience) and HIV. He is co-author with C. Ford

von Reyn of a chapter on BCG vaccine and has made a several presentations at national meetings. Dr. Larkin will play a large role in the infectious disease consult service at Rhode Island Hospital as well as work with the Combined Medicine Pediatrics Residency Program at Brown.

continued from page 1

Pediatric AIDS work in the People's Republic of China

India, and Cambodia. This reputation for excellence has attracted the attention of funders interested in expanding resources for HIV treatment. One organization interested in expanding HIV treatment resources globally is the William Jefferson Clinton Foundation HIV/AIDS Initiative (CHAI). CHAI was established in 2002 and has engaged with more than 40 countries in Africa, South America, the Caribbean, Eastern Europe, and Asia to provide resources for scaling up HIV treatment. Instead of building new infrastructure, CHAI aims to strengthen existing resources primarily by partnering with governments and non-governmental organizations that already have successful programs. Having had successful programs in several CHAI countries, Brown is well-positioned to offer our clinical and academic expertise to further the goal of sustainable HIV treatment programs. Drs. Kenneth Mayer, Timothy Flanigan, Kim Zeller (Family Medicine) and Carpenter have been working closely with CHAI's India programs and have an ambitious plan to train 150,000 physicians to provide HIV treatment services. Dr. David Pugatch (Pediatrics) and I have been asked to work with Cambodia's programs to scale-up pediatric HIV treatment through the development of a training curriculum for Cambodian clinicians.

Last spring I was also asked to contribute to the development and implementation of HIV treatment and prevention programs for children in China. Since July 15th I have spent 9

weeks visiting 7 treatment sites across China and have trained more than 100 physicians and nurses in HIV care for children. I have given 22 lectures in the context of 3 large training symposia and I have evaluated more than 150 children in one-on-one, hands on clinical training sessions.

In addition to the training I have provided, this mission has been a learning experience for me as well. This experience has greatly increased my exposure to pediatric AIDS and tuberculosis, diseases that are very uncommon in the U.S., and has enriched my understanding of the social consequences of stigmatized illness. I have also learned about the gradual dissolution of the once effective Chinese health care system through privatization, and the impact of this dissolution on diseases like HIV and TB. For example, with privatization the financial responsibility for health in China has been decentralized and provinces bear the burden of paying for medical care. However, the HIV epidemic in China is (unusually) primarily a rural epidemic, disproportionately affecting those less developed provinces with the weakest tax base that have the fewest resources available to manage this rather expensive disease. Once again the HIV epidemic is taking advantage of health-care disparities in a country undergoing a major social and economic transformation.

In the coming months I will be working to help CHAI to open up more treatment sites across China. I will also contribute to expanding programs in other countries in the region, including Vietnam, and possibly Laos and Myanmar. These efforts add to the broad scope of Brown's international activities. The support of the Department of Medicine for these activities has a truly global impact.



*1st Row: Mary Silvia RN, Lydia Ramirez, Sherry Cabrera, Dr. Carter, Karen Pope RN, Susan Nutini RN, Margarita Toro,
2nd Row: Alex Martinez, Dr. Degroot, Dr. Kwara, Cecile Martin RN*

RISE TB Clinic – The Only Specialty TB Clinic in Rhode Island

Jane Carter, MD

Tuberculosis remains the most common infection in the world; one third of the world's population is today infected with tuberculosis. A new TB infection occurs globally every second. In Rhode Island – as in the US- the case rates for active Tuberculosis have leveled; there are approximately 50 cases of TB disease in the state of Rhode Island annually, representing a case rate of 5.1 active cases per 100,000 population (2003). Approximately 50% of these cases are infectious forms (pulmonary). 75% of the patients with TB disease are foreign born. Of note, TB in US born individuals is becoming a disease of the elderly (age >65 years). These patients had been infected in their youth at a time when TB was common in the US but only become ill as the immune system ages or intercurrent medical problems contribute to reactivation. It is in the elderly population that delays in diagnosis often occur as they not longer present “the typical face of TB” to the clinician. In RI, 30% of patients with active TB were over the age of 65 at time of diagnosis (2003 data).

The RISE TB Clinic, part of the Immunology Center at the Miriam Hospital, is the only specialty clinic for TB in the state. A satellite pediatric TB Clinic is nested in the pediatric ID Clinic at Hasbro; however, children can be seen at either clinic (all active disease in children is seen in the main TB Clinic at RISE). Sponsored by RI HEALTH, the TB Clinic sees over 7000 visits per year, caring for those with TB disease, those with TB infection, and patients recently exposed to contagious cases. The TB Clinic accepts patients of all ages.

There is no “out of pocket” charge for any services offered at the TB Clinic – medications, physician fees, laboratory services. All services are provided on site. Due to the high ethnic diversity within the patient population, translator services are provided; Secretarial staff is trilingual (Spanish, Portuguese, and English). A Spanish translator is available during all patient care hours. Other language needs are met either through on site interpreters or use of telephone translation services. All services are designed to remove barriers for obtaining care for this airborne infection.

Physicians and nurses supply expert telephone consultation on questions that arise anywhere throughout the state. Suspect active cases will be seen at the next clinic session, but require a physician-to-physician telephone call for referral purposes. Assistance is provided for discharge planning of all hospitalized TB cases through phone consultation as well. This function is a critical one given the airborne nature of the disease; most patients can be managed at home even while contagious with advanced planning – home assessments prior to the patient’s discharge and evaluation/treatment of household members to prevent progression to disease in those exposed.

Complexity of cases has increased over the last decade. Patients present with a variety of complicating social, as well as medical, conditions. The staff at the TB clinic communicates closely with other health care providers – particularly focusing on the needs of HIV co-infected patients, patients requiring treatment with TNF- alpha blocking agents

(Remicade, Embrel, etc.) as well as immunosuppressed patients receiving transplants or chemotherapy. Close collaboration of all health care providers is necessary for these complicated patients at risk. Directly Observed Therapy (DOT) is supplied for all active cases in the state. DOT entails the assignment of an outreach worker to visit the patient daily during the week to administer the complex multidrug regimens required for cure as well as to screen for associated medication side effects. The benefits of the DOT outreach

program include not only an assurance that the multidrug regimens of TB care are given correctly but also the ability to reduce doses often to twice weekly – and in rare instances once weekly – therapy minimizing side effects. In addition, the presence of the outreach worker in the field allows communication between patient and physician without requiring as frequent patient visits to the clinic. This allows for an earlier resumption of routine lifestyles (work, school) and less disruption of patient lives.

The TB Clinic is responsible for the clinical care of TB patients. RI HEALTH is responsible for the public health aspects of TB control- contact tracing, the level III mycobacteriology laboratory for the state, as well as epidemiologic surveillance and reporting the CDC. Collaboration between the two branches of services has been critical to overall control of this illness in the state.

The medical staff of the RISE TB Clinic includes Dr. E. Jane Carter (Medical Director), Dr Awe Kwara, Dr. Anne DeGroot, and Dr. Phyllis Losikoff. All the physicians of the TB Clinic have international experience in TB care as well- Dr. Carter in Kenya and the Philippines, Dr Kwara in Ghana, Dr De Groot in Mali, and Dr Losikoff in Haiti.

The nursing staff of the clinic is lead by Cecile Martin (Clinical Nurse Manager) with staff nurses Mary Silvia, Susan Nutini, Karen Pope, and Beth Weindel. The clinic hours are Monday and Friday mornings, Tuesday, Wednesday and Thursday afternoons, and Tuesday evenings. The RISE Clinic can be reached at 793-2427 and is located at 14 Third Street, two blocks away from the main Miriam Hospital campus.

The RISE TB Clinic, part of the Immunology Center at the Miriam Hospital, is the only specialty clinic for TB in the state. A satellite pediatric TB Clinic is nested in the pediatric ID Clinic at Hasbro; however, children can be seen at either clinic.

New Cardiovascular Research Center at Rhode Island Hospital

Gideon Koren, MD, recently joined the faculty at Rhode Island Hospital to establish the new **Cardiovascular Research Center (CVRC)** in the Cardiology Division. Dr. Koren recruited a fellow researcher from Brigham & Women's Hospital, Ulrike Mende, MD, to jointly unravel fundamental mechanisms of heart disease and to discover novel cardiac therapies. CVRC investigators will investigate the molecular mechanisms of rhythm disorders of the heart (cardiac arrhythmias), heart enlargement (hypertrophy) and heart failure. The ultimate goal is to devise mechanism-based, new therapeutic strategies. Through an inter-disciplinary effort, CVRC investigators will apply a broad spectrum of experimental approaches to identify changes in cardiac excitation and contraction, cell signaling and gene regulation that contribute to cardiac disease. CVRC facilities will include state-of-the-art laboratories for studies in single cells and in genetically modified animal models using

cellular electrophysiology and optical mapping, heart cell physiology, biochemistry, molecular biology, genomics, and proteomics. An important goal of the CVRC is to enhance and promote education and training in molecular cardiology and life sciences. The CVRC is currently located on SWP2 and will move to its new location on the fifth floor of the Coro Center as soon as the space is completed.

DR. GIDEON KOREN is interested in understanding the pathogenesis of cardiac arrhythmias through three main lines of investigation: 1) Genomic studies to elucidate the transcriptional program(s) that control the expression of membrane polypeptides involved in determining the duration of cardiac action potential and early and late afterdepolarizations. Dr Koren group is involved in collaborative project to develop a chip that will examine the



Standing (back row) left to right: GongXin Liu, PhD; Naveed Rana, MD; Jason Centracchio; Scott Ferreira, MD; Gideon Koren, MD; Mohammad Hajjiri, MD; Ulrike Mende, MD. Standing (middle row) left to right: Hitesh Jindal, PhD; Lorraine Schofield; Lenny Chaves; Pat Mastrofrancesco

Research Awards

expression of all transcription factors in different regions of the heart; 2) Investigation of the trafficking and localization of voltage-gated potassium channels in the cardiomyocytes; and 3) Creation of genetically modified animal models for studying sudden cardiac death. Dr. Koren is studying the transcriptional regulation of Kv1.5 and Kv2.1 in order to understand the transcriptional networks that regulate cardiac-cell excitation. His laboratory is also focusing on the molecular mechanisms underlying the trafficking posttranslational modifications and turnover of Kv1.5 and KV2.1 potassium channels in the heart. His group is characterizing the macromolecular complex (channelosome) that modulates the localization and function of a delayed rectifier potassium channels in the heart. In addition, the laboratory plans to analyze and compare the phenotype of two novel models of long QT syndrome (LQT1 and LQT2) in transgenic rabbits with surface ECG; monitoring of alert, free-moving rabbits, programmed electrical stimulation (PES) of the right ventricle of anesthetized rabbits, and analyses of the biochemical and electrophysiological phenotype of rabbit cardiomyocytes derived from the epicardial, mid-myocardial, and endocardial layers of the left ventricle. The insights gained from these studies may lead to the identification of novel mechanisms and new therapies for cardiac arrhythmias and sudden death. Dr. Koren's research is funded by the NIH.

DR. ULRIKE MENDE is interested in defining the role of G proteins (GTP-binding proteins) and their regulators (RGS proteins or Regulators of G protein Signaling) for cardiac signaling and function, with a particular focus on how derangement in G protein-mediated signaling leads to cardiac hypertrophy and failure. Heterotrimeric G proteins couple receptors for many cardiac hormones and neurotransmitters to effector enzymes and ion channels that regulate cardiomyocyte growth, differentiation and contractile function. They are critical for the proper transduction of signals that are initiated at the cell surface to specific second messenger pathways inside the cell. The flow of information must be finely tuned to the cell's demand. For example, the signal transduction machinery must recover quickly to be available for the next incoming signal. The timing mechanism is provided by G proteins, which cycle between an active and inactive form. Deactivation of G proteins is accelerated by RGS proteins. RGS proteins thereby adjust the duration of the cells' responsiveness to external signals. So far very little is known about the role of this newly discovered class of proteins for cardiac signaling. Changes in the expression level, composition and function of G proteins and/or RGS proteins can lead to alterations in signaling with subsequent changes in cardiac function. Dr. Mende's laboratory uses gain- and loss-of-function approaches both *in vitro* (primary cultures of cardiomyocytes) and *in vivo* (genetically modified mouse models) to delineate the functional role of G proteins and RGS proteins. Signal transduction pathways are analyzed with biochemical approaches to measure enzyme function and second messenger levels. Physiological approaches are utilized to assess single myocytes and cardiac function. The insights gained from these studies may lead to the identification of useful new targets for pharmacological or genetic therapies of hypertrophy and failure. Dr. Mende is Principal Investigator on NIH- and AHA-funded research grants.

JANE CARTER MD, in the division of Infectious Diseases has received funding from the Henry M. Jackson Foundation for approximately \$20,000. The funds will be used to provide direct, on-site technical assistance to the Kericho District Hospital in Kericho, Kenya in developing a comprehensive/integrated HIV/TB care and treatment program.

DEVASIS CHATTERJEY, PHD, in the division of Medical Oncology has received funding for a COBRE pilot project titled 'Characterization of RKIP Expression in Human Cancers.' Approximately \$27,000 will be used to test the hypothesis that induction of Raf kinase inhibitory protein (RKIP) expression is required for the chemoresponsiveness of human cancer cells. To test this hypothesis, Dr. Chatterjey will a) delineate the mechanism that is involved in cytokine dependant loss of RKIP and b) examine the expression of RKIP in biopsied malignant human tissue microarrays. This will allow the lab to determine whether the expression of RKIP is predictive of chemotherapeutic outcome and patient survival.

MIRAN KIM, PHD in the division of Gastroenterology, has received a funding from the National Institutes of Health via subcontract from Brown University via a P20 program project grant funded under John Sedivy. These funds averaging \$115,000 direct cost per year for a 'Cancer Signaling Networks' project. The specific aims of this project are to 1) Explore the role of Wnt/ Frizzled/beta-catenin signaling pathway activation during hepatocarcinogenesis; 2) Examine what Wnt ligand expression and subsequent activation of downstream components of the beta-catenin pathway in human tumors, adjacent dysplastic tissue, and uninvolved liver and 3) Determine if blocking Wnt ligand action has anti-tumor effects in animal models of hepatocarcinogenesis. These investigations may provide novel molecular targets for Hepatocellular carcinoma.

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Department of Medicine Grand Rounds – Tuesday Mornings at 8:00 AM

George Auditorium, Rhode Island Hospital • Lecture Hall, The Miriam Hospital (teleconferenced from RIH) • Room 653, VA Medical Center (teleconferenced from RIH)

January 10, 2006: "Wegener's Granulomatosis and Microscopic Polyangiitis"

Peter A. Markel, M.D., MPH, Director, Boston University Vasculitis Center, Section of Rheumatology and the Clinical Epidemiology Unit, Associate Professor of Medicine, Boston University School of Medicine

January 17, 2006: Morbidity & Mortality Conference

Case 1: "A 20-year-old male admitted with rapidly progressive renal failure and proteinuria"

PRESENTER: Meghan Eckstein, M.D., Resident, Medicine/Pediatrics

PANELIST: Susie Hu, M.D., Nephrology

Case 2: "A 40-year-old female with history of glomerulonephritis now presenting with progressive blurry vision"

PRESENTER: Catherine Smitas, M.D., General Internal Medicine

PANELISTS: To Be Announced

January 24, 2006: Cardiology Update

"RISDI: The Rhode Island Sudden Death Initiative – Towards Reducing the Problem of Sudden Cardiac Death in our State"

Alfred E. Buxton, M.D., Director, Cardiology Division, Rhode Island and Miriam Hospitals, Executive Director, Cardiology, VA Medical Center, and Memorial Hospital of RI, Professor of Medicine, Brown Medical School

January 31, 2006: "Bariatric Surgery"

MODERATOR: David T. Harrington, M.D., FACS, Director, Surgical Intensive Care Unit, and Surgical Clinic, Rhode Island Hospital, Associate Professor of Surgery, Brown Medical School

"History and Outcomes" – Harry C. Sax, M.D., Surgeon-in-Chief, The Miriam Hospital, Professor of Surgery, Brown Medical School, Adjunct Professor of Surgery, University of Rochester School of Medicine and Dentistry

"Operations, Complications, and Rationale" – G. Dean Royce, M.D., Director, Bariatric Surgery Program, Rhode Island Hospital, Assistant Professor of Surgery, Brown Medical School

February 7, 2006: Morbidity & Mortality Conference

February 14, 2006: Hematology/Oncology Update

"Coagulation"

Anita Kestin, M.D., Professor of Medicine, Brown Medical School

"Upper GI Malignancies"

Howard Safran, M.D., Professor of Medicine, Brown Medical School

February 21, 2006: CANCELED

- The Rhode Island Hospital fully intends to comply with the legal requirements of the Americans with Disabilities Act. If any participant of this conference is in need of accommodation, please contact the Rhode Island Hospital CME office at (401) 444-4260.
- Rhode Island Hospital Continuing Medical Education has reviewed this activity's speaker disclosures and resolved all identified conflicts of interest, if applicable.

- The Department of Medicine Grand Rounds series is supported by an unrestricted educational fund as contributed by: Abbott Laboratories, Hoechst Marion Roussel, Merck & Co., The Liposome Company, Parke-Davis, Schering, Pfizer, Wyeth-Ayerst Laboratories, Eli Lilly and Company, Berlex Laboratories, AstraZeneca.