

## Clinical Research Center

The Clinical Research Center (CRC) was established in 1964, with grant support from the National Institutes of Health (NIH), to provide a facility in which Massachusetts Institute of Technology (MIT) investigators and their collaborators could apply the Institute's expertise in basic biochemical and biophysical mechanisms to the analysis of normal and pathologic processes in humans. MIT's CRC was the first federally supported clinical research center located in a university and not within a hospital, and remains one of only two or three such centers. It was anticipated that in spite of its university venue, numerous qualified physicians and clinical scientists from MIT's faculty and staff would utilize CRC to study normal volunteers, or patients with chronic diseases.

Scientists and physicians authorized to carry out research protocols using CRC facilities include professors, research scientists who work exclusively at MIT, and investigators with primary appointments in local medical institutions whose research interests overlap extensively with those of MIT investigators. Research protocols must be approved by the MIT Committee on the Use of Humans as Experimental Subjects (COUHES) and the CRC Advisory Committee before they can be implemented. The CRC Advisory Committee, chaired by Dr. Daniel Shannon, professor of pediatrics at Harvard Medical School and professor of health sciences at the Harvard-MIT Division of Health Sciences and Technology (HST), consists of 10 voting members plus nine nonvoting members from CRCs program and operating staff. The committee used to report to the principal investigator of CRC's NIH grant, Martha Gray, professor and codirector of HST. With CRC's administrative merger with the Massachusetts General Hospital's General Clinical Research Center (MGH GCRC), it now reports (for NIH grant purposes) to Peter L. Slavin, MD, principal investigator of the joint NIH grant and president of MGH. The Advisory Committee meets bimonthly to evaluate protocols for their scientific quality, experimental design, ultimate statistical validity and potential risk to human subjects. The committee also sets general policies for and reviews CRC operations.

### Administration

CRC has a dual administrative locus within MIT. As a research unit, it reports through HST to the vice president for research and associate provost, Professor Alice Gast. As a patient-care unit, CRC is part of the MIT Medical Department and reports to Dr. William M. Kettyle, the director of the Medical Department. CRC members participate in the Medical Department's activities, such as its Quality Improvement, Pharmacy and Therapeutics, Medical Records, and Safety committees.

Several years ago CRC was approached by the General Clinical Research Centers administration of the NIH, which funds this and all other CRCs, and asked us to consider becoming a "network" CRC. This would involve implementing at the MIT CRC some research projects generated at other local CRCs, and, conversely, implementing some of our projects (e.g., those involving very sick patients) at those other centers. Additionally, CRC would, where possible, coordinate the activities of the

core laboratories, nutrition programs, and nursing programs, with those of other local institutions, in order to increase their efficiency, and would use this networking as a platform from which to solicit additional common NIH grants. As a consequence, CRC successfully developed a structured relationship with the MGH GCRC in 2001. Since that time, the MIT CRC has functioned as an autonomous satellite of the larger MGH CRC. To date, 39 MGH protocols have been approved and implemented at the MIT CRC, and several MIT protocols have been implemented at the MGH GCRC. The senior program staffs at the two institutions meet monthly to anticipate and solve potential problems related to their integration. COUHES and its MGH counterpart also work together to evaluate network protocols from a safety standpoint. The MIT and MGH centers successfully collaborated on a joint NIH renewal grant application, for five years of support, which was funded, starting in December 2002. The score, reflecting the reviewers' analysis of the joint application, was the best that MIT has received for its applications.

Developing this type of "network" relationship with the MGH GCRC has allowed the MIT CRC to solve a continuing chronic problem, i.e., the small pool of medical doctors conducting clinical research in this facility, a consequence of the tendency during the last decades of MIT's academic departments not to appoint such people as professors. Moreover it has proved a source of physician scientists to collaborate with MIT biomedical scientists who hold doctoral degrees. The reputations of the two CRCs apparently are excellent, and the strengths of each institution complement those of the other. CRC also continues to "network" with other Boston-area general clinical research centers, such as Beth Israel Deaconess Medical Center, and all interested parties agree that CRC should continue to do so in the future.

### **Education**

The MIT CRC provides formal training in clinical investigation to advanced postdoctoral fellows taking a graduate degree (in clinical research) at Harvard Medical School, and to individual postdoctoral (medical) fellows working with CRC principal investigators and other researchers. These fellows and students utilize CRC's facilities to initiate research protocols and participate in ongoing projects supervised by senior investigators and faculty. (See section on the Center for Experimental Pharmacology and Therapeutics below). CRC also affords opportunities to MIT undergraduate and graduate students to participate in clinical research projects. In the spring term of 2005, Ravi Thadhani, MD, assistant professor of medicine at Harvard Medical School and an assistant program director at the MIT CRC, again taught a formal undergraduate course in clinical investigation. The course was very well received and will be offered again in spring 2006.

### **Affirmative Action**

The hiring of women and minorities continues to be a high priority commitment for CRC. The center does have one continuing problem in meeting affirmative action objectives— attracting qualified minority members. The traditional means of locating such personnel, by advertising and posting positions in local colleges, universities, medical institutions, and minority organizations, have not generated a significant response. Of the seven visiting scientists appointed by CRC in 2004–2005, four were

women and one was a minority. CRC will continue its efforts to increase the pool of qualified minority applicants as positions become available.

CRC has, however, been highly successful in recruiting women and minorities as study subjects. During 2004–2005, approximately 66% of all study subjects were women and 23% of the total study population were minorities (18% black, 2% Asian, 1% American Indian, and 2% other).

### Research Activities

During 2004–2005, CRC continued to maintain major commitments to the research activities associated with three clinical areas, each led by a senior professor. These areas were:

- *Nutrition/Metabolism*. During 2004–2005, the gas chromatography/mass spectrometry (GCMS) laboratory of the late Dr. Vernon R. Young was consolidated into the Core Laboratory of CRC. This laboratory for assaying compounds in human body fluids by GCMS has continued to develop over the past year and is now overseen by the CRC Mass Spectrometry Lab Committee, whose members are Joanne E. Kelleher, PhD, Gregory Stephanopoulos, PhD, and Colleen Hadigan, MD. In addition, the infusion team assembled in 2003–2004 and led by Dr. Colleen Hadigan has continued to conduct insulin clamp and intravenous glucose tolerance test procedures on a regular basis.
- *Neurochemistry/Neuropsychopharmacology* (Richard J. Wurtman, MD, Cecil H. Green distinguished professor and program director, MIT CRC), which studies the effects of drugs, foods, and hormones on brain composition and behavior; the effects of melatonin on sleep; and a set of diseases characterized by affective and appetitive symptoms (i.e., depression, premenstrual syndrome, smoking withdrawal, carbohydrate craving, and obesity), which relate to brain serotonin.
- *Behavioral Neuroscience* (Emilio Bizzi, MD, Eugene McDermott professor in the brain sciences and human behavior and Lee H. Schwamm, MD, associate professor of neurology at Harvard Medical School and assistant program director, MIT CRC) and *Neuroendocrinology* (Steven K. Grinspoon, MD, associate professor of medicine at Harvard Medical School, and Anne Klibanski, MD, professor of medicine at Harvard Medical School and codirector, MGH CRC). The behavioral neuroscience component now focuses on strategies for accelerating the return of various brain functions in people who have suffered strokes; the neuroendocrinology component focuses on neuroendocrine concomitants of AIDS, pituitary malfunction, and gender-dependent changes in calcium metabolism.

Groups collaborate on multidisciplinary projects such as obesity, depression, and Alzheimer's disease. The scope of CRC's activities has expanded broadly: in the past year it also supported research protocols involving, for example, toxicology, pediatrics, psychopharmacology, women's health, HIV, biomedical engineering, and diabetes.

During 2004–2005, the CRC patient census totaled 1,454 outpatient visits. NIH's General Clinical Research Center branch had provided, based on prior years' activities, support

for up to 2,172 outpatient visits. The lower-than-anticipated census could be explained by the completion of the data-gathering portions of several large projects. During the past year, CRC has not used inpatient days; protocols requiring inpatient stays are now conducted at the MGH GCRC.

### **Center for Experimental Pharmacology and Therapeutics**

The HST Center for Experimental Pharmacology and Therapeutics (CEPT), based at the MIT CRC, continues to have educational and research missions. This center, directed by Dr. Robert Rubin (HST), Osbourne professor of health sciences and technology, annually admits 10 MDs who have completed their clinical training. They enter a two-year program that provides both hands-on research experience and didactic training in clinical investigation and experimental pharmacology. At the end of this period, after passing a qualifying examination and fulfilling a thesis requirement, the graduates receive a master of medical science degree in clinical investigation from HST. A parallel program for PhD scientists is being established as well. This will involve HST, the Sloan School, the Department of Biology, and the School of Engineering, and will again be centered in CRC. Research-wise, the emphasis of CEPT has been in the application of positron emission tomography, magnetic resonance imagery, ultrasound, and other measurement technologies to the development of new drugs. With the development of imaging at MIT, these technologies will be greatly facilitated.

### **Computer Facility**

CRC's computer facility provides hardware and software support for CRC staff and investigators and statistical assistance to all researchers. The computer staff continues to develop and upgrade the CRC operations system with the addition of computer systems for CRC and its investigators. These systems use an ORACLE relational database, and support the day-to-day CRC operations. During 2004–2005, the computer staff has continued to work with their MGH counterparts to maintain and customize the Turbo software package, which has streamlined the protocol application process and NIH annual reporting requirement for both CRCs. Researchers also continue to make use of the SAS statistical software available on the CRC computer system.

### **Core Laboratory/Mass Spectrometry Facility**

The Core Laboratory specializes in assays that directly support the research efforts of CRC investigators and are not readily available commercially. The complex assays are undertaken by the Mass Spectrometry Facility, where stable isotope tracer analyses are performed. The Mass Spectrometry Facility is a shared instrument facility that allows CRC investigators to conduct human metabolic studies using stable nuclide tracers. Principal areas of investigation concern the regulation of energy substrate metabolism in health and disease, and the regulation of whole body amino acid metabolism, with particular reference to the nutritional requirements for indispensable and conditionally indispensable amino acids. Research at the MIT CRC has made important contributions to the further development of national and international dietary standards and the establishment of sound food and nutrition policies and programs. Studies have examined the role of dietary arginine as a precursor of the signal transducer nitric oxide. The novel doubly labeled water ( $^2\text{H}_2^{18}\text{O}$ ) method is being used to define the energy

requirements for adolescent and elderly subjects, and the factors, which affect these needs. These various investigations offer new basic knowledge about the physiology of human energy substrate and amino acid metabolism and, additionally, make practical contributions to problems in human nutrition.

The Core Laboratory also utilizes high performance liquid chromatography (HPLC) techniques. A Beckman System Gold Amino Acid Analyzer HPLC provides resolution of up to 42 physiologic amino acids. Other HPLC assays include tests for choline, tryptophan, the catecholamines, cytidine, and melatonin.

MIT Core Laboratory personnel are in frequent contact with their counterparts at MGH. This facilitates coordination of services and study planning (anticipating freezer space and reviewing Core Laboratory components of submitted protocols). Also, in an effort to recruit more Core Lab users, the Core Lab actively networks with other GCRC labs. The Core Lab posts a list of available assays on the national GCRC Core Lab website and a Core Lab representative attends the GCRC National Annual Conference. This networking has generated a number of Core Lab Only protocols.

## **Research Highlights**

### **Linda Bandini**

Dr. Linda Bandini and her colleagues have concluded their longitudinal study of the effect of energy expenditure on growth and development in pre-adolescent girls; however, Dr. Bandini continues to prepare and publish articles concerning this study, which sometimes requires her continued presence at CRC. During the past two years, 12 articles have been submitted to journals on various aspects of this study.

### **Emilio Bizzi and Lee Schwamm**

The Bizzi group had previously developed a computerized virtual environment-based motor retraining system for use with patients with stroke. In the current project, additional development of the system was undertaken to produce a fully interactive virtual environment (VE)-based Telerehabilitation system. This system is designed to provide motor retraining to stroke patients in their homes. Patients are connected, via the internet, to a remotely located therapist (at CRC) who then directs treatment sessions through software on the patient's home computer. This connection is accomplished using commercially available residential high-speed internet providers. We are the first group to succeed in implementing such real time VE training over the internet in a home environment.

The special software they have developed makes use of a VE to provide augmented feedback to the patient during the motor retraining exercises. The exercises are displayed by a virtual "teacher" on the computer screen in the patient's home via a series of "scenes." Each scene is a 3-D picture in the VE designed to suggest a functional task or goal. The scenes provide a way to adjust task difficulty for the patient and to customize a practice sequence during training. The training session can be semiautomated by using a "script" feature, which allows a sequence of scenes and related training options to play automatically one after the other, in effect simulating a



typical rehabilitative therapy session. In addition to the VE program, displayed on one monitor, a second monitor allows the patient and therapist to see and hear each other, similar to a standard videoconference set-up.

During 2004, they completed the clinical feasibility testing of the system on 12 subjects with stroke (30 sessions/subject) and a four-month follow-up evaluation of those subjects. The experience in patients' homes has also allowed them the opportunity to solve a variety of logistical and technical problems that were encountered in trying to implement the use of the Telerehabilitation system in a home environment.

The subjects have shown improvements in their motor performance, as measured both by standard clinical tests and by quantitative kinematic measures derived from 3-D motion tracking data collected during behavioral tasks performed with the upper extremity. The improvements suggest that VE training conducted remotely over the internet is feasible and may be a viable new method for neurorehabilitation. More importantly, results indicate that subjects can generalize motor training received in a virtual world to real world performance. Gains made during therapy appear to be retained or even increased at four-month follow-up. The results also support the findings of others that many stroke patients can continue to demonstrate improvements in motor performance when provided additional treatment, despite being many years post infarct.

### **Steven Grinspoon**

Over the past year, substantial progress has been made by Dr. Steven Grinspoon's group in three key areas. First, Dr. Grinspoon and Dr. Hadigan continue to investigate the mechanisms and consequences of lipodystrophy in HIV-infected patients. The group has published on the effects of exercise and metformin on body composition, demonstrating critically important effects of exercise to reduce intramuscular adiposity. In addition, the effects of increased visceral adiposity and excess free fatty acids on growth hormone were investigated using acipimox. Increased free fatty acids were shown to contribute to low growth hormone (GH) in this population. Body composition studies performed at MIT demonstrated that use of a GH-stimulating analogue, growth hormone releasing hormone (GHRH), resulted in relative redistribution away from the abdomen and toward the extremities. In a final set of studies, Dr. Grinspoon is investigating the effects of a novel strategy to reduce inflammatory indices and improve cardiovascular risk indices in patients with the metabolic syndrome using an anti-tumor necrosis factor medication. Working with Dr. Elizabeth Bernstein, winner of the 2004 Lilly Endocrine Scholars Award, Dr. Grinspoon pursued a new strategy to improve metabolic indices in this emerging population of patients.

### **Colleen Hadigan**

Dr. Colleen Hadigan, whose previous investigations here evaluated the utility of insulin-sensitizing agents for HIV lipodystrophy, is currently conducting a randomized, placebo-controlled trial investigating the benefits of extended lipolytic blockade to treat hyperlipidemia and insulin resistance in patients with HIV infection.

**Ravi Thadhani**

Dr. Ravi Thadhani and his group have continued to examine hypertension and diabetes in pregnancy. Hypertension and diabetes represent the most common medical complications of pregnancy, affecting some 500,000 women each year. The cause for each of these conditions remains unclear. Importantly, most pregnancy-related studies have been cross-sectional in design, tremendously limiting any conclusion about potential causal mechanisms. In 1999, this group initiated a prospective cohort study of pregnant women, collecting blood and urine samples in the first and second trimester of pregnancy. To date, this study (based at MGH) had enrolled more than 10,000 women (one of the largest studies of its kind in the world), yielded more than 25 original manuscripts and over 35 abstracts, funded four investigators by such agencies as NIH, the American Heart Association, and the American Diabetes Association, and has been the centerpiece of collaborations with Harvard School of Dental Medicine, the Channing Laboratory, Beth Israel Deaconess Medical Center, University of Pittsburgh, University of California at San Francisco, National Institutes of Child Health and Disease, and the National Cancer Institute. The primary goal of this research is to understand alterations that antedate clinical disease in pregnancy; hence the group has focused on alterations in the first trimester that identify those at risk for adverse outcomes later in pregnancy. The focus has been on metabolic alterations, inflammation, and alterations in angiogenesis evident in the first trimester, and important interactions between these alterations have been discovered. Finally, this group brings a subset of women (more than 150 to date) back to the MIT CRC one year after pregnancy and has begun to uncover alterations in insulin resistance and angiogenesis that persist one year postpartum, which may explain why these women develop hypertension and diabetes in future years.

**Richard Wurtman**

Dr. Richard Wurtman and his colleagues have continued to examine the effects of drugs, foods, and hormones on brain composition and behavior. Pharmacokinetic studies continue to be performed on compounds, in advance of using these compounds, to study behavioral or physiological mechanisms. These are melatonin, 5-hydroxytryptophan (5HTP), and uridine monophosphate (UMP).

Drs. Judith and Richard Wurtman and their associates previously showed that administering a mixture of carbohydrates to people with mild premenstrual syndrome (PMS) can ameliorate such symptoms as anger, emotional instability, diminished cognitive functions, and “carbohydrate craving,” and can also suppress the weight gain often associated with the premenstrual period in such patients. The carbohydrate mixture used provides three types of carbohydrates: glucose, which is metabolized rapidly; maltodextrin, which takes longer to metabolize; and potato starch, which takes the most time. The carbohydrates produce their behavioral effects by eliciting insulin secretion, and the insulin enhances the uptake of the amino acid tryptophan into the brain (by lowering blood levels of other amino acids, such as the branched-chain compounds leucine, isoleucine, and valine, which compete with tryptophan for passage across the blood-brain barrier). The level of brain tryptophan, in turn, controls the rates at which brain neurons produce and release the neurotransmitter serotonin, which underlies the mixture’s therapeutic effect.

During this past year, studies have been initiated, and extended, on two other possible uses for such mixtures—“winter blues” (or subclinical seasonal affective disorder syndrome) and stress-related overeating leading to obesity. Both of these disorders were previously shown to respond positively to drugs that increase intrasynaptic serotonin, thus both might be considered candidates for nutritional mixtures that also raise serotonin. The studies are still in progress.

### **CRC Investigator-initiated Programs**

Three investigator-initiated programs continue to contribute to CRC. In addition to fulfilling their scientific goals, these programs also provide opportunities for increased collaboration between the MIT and MGH CRCs.

The Program in Nutrition and Metabolism, directed by Steven Grinspoon, MD, is investigating the relationships among nutrition, body composition, and hormonal function. One of the program’s chief therapeutic targets is HIV-lipodystrophy, which involves potentially unhealthy redistribution of body fat and changes in blood lipid levels that are often found in persons affected with the virus that causes AIDS.

The Program in Women’s Health, directed by Judith Wurtman, PhD, was established to study psychological and neurochemical aspects of PMS and menopause. This effort will hopefully identify promising leads for new treatments for the discomfort that may accompany these normal components of the human female life cycle.

The Program in Applied Technology and Communications in Healthcare, directed by Lee Schwamm, MD, seeks to develop new avenues for healthcare delivery through the strategic application of novel technologies. The program targets areas where barriers exist to the clinical implementation of evidence-based medicine, and seeks out technological solutions to overcome these barriers. Focus areas include low-bandwidth transmission of medical multimedia content for education or decision support, high-bandwidth interactive medical evaluation or therapy, and wireless and handheld extensions of conventional bandwidth applications.

**Richard J. Wurtman**

**Director**

**Cecil H. Green Distinguished Professor of Neuropharmacology and Health Sciences and Technology**

*More information about the MIT Clinical Research Center can be found online at <http://web.mit.edu/crc/www/>.*