Summer 2006

healthpoints

ALL THE POSSIBILITIES OF MODERN MEDICINE

Columbia University Medical Center
Department of Surgery
NewYork-Presbyterian

Jean C. Emond, MD
Vice Chairman and Chief of Transplantation at NewYork-Presbyterian/ Columbia University Medical Center

When Dr. Emond joined the faculty in 1997, he applied a multidisciplinary model to the liver transplant program, and established a joint collaboration between hepatology and surgery. In the decade since then, the program has transformed into one of the largest and most innovative in the country. His dedication to finding new and better solutions for transplant patients continues to raise the bar of excellence and inspire creative advances throughout the transplantation programs at Columbia University Medical Center.

Innovations in Time

1969

Joseph Buda, MD, performs the first kidney transplant at Columbia-Presbyterian Medical Center.*

Kidney Transplantation, page 3

1977

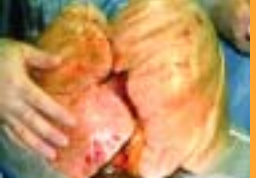
First heart transplant at at Columbia-Presbyterian Medical Center.

Heart Transplantation, page 10

1986

Lung transplantation begins at Columbia-Presbyterian Medical Center.

Lung Transplantation, page 5

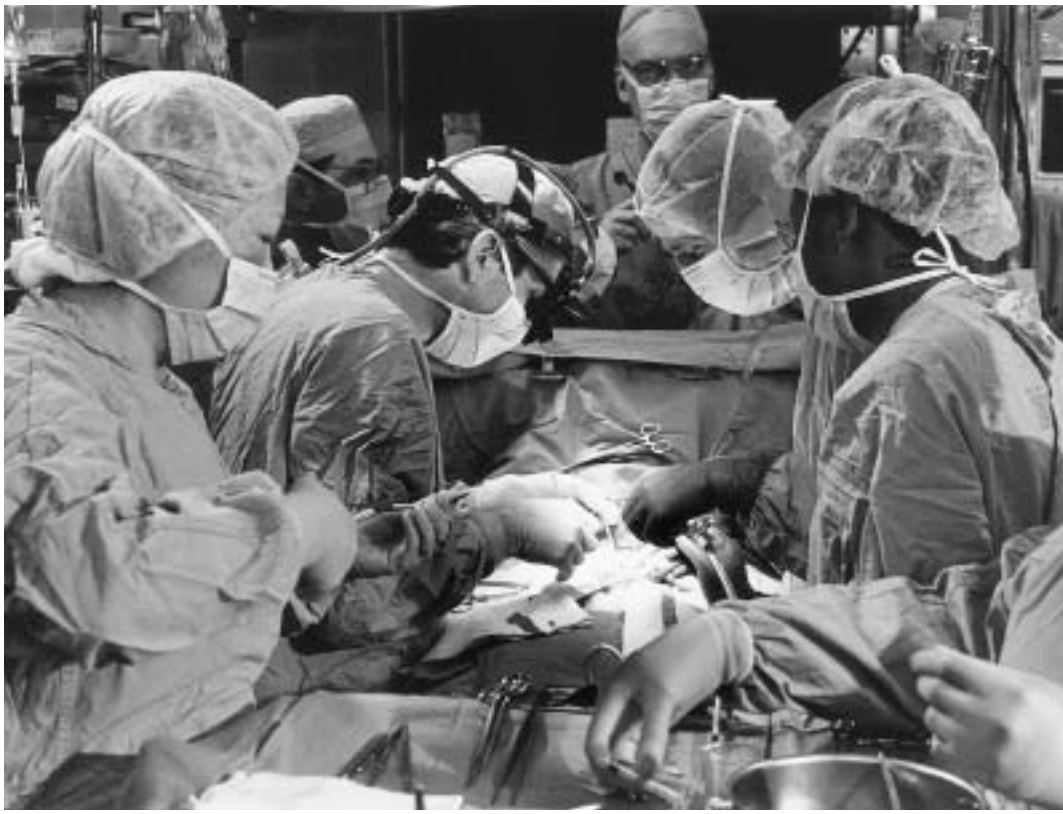


Transplantation:

Where we've been, where we're going

When he transplanted a chimpanzee kidney into a human patient in the late 1960's, the late **Keith Reemtsma, MD,** then Department of Surgery Chairman at Tulane University, revolutionized treatment of end-stage organ failure and initiated an era of unprecedented exploration into organ transplantation that would affect the lives of patients around the world.

Transferring to Columbia-Presbyterian Medical Center in 1971, Dr. Reemtsma recruited **Mark A. Hardy, MD**, who laid another cornerstone of organ transplant medicine by founding the program for dialysis and kidney transplantation. Dr. Hardy based the new program on the principle of collaborative clinical care between surgeons and nephrologists. During a time when renal transplant programs were managed by one or the other discipline but never by both simultaneously, the medical



Eric A. Rose, MD, left center (current Chairman, Department of Surgery), performing the first successful pediatric heart transplant in 1984. This special issue of *healthpoints* is dedicated to transplant pioneer Keith Reemtsma, MD, who is overseeing the operating field (top of photo).

Innovations in Time

1997

National search assembles team to establish Center for Liver Disease and Transplantation, for adults and children.

Liver transplantation, page 8

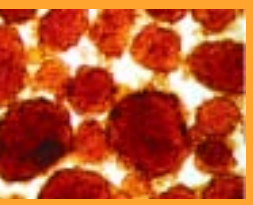
2004

Intestinal Rehabilitation and Transplantation program opens at NewYork-Presbyterian/Columbia.

Pediatric intestinal and liver transplantation, page 5

2004

First pancreatic islet cell transplantation at Columbia.



2005

NewYork-Presbyterian Hospital sets U.S. record for number of heart transplants performed in one year, at 119.

2006

First 3-way kidney swap at NewYork-Presbyterian/Columbia.

** In 1998, Columbia-Presbyterian Medical Center and New York Hospital merged to form NewYork-Presbyterian Hospital.*

community regarded the concept as folly. Yet the program grew steadily, as did the program's *immune tolerance* research initiatives to induce the transplant recipient's body to accept a donor organ. This multidisciplinary cooperation also led to major contributions in immunogenetics, immunosuppression, and treatment of autoimmune diseases and lymphoma — and it ultimately became the overarching principle for all the NewYork-Presbyterian Hospital transplant services.

Colleagues universally give credit to **Eric A. Rose, MD,** who co-founded the heart transplantation program with Dr. Reemtsma, for his successful transformation of the program into the outstanding center it is today. A parade of achievements marks the history of the heart transplant program, including the first mechanical bridge-to-transplantation using intra-aortic balloon pumps in the 1970's, and the first successful pediatric heart transplant, performed by Dr. Rose in 1984. Under the guidance of Dr. Rose and his successors, the program has pioneered research in immunosuppressant medications, mechanical assist devices, and minimally invasive surgical procedures. It currently performs over 100 heart transplants yearly, with among the highest success rates in the nation.

In 2004, **Dominique M. Jan, MD,** created a new rehabilitation and transplant service for children with liver and small bowel diseases, also in a fully interdisciplinary fashion. Its team approach is unique in the U.S., combining the efforts of pediatricians, hepatologists, and liver transplant surgeons. "Every problem is discussed by both pediatric specialists and surgeons, and this gives patients the best results," says Dr. Jan.

Also in 2004, **Lloyd E. Ratner, MD,** succeeded Dr. Hardy as director of the renal and pancreas transplant program. One of the first to perform laparoscopic donor operations, Dr. Ratner has found creative solutions to overcome immune barriers to kidney transplantation. The program now routinely uses extended-criteria donor organs, performs transplants among incompatible donors, and is a leader in coordinating "donor swaps" to maximize availability of compatible donor organs. Since Dr. Ratner's arrival, this program has doubled its volume, performing over 300 kidney transplants per year.

Under the leadership of Dr. Hardy and **Kevan Herold, MD**, Columbia has been designated one of ten regional islet resource centers in the U.S. that isolate and transplant pancreatic cells to treat type 1 diabetes as part of a limited protocol controlled by the FDA. Recent progress in visualization of pancreatic islets using PET technology, under the guidance of **Paul Harris, PhD**, has been recognized by the scientific community as a milestone in this developing field.

While the transplantation program as a whole forecasts over 600 solid organ transplants this year, transplantation of cells, rather than organs, is emerging as a therapy with enormous potential. Transplantation of either a patient's own or a foreign donor's bone marrow cells, for example, offers hope of regenerating the heart so that patients with heart failure may be able to avoid heart transplantation. The SCCOR trial, a pivotal NIH-funded study including cell transplantation in patients with heart failure, is enrolling patients now.

In introducing the transplantation programs, it would be remiss to neglect mention of the yet another dimension in which they excel – education. "Because this is an academic medical center, physician training is a top priority along with patient care and research," says Dr. Rose. "We have trained many of the greatest transplant surgeons over the last 20 years, including many of the leaders of transplant programs throughout the U.S."

This special issue highlights just a few recent exciting developments in transplantation research and patient care. Readers can learn more by visiting www.columbiatransplant.org or by calling the department.

Kidney Transplantation: Thinking Outside the Box

Kidney transplantation has come a long way since the first successful transplant between identical twins in 1954. Since then, improvements in surgical technique, medical management, and immunosuppressive therapy have facilitated transplants from family members, genetically unrelated living donors, and deceased donors. In 2005, over 16,400 kidney transplants were performed in the U.S., approximately 60% from deceased donors and the remainder from living donors. Success rates have increased steadily, and now exceed 90% at one year and 50% at ten years. Despite this extraordinary success, however, many challenges remain.

Topping the list is the chronic shortage of organs, which creates dilemmas about fairly allocating kidneys to patients with varying degrees of need, risk, and potential benefit. Another major challenge is medical in nature – finding safe and effective ways of overcoming the body's natural tendency to reject the new kidney. At NewYork-Presbyterian Hospital/Columbia University Medical Center, the Renal and Pancreatic Transplantation Program is leading the nation in addressing both of these critical areas. "Our goal is to successfully transplant as many patients as possible so they can return to normal, productive lives," says **Lloyd E. Ratner, MD,** *Director*. "We are not content to accept the status quo."

Meeting the challenge of organ shortage

To meet the high demand for donor organs in the New York metropolitan area, the program has developed new ways to safely use more organs than ever for transplantation. First, it has implemented new protocols for using *extended criteria* organs that may not meet the usual criteria for transplantation, but are healthy enough for a successful transplant. Donor kidneys that might go unused in regions with fewer people on the organ waiting list can be matched with appropriate candidates in areas with greater demand, according to Dr. Ratner.

Organs in this category include those from donors who are older, have hypertension or diabetes, or who at the time of their death suffered mild kidney injury. As is the case with heart, liver, and lung transplantation, the use of extended criteria kidneys is proving highly successful, especially among older recipients and those doing poorly on hemodialysis.

Second, the program has developed strategies to address immunologic issues that, until recently, were thought to preclude transplantation. Using new methods to "clean" mismatched antibodies from the recipient's blood, the program now performs *incompatible donor* transplantation of kidneys into recipients whose immunologic makeup would normally result in rapid rejection of the new organ. The long-term survival rate for incompatible transplants is exactly the same as for compatible transplants at NewYork-Presbyterian/Columbia, one of of the few institutions in the world offering this option today.

To further maximize transplant

continued on page 9

Courtesy of Biomedical Communications

In many cases of living donor transplantation, family members donate organs to their loved ones. In the case of the rare three-way kidney swap performed May 30, 2006, altruistic donor John McGuinness did not know any of the recipients, but just wanted to help.

Public service is a way of life for John, who came from a family with a strong background in volunteer work. Today he volunteers as a firefighter and as a wrestling coach, serves in his church, and regularly donates blood. Yet he wanted to do even more, and after a fellow firefighter and friend of ten years died in Iraq, John decided to give someone else the gift of a new life.

He contacted the living donor kidney transplant program at Columbia in February 2006. By April, there was a match. The recipient was so ill that dialysis no longer worked, and there were no other options left. John gave his left kidney, and in so doing, facilitated the swap that enabled three recipients to be matched with three compatible donors.

For John, donating his kidney was not too much to do for a stranger. "There are thousands of people on the waiting list, but very few receive a deceased-donor kidney each year," he says. "These are average people who will die if they don't get the organ they need. So why not give someone a whole new way of life? If other people knew they could step up to the plate and do living donor transplantation, so many other people could be helped too."

Transplantation for Short Bowel Babies

When Kyle was 14 months old, he had no functional intestine. His duodenum was so short it did not reach the skin, and had to be surgically vented through the stomach. The parents had sought multiple opinions at other centers, and were advised he needed both an intestinal and a liver transplant.

Despite assertions by Kyle's previous physicians that he would not survive without both intestinal and liver transplants, the team at the Pediatric Intestinal Rehabilitation and Transplant program was able to complete an isolated intestinal transplant while saving his liver. "Today he is doing very well," reports **Steven J. Lobritto, MD,** *Interim Chief of Pediatric Gastroenterology.*

Kyle Cramer (center) **received an intestinal transplant at age 14 months in October 2005 and no longer needs TPN (total parenteral nutrition). Kyle is flanked by surgeon Dominique Jan, MD** (far left)**, Kara Ventura, NP, and his parents, Cara and Ben Cramer.**

This scenario is emblematic of the way the program defies the odds on a regular basis, performing heroics in a field not always known for great optimism. Under the direction of **Dominique M. Jan, MD,** *Professor of Clinical Surgery,* the program offers a unique method of independent management of children with intestinal failure and liver disease. Its strength lies in a comprehensive team approach: a multidisciplinary group including a pediatric surgeon, a transplant surgeon, gastroenterologists, hepatologists, nutritionists, and nurse practitioners, works together to determine the best course of treatment for each child. According to Dr. Jan, "This team approach results in far superior care than is available at centers that rely on a surgical or medical approach alone."

Intestinal rehabilitation

Most children with Short Bowel Syndrome (little or no functional intestine) have to be nourished by total parenteral nutrition (*TPN*, or nutrition through an intravenous line), which can contribute to the development of liver failure. The center has special expertise in minimizing this risk, says Dr. Lobritto. "Proper management of the nutritional balance in TPN is one of the most important keys in preventing liver damage. With proper balance of nutrients, it is often possible to avoid both liver and intestinal transplantation, and to even encourage oral feeding."

"We make every effort to use the intestine that a patient has left, and give the patient a chance to adapt," explains **Robert A. Cowles, MD**, *Assistant Professor of Surgery*. When nutritional rehabilitation is not sufficient, however, the program provides the full spectrum of surgical options. Some children may be candidates for the Serial Transverse Enteroplasty procedure (STEP), an operation to lengthen and reshape a segment of intestine into a longer, thinner intestine. Dr. Jan, who has performed many intestinal transplants worldwide, emphasizes that "if patients with short bowel syndrome receive proper treatment early on, many complications — and potentially the need for intestinal or liver transplantation — can be avoided."

Biliary atresia

In children with biliary atresia (a congenital defect of the bile duct that prevents the liver from excreting bile), emergency surgery called *porto-enteros-*

continued on page 12

Lung Transplant Surgery

René Perez

Since Drs. Selim M. Arcasoy and Joshua R. Sonett were recruited to lead the Lung Transplant program five years ago, success rates have soared dramatically. Survival rates for lung transplant patients at Columbia are 93% after one year, and 78% after three years, which far surpass the national average of 79% and 62% respectively.

Combating organ rejection

Highly effective treatments can successfully protect patients against the threat of the acute form of rejection that occurs immediately after transplant surgery. Yet even the best medical therapies are powerless against the tide of chronic rejection, which slowly and steadily undermines the health of over half of lung transplant patients during the first three to five years after transplantation. Since chronic rejection may lead to the demise of transplanted lungs in five to ten years, and is the leading cause of death among lung transplant recipients, it is "the major Achilles heel in lung transplantation," according to **Joshua R. Sonett, MD**, *Surgical Director* of the Lung Transplant program.

Frank D'Ovidio, MD, PhD, *Assistant Professor of Surgery* in the Section of Thoracic Surgery and the Lung Transplant program, has shed light on the role of gastro-esophageal reflux (GER) as one of the causes of chronic lung transplant dysfunction, and/or chronic rejection.

Many people think of "reflux" as an annoying condition that can be treated with anti-acid medications. But for patients who undergo lung transplantation, reflux may be a far more serious problem because it can expedite the body's rejection of the transplanted lung. It has been recognized since the 1990's that GER contributes to the deterioration of lung tissue among lung transplant recipients. Until recently, however, no studies defined the way in which GER might actually lead to chronic lung rejection, or established which patients would truly benefit from anti-reflux surgery (known as gastric fundoplication).

Among those patients who experience GER (the passage of fluid from the stomach upward into the esophagus), some also aspirate the refluxed fluid into the lungs. Although not all lung transplant patients with GER aspirate, those who do usually remain unaware of this danger because it occurs in small quantities and causes no unique symptoms. Chronic micro-aspiration of gastric content as bile acid is toxic to lung tissue, creating an inflammatory process and possibly disrupting the innate immune system (which normally responds to the presence of infectious agents, dusts, and allergens in the environment). "The ongoing inflammatory state induced by chronic micro-aspiration is likely to cause an earlier development of chronic rejection," says Dr. D'Ovidio.

By testing samples of patients' broncho-alveolar lavage fluid collected during bronchoscopies after transplantation, Dr. D'Ovidio is the first researcher to confirm an association between the presence of bile acid in the airways as a marker of and toxic agent in GER, and clinical outcomes among lung transplant patients. He found micro-aspiration of bile acid to be a predictor of early chronic lung transplant dysfunction. Also known as *bronchiolitis obliterans syndrome*, chronic lung dysfunction has been considered a clinical indicator of chronic rejection.

"The documentation of the relationship between aspirated bile acid and bronchiolitis obliterans syndrome validated previous observations that GER could contribute to chronic lung rejection. In fact it provides evidence that GER is truly a problem for some lung transplant recipients," explains Dr. D'Ovidio.

Moreover, Dr. D'Ovidio's research has provided a potentially far more useful diagnostic test in the lung transplant context than has been available to date. Until now, tests to detect reflux have relied on pH-testing methods. These detect stomach acid reflux, but miss the *non-acid* type of reflux that can occur with bile acid. Most importantly, pH testing misses the most dangerous aspect of reflux for lung transplant recipients – the aspiration. "Not all patients with reflux end up aspirating," says Dr. D'Ovidio.

Various lung transplant centers have been performing Nissen fundoplication, a relatively safe, laparoscopic anti-reflux surgical procedure, in the majority of their lung transplant patients with GER. This treatment has likely helped to curtail chronic rejection in some patients, says Dr. D'Ovidio, but "not every lung transplant patient with GER needs to have surgery." The lung transplant program is now developing protocols to routinely test patients for aspiration about three months post-transplant. Testing is done via broncho-alveolar lavage during rou-

continued on page 11

PET at the Click of a Mouse

While patients used to arrive at their doctor's office holding large envelopes of films and pictures, today they can come with a CD of digital images. But as is the case with much computer technology, standardization is lacking among the systems used to create the data, so that in some cases, doctors may not be able to view test results taken at another facility. "Many programs out there are very difficult to use," says **Paul F. Simonelli, MD, PhD, FCCP**, a pulmonologist and *Assistant Professor of Clinical Medicine* in the Division of Pulmonary, Allergy & Critical Care at the Columbia University College of Physicians and Surgeons.

But for physicians referring patients to Columbia for PET or PET/CT, this is not a problem. As of 2005, the Columbia Kreitchman PET Center has adopted an advanced system for viewing PET and PET/CT scans. Because the Philips iSite Stentor system is web-based, physicians can access it anywhere, anytime, and from any computer, via the Internet.

Using the Kreitchman PET Center's iSite Stentor system, Dr. Paul Simonelli can access all of the slices of his patients' PET/CT scans from his desk.

"Stentor has revolutionized how we communicate with referring physicians and how these same physicians communicate visually and verbally with their patients," says **Ronald L.Van Heertum, MD**, *Professor of Radiology*, Columbia University College of Physicians and Surgeons, and *Director, Columbia Kreitchman PET Center.*

For doctors, the system has markedly improved the way they can view PET or PET/CT images, translating to vastly improved accessibility, readability and flexibility. For patients, Stentor means better treatment. For example, using a laptop with Internet access, physicians can import scans during conferences about patient treatment and progress. "Important treatment decisions are made in these conferences, so it's ideal to have everyone — the oncologist, the radiation oncologist, the surgeon, and the pulmonologist — viewing the image at the same time," says Dr. Simonelli.

Dr. Simonelli uses Stentor to view his lung cancer patients' PET/CT scans. PET (positron emission tomography) visualizes chemical activity, which is elevated in the presence of any cancer, and CT (or CAT) scans visualize the body's anatomical structures. PET/CT fuses these images into a single, overlapping picture that shows precisely where the cancer is located.

PET and PET/CT capture three-dimensional pictures that are viewed in cross sections known as "slices." Previously, hard copies of selected slices were delivered to the physician a few days after the patient's scan. If the physician wanted to view all of the scan slices, he was compelled to visit the scanning facility. Stentor now provides all slices as soon as the scan is complete. Accessing them on his computer, the referring physician is able to easily navigate through these images and compare them. "You're in essence creating a 3-D picture that you can scroll through and manipulate," says Dr. Simonelli.

When patients come to the Kreitchman PET Center for a scan, the technician saves the images to a server under the referring physician's name. At that point, they become immediately available for the Columbia or outside referring physician to access by logging on to the Center's iSite Stentor server with a password. No special software beyond a browser is required, and physicians can access the system in the office, in a conference room, or at home. Navigation buttons and tools to manipulate and store copies of the scan appear when the program is opened in the browser.

"When people talk about 21st century medicine, this is it," says Dr. Simonelli.

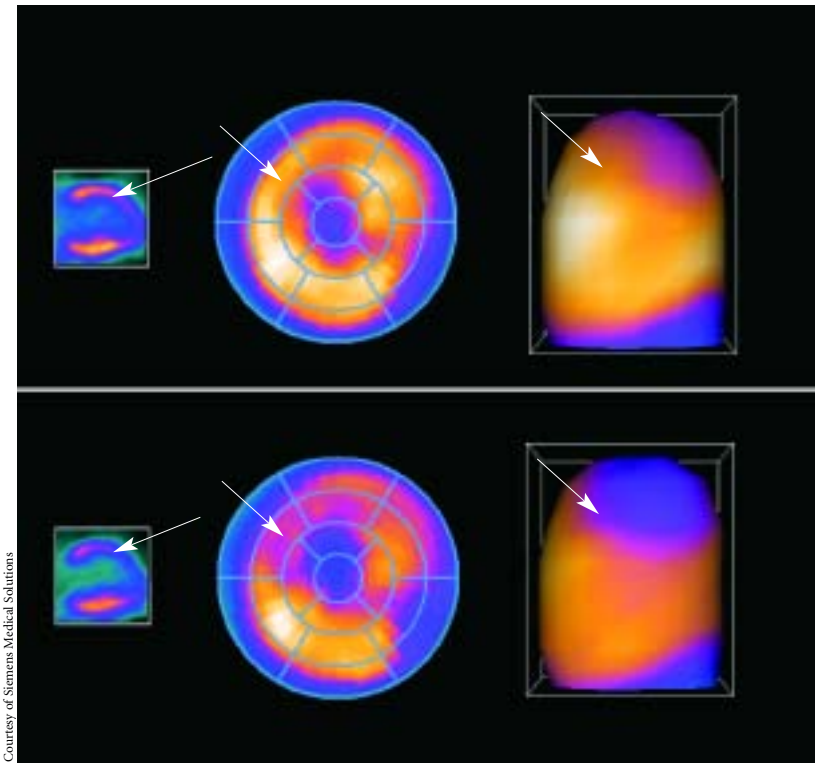
If you are a physician and would like to set up a Stentor account with the Columbia Kreitchman PET Center, please contact Judy Parenta at 973.650.2133.

A Second Chance for the Ailing Heart

Advances in biomedical technology are making organ transplantation safer and more effective. For some, it is even helping to avoid the need for transplantation altogether. Patients with severe coronary artery disease may become candidates for heart transplant when prolonged nutrient and oxygen deprivation due to blocked arteries has killed portions of their heart muscle. But using PET (positron emission tomography) imaging to detect cardiac viability can offer these hearts a second chance.

When an area of the heart is starved of blood by a blocked artery, the heart muscle (or myocardium) in that area dies and forms scars. If enough of the heart muscle has been compromised in this way, the organ can no longer do its job of pumping blood through the body. Decreased blood flow doesn't always kill myocardium, however. It can also simply render portions of the heart muscle dormant. Often referred to as "hibernating myocardium," such living muscle is under-active, but can be revived by procedures to restore blood flow (revascularize) such as coronary artery bypass or angioplasty and stenting.

But first, hibernating myocardium must be properly detected. Routine tests that measure the amount of blood flow (perfusion) to the heart, such as the thallium test, can underestimate the amount of hibernating myocardium that is present. PET, with its ability to detect cell metabolism, can distinguish the faint activity of dormant heart muscle. For this purpose, PET is recognized as offering the highest accuracy level of any non-invasive cardiac test. "In analyzing a given area of the myocardium, a PET scan will reveal living cells in 40% of patients whose thallium test showed no living tissue," Says **Sabahat Bokhari, MD**, *Assistant Professor of Medicine*, and *Director of Cardiac PET* at the Columbia University Kreitchman PET Center. In addition to being more precise, PET is safer than other nuclear cardiac scans because the radioactive "tracer" compounds administered during PET scans are short lived (or have a short half-life), remaining in the body for a much briefer amount of time.



Courtesy of Siemens Medical Solutions

HIBERNATING HEART MUSCLE
An FDG PET scan (top) **indicates there is living muscle in a place where a blood flow scan** (bottom) **shows there is little circulation.**

Before undergoing a PET scan for myocardial viability, patients receive an injection of a radio-labeled glucose compound called FDG that can be tracked by the PET scanner. Glucose (a form of sugar) is required by the body's cells for nutrition, and the FDG taken up by the tissues appears on the PET scan as areas of increased brightness. Scar tissue in the myocardium, where there is no living activity, appears dark. Hibernating myocardium, meanwhile, appears brighter. With such a picture, the cardiologist is in a position to make an informed decision about whether the patient requires heart transplant, or whether they would benefit from a revascularization procedure. Furthermore, the scan can assist the physician in deciding which type of treatment will be right for the patient.

For a PET cardiac viability referral, please contact your cardiologist. For more information, call the Columbia Kreitchman PET Center at 212.923.1555.

The Centers for Medicare and Medicaid Services (CMS) currently has approved reimbursement for cardiac PET scans in patients with cardiovascular disease. Some private insurers also cover cardiac PET on a case-by-case basis. Cardiac PET is used to:

- *Delineate* blood-flow patterns
- *Assess* the viability of heart muscle
- *Determine* the optimal treatment path — identifying whether a patient is a candidate for coronary angioplasty, coronary artery bypass graft surgery, or heart transplantation.

Living Donor Liver Transplantation Saves Lives

Because of the manner in which the national organ donation system is organized, some regions, such as the New York tri-state area, have longer waiting lists than others. As a result, patients in New York face longer waiting times for deceased-donor organs, and consequently, a higher risk of dying while on the waiting list. At this time there are eight patients on the waiting list for every available liver – and many patients are considered too sick or too old to even get a place on the list. To address this serious shortage, the **Center for Liver Disease and Transplantation** (CLDT) is pioneering methods of increasing access to liver transplantation.

Living donor liver transplantation offers one solution. In this procedure, a healthy adult undergoes a surgical procedure to remove part of his or her liver. The donated portion is then transplanted into a blood-type compatible adult or child with end-stage liver disease. For an adult transplant, up to 60% of a donor's organ may be removed, while a child's transplant may require 20-25% of a donor's liver tissue. In some cases, family members or friends choose to donate a portion of a liver, which saves a patient from having to wait on the list for a donor.

Although some potential donors are reluctant to take the risks associated with donation, the risks are low, according to **Jean C. Emond, MD**, *Chief of Transplantation.* The donor's liver regenerates to its original size in several weeks, and donors are able to return to normal activity in about a month. Dr. Emond, a member of the team that performed the first living donor liver transplant in the United States, in 1989, brings the perspective of nearly 20 years of experience with living donation to the center.

CLDT is a lead center among the nine participating in the Adult to Adult Living-donor Liver Transplant (A2ALL) study, a seven-year trial funded by the NIH to investigate the outcomes of living donor liver transplantation. "Data indicate that by using living donor liver transplantation, centers may reduce patients' risk of dying by 20-40%," says **Robert S. Brown, Jr., MD, MPH**, *Chief of the Center for Liver Disease and Transplantation.* "It is not that living donor transplantation is a better operation, but it improves access to transplantation."

Milan Kinkhabwala, MD, FACS, *Surgical Director of the Living Donor Liver Transplant Program,* is careful to note that at this center, living donor transplantation is "facilitated, but never pushed." An Independent Donor Assessment Team (IDAT) performs medical evaluations of every potential donor, educates them about the procedure, and serves as a dedicated donor advocate. Even when a parent is considering donation to a child, a separate doctor assesses the parent in order to protect his or her best interests. "We are especially vigilant about ensuring that there is no coercion involved in the donor's decision," he adds. The recipients' insurance pays the costs involved with evaluation, education, and donation.

To provide yet another method of increasing access to liver transplantation, **John F. Renz, MD, PhD**, *Surgical Director of CLDT*, specializes in "extended criteria" transplantation, or the use of organs that don't meet the usual criteria for transplantation due to various health problems, but are still healthy enough for a successful transplant. Dr. Renz explains that "EDC recipients accept a slightly higher risk of a donor-transmitted disease, but EDC livers are used in patients who are not as sick as those who receive optimal organs." Regular and EDC liver recipients have equivalent survival rates.

In addition to the A2ALL study, about 40 other studies related to liver function are underway at this center. A number of these address hepatitis C, which is the leading indication for transplantation and a major cause of organ failure after transplantation.

In a living donor liver transplant, the donor gives up only a portion of his liver. Within several weeks, the organ will regenerate until it reaches full-size in both the donor and recipient.

To learn more about the Center for Liver Disease and Transplantation, please visit www.livermd.org.

WARM WELCOME TO NEW SURGEONS IN THE CENTER FOR LIVER DISEASE AND TRANSPLANTATION

Sarah Bellemare, MD
Assistant Professor of Surgery
Dr. Bellemare specializes in laparoscopic liver surgery, living donor liver transplantation, and hepatobiliary and pancreatic surgery.

James V. Guarrera, MD
Assistant Professor of Surgery
Dr. Guarrera brings expertise in liver and kidney transplantation and hepatobiliary surgery. His research interests are in organ preservation, ischemia, and reperfusion injury.

Benjamin Samstein, MD
Assistant Professor of Surgery
Dr. Samstein's expertise includes kidney, liver, and pancreatic transplantation, and advanced laparoscopic liver surgery. His research endeavors focus on immunology and prevention of organ rejection.

Kidney Transplantation

continued from page 3

opportunities, the program has instituted an aggressive approach to its waiting list. Its *Top 40 List* identifies the ten patients from each of the four blood groups who are most likely to receive a kidney transplant in the near future. These patients are specially evaluated so that any medical or psychosocial problems, or new financial or insurance issues that would affect transplantation, can be addressed. Patients unfit for transplantation are placed on the inactive list while these issues are resolved. This process is repeated every two to four weeks, ensuring that all patients on the list are "optimized" — healthy, ready, and available to undergo transplant when a kidney becomes available. A study by nurse coordinator **Johanna Camacho-Rivera, RN**, which won the *Quality Assurance/Improvement* prize at the UNOS Transplant Management Forum in April 2006, found that during the strategy's first year, waiting time for transplantation at Columbia was better than halved, from about six to two or three years.

Dr. Ratner has pioneered still other creative strategies to make use of a potentially viable donor organ. He is the first physician to perform dual renal transplantation, the transplant of two adult kidneys into a single recipient. "If one suboptimal kidney would not provide sufficient function, two may give excellent renal function," says Dr. Ratner.

In another first, Dr. Ratner performed the first *paired kidney exchange* ("swap") in New York City in 2004. Kidney swaps entail trading the healthy and willing, but incompatible, donors of two patients, enabling both patients to receive compatible kidneys. A unique procedure, kidney swapping requires four simultaneous operations (the two donations and two transplants). Moving from a double to a triple swap, the team performed the region's first three-way kidney exchange, which required six concurrent operations, on May 30, 2006.

"The beauty of this approach is that by simply working out the logistics, we can give people straightforward transplants, with excellent results," explains Dr. Ratner.

"There is an urgent need for donors," according to **Joan Kelly, RN**, *Renal Transplant Coordinator*. "We hear from 50 people every month who need transplants. Often family members would be willing to donate, but don't realize they can be donors." To provide the best care possible for those considering donating a kidney, the program has established an extremely thorough and exemplary system of living donor evaluation and advocacy.

Preventing rejection after transplant

Investigators in the Departments of Surgery and Medicine are now testing new immunosuppressant drugs with fewer uncomfortable side effects. "It is critical to develop new and better ways to prevent rejection," says **Mark A. Hardy, MD**, *Director Emeritus* and founder of the Renal and Islet Transplantation program. Dr. Hardy is Principal Investigator of a multicenter clinical trial exploring a combination of two immunosuppressant drugs, sirolimus and tacrolimus. "Both of these drugs prevent the activation of T-cells," says Dr. Hardy. He and colleague **David J. Cohen, MD,** *Medical Director of Renal Transplantation,* hope this combined medical therapy will reduce rejection episodes and lead to improved kidney function in the long term. In another study, they are evaluating new classes of immunosuppressive medications which hold great promise in avoiding many of the side effects of currently used drugs. They are also investigating methods of *induction therapy*, which promotes tolerance to the foreign kidney, including Campath 1-H, thymoglobulin and monoclonal antibodies for Il2R, and HLA allopeptides.

A new program with the Department of Obstetrics and Gynecology provides women undergoing renal transplantation with specialized care in fertility and pregnancy. Another program, with the Department of Dermatology, treats skin cancer and other dermatologic diseases in transplant patients. For information about these programs or about becoming a living donor, please visit www.columbiatransplant.org or call 201.342.7001.

Blood Test Replaces Heart Biopsy

Since the 1970's, heart transplant patients have had to regularly undergo an invasive, uncomfortable, and potentially risky test for signs of rejection, a leading cause of death among heart transplant recipients. The test, *endomyocardial biopsy*, or EMB, involves inserting a catheter into a vein in the neck and threading it into the heart, so that a tiny amount of the heart muscle can be sampled for analysis. Now, a quick, easy-to-administer blood test is rapidly replacing EMB as the gold standard for diagnosing rejection of the donor heart.

The test, a product of a five-year, multicenter study conducted with biomedical company XDx, was based on the hypothesis that a genetic test could detect the absence of rejection in heart transplant recipients. "We believed that using the knowledge gained by the mapping of the human genome, it might be possible to detect gene expression variations that correspond to immune activity during rejection. If so, these changes could be identified by testing a regular blood sample," explains **Mario C. Deng, MD**, *Director of Cardiac Transplantation Research* at Columbia University, Department of Medicine, Division of Cardiology, and Co-Principal Investigator of the Cardiac Allograft Rejection Gene Expression Observational study (CARGO).

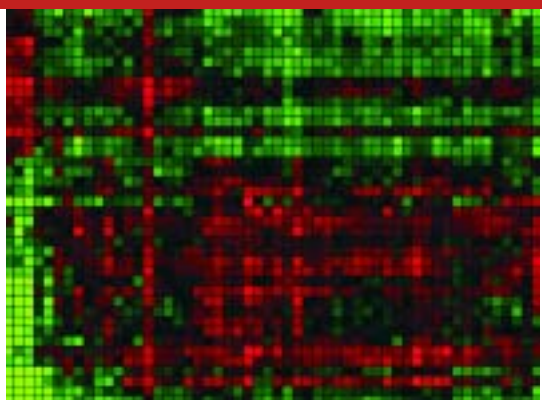
CARGO proceeded in three phases, and involved testing of over 600 patients in eight U.S. centers.

PHASE 1: GENE DISCOVERY

During the first phase of the study, the researchers determined the genetic changes associated with the immune process involved in rejection after heart transplantation. They constructed *DNA microarrays* and analyzed over 7000 genes identified in medical literature as involved in immune activation by cells known as leukocytes. In contrast to older methods of studying the activity of single genes, powerful DNA microarrays arrange the entire genome on a single chip, and can provide a picture of the activation status of thousands of genes at once. Screening of more than 7000 genes during Phase 1 refined the researchers' gene selection to 252 candidate genes.

PHASE 2: DEVELOPMENT OF A DIAGNOSTIC TOOL

Further analysis of the 252 candidate genes then narrowed the pool to a set of 62. During this phase, Dr. Deng and the study team worked with XDx to analyze each of these genes in patients who did and did not experience rejection to determine their levels of activity. From there, further analysis produced an 11-gene set of the most significant genes associated with the immune changes in organ rejection. Using these 11 genes and another 9 for control, the company developed the AlloMap™ molecular expression test – a tiny chip with 20 genes used to evaluate a cardiac patient's blood sample.



So-called "heat maps" like the one above show which genes are upregulated (red) and downregulated (green) during rejection of a transplanted heart.

PHASE 3: VALIDATION

During this phase, a prospective, blinded study of post-transplant patients was conducted to verify whether the 20-gene test could accurately detect the absence of organ rejection.

Results: The test was able to consistently detect the absence of rejection. Patients with low scores had a very low risk of rejection, while those with higher scores were more likely to experience moderate to severe rejection.

As a result of this clinical trial, AlloMap™ testing for rejection after heart transplantation has been certified in all 50 states and is now covered by insurance. "This represents a paradigm change in how transplant rejection will be monitored," Dr. Deng states. "For many patients, this simple blood test can now be used instead of invasive biopsy." Results of the CARGO study were published in 2006 in the *American Journal of Transplantation.*

GENOMICS AT NEWYORK-PRESBYTERIAN HOSPITAL/ COLUMBIA UNIVERSITY MEDICAL CENTER

Human genomics, or the study of the 20,000-25,000 genes in the human body, has been made possible during the last decade by advances in key technologies such as DNA microarrays, sophisticated data analysis tools, imaging equipment, robotics, and other developments. The NIH has recently awarded the Columbia Genome Center over $50 million in grants for genomic work, capitalizing on the university's diverse strengths in these areas.

IMPLICATIONS FOR LUNG TRANSPLANTATION AND BEYOND

While the CARGO study is already benefiting heart transplant patients, the success of its approach holds tremendous potential for applications throughout clinical medicine. Researchers in the Lung Allograft Rejection Gene expression Observational study (LARGO) are already applying the lessons of CARGO to help detect rejection after lung transplantation.

At this time, LARGO is in the first phase, and second year of progress, in ten U.S. centers. "Once we pinpoint which genes are over- or under-expressed during lung rejection, we will be able to develop a diagnostic molecular expression test to detect them," says **Selim M. Arcasoy, MD**, *Medical Director* of the Lung Transplant program, and co-investigator in LARGO. With a simple blood test to detect rejection, lung transplant patients could avoid the need for continuous bronchoscopies, which are invasive, uncomfortable, and potentially risky.

Moreover, a blood test for rejection may enable physicians to detect subtle forms of rejection before symptoms develop, according to Dr. Arcasoy. "Most diagnostic tools identify a problem only after it has progressed to a point where treatment is difficult and there is risk of permanent damage to the involved organ. The genetic test has the potential to identify subtle rejection long before the patient notices any symptoms," he explains. "This could make it possible to prevent symptomatic rejection or combat it earlier and more successfully."

Learn more about the CARGO: http://cardiactransplantresearch.cumc.columbia.edu or by calling 212.305.0200.

Courtesy of Thoratec Corporation

LEFT VENTRICULAR ASSIST DEVICES

The expertise of the heart transplantation program is complemented by an equally strong program in cardiac assist devices, which provide mechanical support to failing hearts. The most common type of cardiac assist device is a *Left Ventricular Assist Device*, or LVAD. Although they were originally intended to serve as a "bridge to transplantation" for patients with heart failure, LVADs are also approved as "destination," or permanent therapy, in patients who are not eligible for transplantation.

Approval for the use of LVADs as destination therapy was based on the landmark REMATCH trial (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure), which was led by **Eric A. Rose, MD,** *Chairman of the Department of Surgery*. This trial found that end-stage heart failure patients who received an LVAD device were twice as likely to survive at one year compared to patients who received medical treatment.

Columbia University Medical Center is now participating in an important clinical trial of the HeartMate® II Left Ventricular Assist System (LVAS). In another study, funded by the NIH for $17 million, the center is investigating ways of stimulating recovery of the native heart, combating infection, and improving outcomes overall for patients with ventricular assist devices.

More about mechanical cardiac assist devices is available at www.columbiaLVAD.org.

Lung Transplant Surgery

continued from page 5

tine bronchoscopy, so that patients need not come in for extra appointments. Those found positive for aspiration of bile acid are then considered for treatment by Nissen fundoplication.

"With early testing now available, we may be able to block or prevent this relentless inflammatory agent in patients with proven reflux," says Dr. Sonett.

In addition to providing key evidence about aspiration and a new diagnostic tool to detect it, Dr. D'Ovidio's work has opened the door to understanding how the lung's specific innate immune system may influence chronic lung rejection. As he studied the way in which bile acid disrupted his patients' lung innate immunity and in particular the lung surfactant system, Dr. D'Ovidio discovered that genetic variations of certain proteins, called surfactant proteins, were associated with earlier dysfunction of the transplanted lung. This suggests that the ability of some transplanted lungs to be more or less able to withstand injury, infection, and other assaults, may be determined at a genetic level. "Further study in this area may help explain why certain lungs, despite our best selection criteria, fare worse than others after transplantation." In time, he suggests, genetic tests might be used to better modulate medical therapy or even match organs with recipients. For this outstanding contribution, Dr. D'Ovidio was awarded the 2005 *Philip K. Caves Award* by the International Society for Heart and Lung Transplantation. More about this genetic work will be published in scientific journals later in 2006.

For more information about lung transplantation, please visit www.columbiatransplant.org.

Transplantation for Short Bowel Babies

continued from page 4

tomy, or the Kasai procedure, is essential. "If this is done early enough, the injured bile duct can be reconnected with the small bowel before the liver is destroyed," says Dr. Jan. Although a number of U.S. institutions perform the Kasai procedure for biliary atresia, their survival rates fall short of the 98% survival rate achieved by **R. Peter Altman, MD**, *Surgeon-in-Chief at Morgan Stanley Children's Hospital of NewYork-Presbyterian*, and his colleagues. "Our surgeons perform reconstructions of the biliary system with incredible expertise," says Dr. Jan. Dr. Altman, who is world-renowned among the best pediatric surgeons for this procedure, is currently training other surgeons at Columbia University Medical Center in the procedure.

Liver failure

When a child requires a liver transplant, a family member will frequently volunteer to donate a portion of their liver, according to Dr. Lobritto. Using tissue from living donors has several advantages, including the ability to choose a healthy donor and to plan the transplant in advance, so that the child's medical team can ensure he or she is fully optimized for the operation.

Surgeons at this center regularly perform operations that many centers won't consider, in children of every age. "Our knowledge of the liver gives us the ability to do things that other centers simply don't do," states Dr. Lobritto. In this past year, Dr. Jan performed a successful living-related liver transplant in a premature, failure-to-thrive newborn who weighed only five pounds, and in a five-day old baby with metabolic liver disease.

"We are not doing transplants to give our patients an extra six months," says Dr. Lobritto. "That would be a failed transplant. We do them to help them grow normally and have normal lives. That is what we look forward to."

For further information, please contact the Intestinal Rehabilitation and Transplantation team at 212.305.5300.

healthpoints is published by Columbia University Department of Surgery as a service to our patients. You may contact External Affairs for additional information, to be added to our mailing list, and to request additional copies. Please call 201.346.7001.

For physician referrals, please call
1.800.227.2762

Deborah Schwarz-McGregor, PA
Executive Director, External Affairs

M. El-Tamer, MD
Medical Editor

Sherry Knecht
Managing Editor

Tanya Krawciw
Creative Director

Affairs of the Heart™

The Cardiovascular Health Education Center of NewYork-Presbyterian/Columbia University Medical Center held its first free cardiovascular health fair, sponsored by **Affairs of the Heart™**, on Saturday, May 20th. Over 150 participants from the tri-state area received massages, peripheral vascular and blood pressure screenings, and more. Presentations on prevention and risk factors for cardiovascular disease, nutrition, diabetes, Medicare part D, and other topics were given in both English and Spanish by the Integrative Medicine Department, the Naomi Berry Diabetes Center, and other volunteers.

healthpoints
ALL THE POSSIBILITIES OF MODERN MEDICINE

Columbia University Medical Center
Department of Surgery
External Affairs
630 West 168th Street, Box 94
New York, NY 10032-3784