Winter 2006
SPECIAL ISSUE

healthpoints

ALL THE POSSIBILITIES OF MODERN MEDICINE

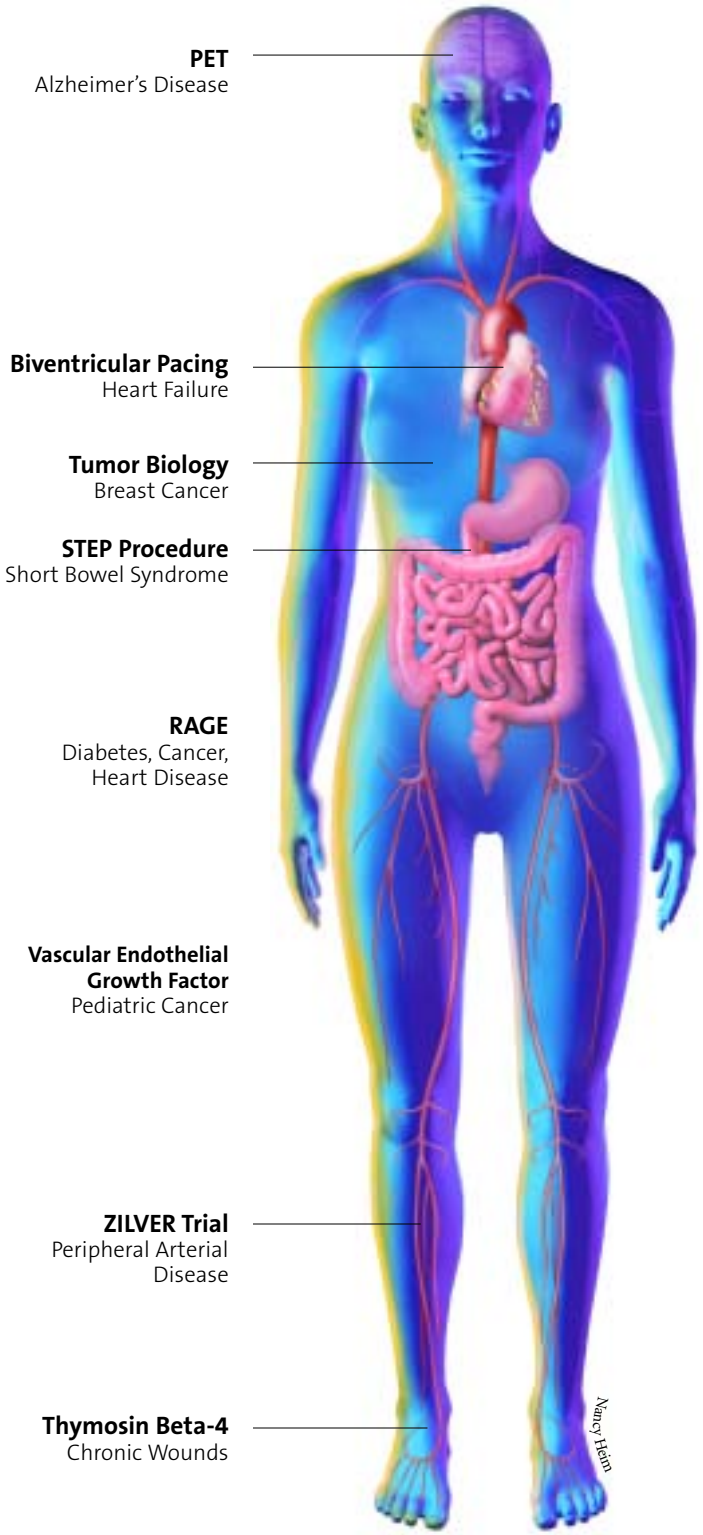
Columbia University Medical Center
Department of Surgery
NewYork-Presbyterian

"Clinical trials are underway across every specialty at the Department of Surgery. Our first special issue on clinical trials, *the Bridge to Medical Innovation* (summer 2004), received accolades from patients and physicians alike, and won the platinum MarCom Creative Award for 'best external newsletter from an educational institution.' In light of such positive feedback, we felt it was incumbent upon us to continue reporting on the studies that make possible all medical innovation and advancement."

Eric A. Rose, MD
Morris and Rose Milstein/
Johnson & Johnson Professor
of Surgery
Chairman, Department of Surgery
Surgeon-in-Chief, NYPH/CUMC

CLINICAL TRIALS

Impacting Your Health



Because of intensive research on every area of the human body, the horizons of medicine are constantly expanding, as are treatment options available to patients today. In this special issue, readers are invited behind the scenes to learn about a few of the research studies currently underway in the Department of Surgery. Studies like these lie at the heart of medical advances that are saving lives every day. It is hoped that this peek behind the physicians' doors will encourage patients and their families to speak with their doctors about all of the possibilities of their care.

Medical research evolves through *basic, translational,* and *clinical* stages of development. This issue focuses primarily on the clinical stage, which involves studying potential therapies through carefully controlled trials with patients.

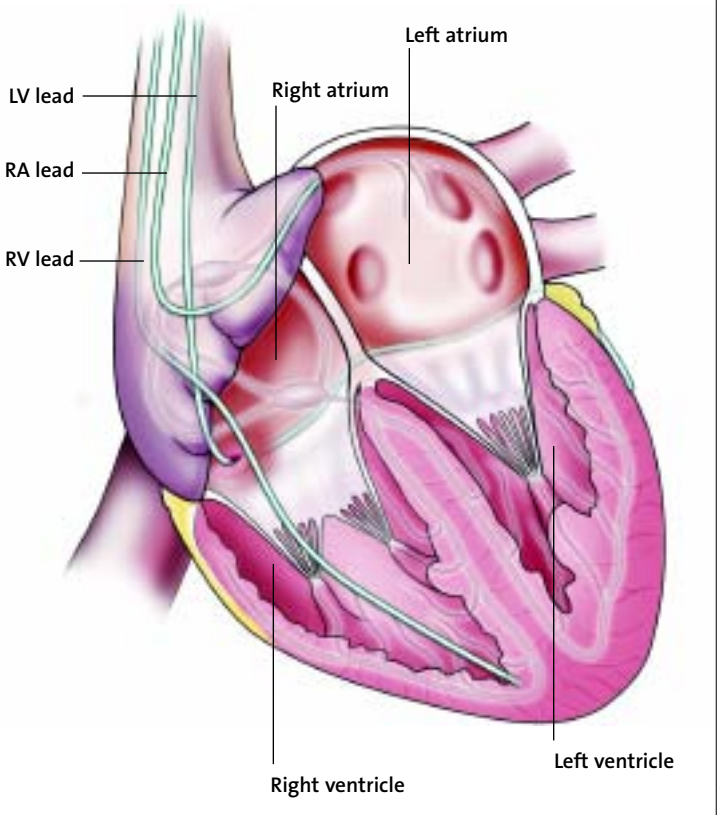
Glossary inside

Special Issue : Clinical Trials Update

BIVENTRICULAR PACING
for Heart Failure

Therapeutic options for patients with heart failure just broadened – again. The recent introduction of biventricular pacing has meant a valuable addition to the cardiologist's toolbox, good news for the five million Americans who have congestive heart failure. **Henry M. Spotnitz, MD,** *George M. Humphreys II Professor of Surgery* at Columbia University College of Physicians and Surgeons and *Vice Chairman for Research and Information Systems* at the Department of Surgery, is working to gain the fullest potential of this extraordinary technology. He and his team are now researching ways to bring its benefit to other kinds of patients and to optimize its function for those who benefit from it already.

The first of two trials being conducted by Dr. Spotnitz investigates the use of biventricular pacing in patients who develop acute heart failure. The second seeks to maximize the effectiveness of the biventricular pacemaker by altering the location of pacemaker lead wires and the timing of their electrical stimulation.



Nancy Heim

Electrical signals from three pacemaker lead wires stimulate the ventricles to contract simultaneously, making the heart beat properly and efficiently.

While a standard pacemaker corrects a heart rhythm that is too slow or too fast, biventricular pacing corrects heartbeats that have normal rhythm, but are inefficient because the walls of the left ventricle (the main pumping chamber of the heart) fail to contract simultaneously. Such inefficiency occurs in 20 to 30% of people with heart failure.

Heart failure, marked by an inability of one or more of the heart's chambers to pump enough blood to meet the body's needs, can cause dangerous enlargement of the heart, leakage of blood through the mitral valve, congestion in the lungs, and symptoms such as shortness of breath and pain, swelling in the legs, kidney failure, and other problems. In *chronic* heart failure, the gradual development of the problem allows the heart to compensate by thickening or enlarging. When the condition develops suddenly, in *acute* heart failure, such as after a heart attack or a surgical procedure, the heart does not have time to compensate for electrical impulses that have gone awry, and it is often fatal.

Also called cardiac resynchronization therapy (CRT), biventricular pacing synchronizes contractions of the opposing walls of the left ventricle. In so doing, it coordinates the walls of the left ventricle to pump together correctly. Placement involves implantation of a dual-chamber pacemaker with a third lead wire into the back of the heart. Biventricular pacing is a standard treatment for chronic heart failure today, offering improvement in patients' symptoms, exercise capacity, and quality and length of life. Dr. Spotnitz believes that the benefits of biventricular pacing for patients with chronic heart failure may also be applied to save the lives of patients with acute heart failure.

Trial 1: In the acute heart failure study, Dr. Spotnitz's team is comparing the effects of biventricular pacing with no pacing in patients with heart failure after undergoing coronary artery bypass grafting (CABG) surgery. "Immediately after open heart surgery, some patients require treatment for low cardiac output. Conventional drug treatments may pose dangers during this vulnerable time, including arrhythmias, impaired oxygenation of some areas of the heart, and increased oxygen consumption. Biventricular pacing may be able to restore the

continued on page 14

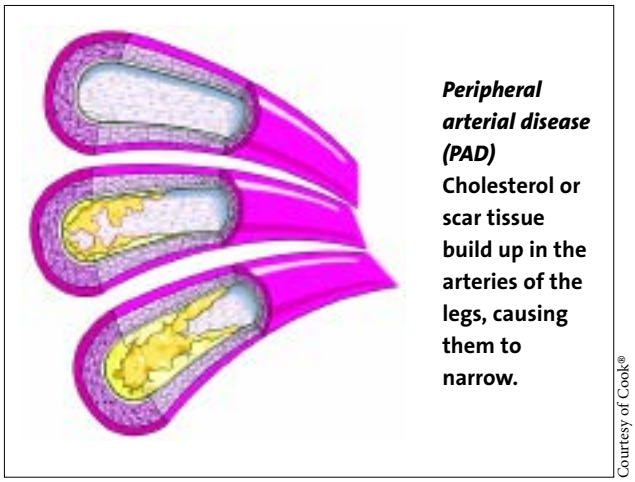
Advancing Treatment of VASCULAR DISEASES

Surgical techniques for treating major vascular diseases are rapidly evolving, becoming safer, and becoming available to more patients. What makes such advances possible is rigorous research to define which situations demand open or minimally invasive techniques; to examine public health issues such as cost, length of stay, and screening; and to monitor surgical techniques for complication rate, safety, and efficacy. As a leading institution in the quest to refine and advance open and minimally invasive procedures for major vascular disorders, NewYork-Presbyterian Hospital is currently conducting 16 clinical trials.

Trials of open procedures include techniques to treat carotid stenosis, stroke, peripheral vascular arterial insufficiency, and aortic aneurysms. Minimally invasive procedures under study include those for carotid stenosis, peripheral vascular occlusive disease and abdominal and thoracoabdominal aneurysms. "The hope is that we will identify patients who need treatment earlier and be able to intervene more effectively, with the proper individualized procedures and with less complication and cost," explains **Roman Nowygrod, MD**, *Professor of Surgery* and *Director of the Vein Disorder Treatment Center* at the Department of Surgery, Columbia University College of Physicians and Surgeons.

For the treatment of carotid stenosis, studies at NewYork-Presbyterian Hospital are comparing open carotid endarterectomy with minimally invasive balloon angioplasty procedures. For the treatment of aneurysms, researchers are investigating both FDA approved and new endovascular stent grafts, and, in parallel, evaluating the outcomes and cost of endovascular repair compared to open repair of aneurysms. Another clinical investigation focuses on embolization, or the dislodgement of clots, during balloon angioplasty in the leg.

Trials being conducted in conjunction with the International Center for Health Outcomes and Innovation Research (InCHOIR) are evaluating the safety of new minimal access treatments for vascular disorders. In these investigations, researchers in the Division of Vascular Surgery are examining trends during the last 20 years that have changed patterns of treatment, mortality, and complication rates. Examples of their findings include the following:



Peripheral arterial disease (PAD) **Cholesterol or scar tissue build up in the arteries of the legs, causing them to narrow.**

Courtesy of Cook®

➤ **Aneurysm surgery** – today almost half of patients with abdominal aortic aneurysms nationwide are treated with minimally invasive endovascular surgery, compared to just ten years ago when nearly all patients had open surgery to treat these conditions. At NewYork-Presbyterian Hospital, about 80% of patients are now treated with endovascular methods, with mortality and complication rates significantly lower than the traditional surgical approaches.

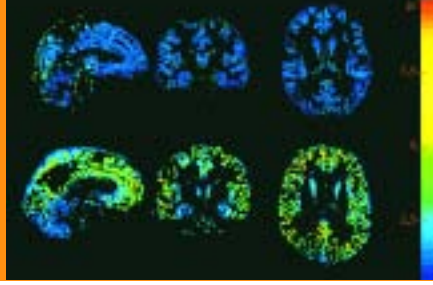
➤ **Carotid stenosis and lower extremity arterial occlusive diseases have undergone similar trends:** high-risk patients are now often treated with balloon

continued on page 9

Courtesy of Cook®

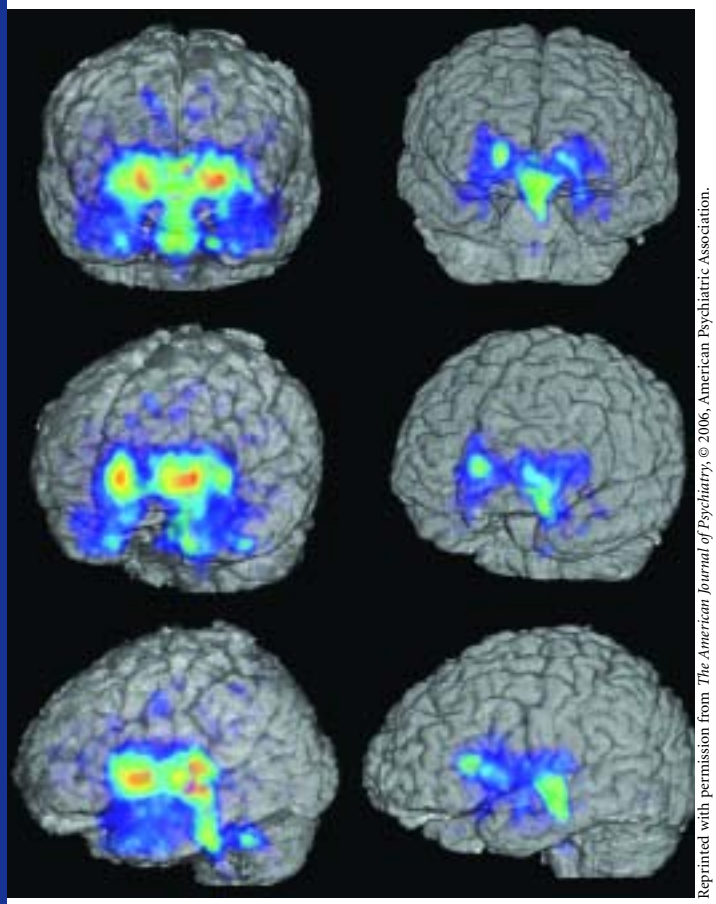
The ZILVER® stent is the first paclitaxel-coated stent to be tested for treatment of peripheral arterial disease. Physicians insert the stent through a tiny hole in the groin and advance it through a catheter to the narrowed segment of the artery. After the stent is deployed, it expands and keeps the artery open indefinitely. The addition of paclitaxel may help to prevent restenosis, or recurrent narrowing of the artery.

Visualizing Mental Illness:
Using PET to improve diagnosis and treatment



The science of diagnosing and treating psychiatric illnesses has always depended heavily on clinical judgment. Even administering psychiatric medication – a relatively direct process in most physical illnesses – is rarely guided by laboratory tests. A patient's improvement is judged clinically, and sometimes patients and doctors have different perceptions of benefit. For some drugs, it can take weeks or months to determine effectiveness, and determining optimal dosages may require numerous attempts. For patients with severe disorders, even one week can be too long to wait for improvement.

Now, two clinical studies using positron emission tomography (PET) to track biomarkers of psychiatric illnesses may remove some of the guesswork. These studies, based on the measurement of brain chemicals, have the potential to improve diagnosis and treatment of a host of psychiatric diseases. "A biomarker is a physical trait that can be measured biologically, such as a specific chemical in the blood or DNA," says **Ramin V. Parsey, MD, PhD,** *Assistant Professor of Clinical Psychiatry* at NewYork-Presbyterian Hospital/ Columbia University Medical Center. "By using PET to view biomarkers such as beta amyloid and serotonin, it is possible to track the progression of disease and the response to treatment."



Reprinted with permission from *The American Journal of Psychiatry*, © 2006, American Psychiatric Association.

PET scans of a healthy volunteer (left panel) and a depressed patient (right panel). Increased concentrations of red indicate the presence of more serotonin transporters in the healthy patient than in the depressed patient.

PET scans can reveal the state of the brain at the level of the neurotransmitters by viewing how chemicals in the brain rise or fall in association with the progression of psychiatric illnesses. Examples include beta amyloid, which accumulates in the brain as Alzheimer's disease progresses, and serotonin, levels of which are abnormal in the brains of people with major depression and bipolar disorder, or manic depression.

Study 1: **Understanding Alzheimer's Disease**

In one study of elderly patients, researchers at the Columbia Kreitchman PET Center are investigating how much beta amyloid is present in the brain during the early stage of Alzheimer's disease. Using PET, they are comparing brain images of people with normal memory, people with mild cognitive impairment but not Alzheimer's disease, and people with early, mild Alzheimer's disease. "Measuring beta amyloid may allow physicians to detect Alzheimer's disease much earlier – before patients develop memory deficits," explains **J. John Mann, MD,** *Professor of Radiology and Psychiatry* at Columbia University College of Physicians and Surgeons. This study will then provide a baseline for a second stage of research on drugs used to reduce levels of beta amyloid in patients with Alzheimer's disease.

PET can also help physicians monitor how well drugs work by measuring their impact on biomarkers, instead of waiting for patients to develop debilitating symptoms such as memory loss. "Sometimes drugs work by preventing a problem such as memory loss from getting worse, rather than helping it to get better. Examining the level of beta amyloid in the brain can provide a more sensitive biomarker of whether the drug is working well," says Dr. Mann.

Study 2: **Major Depression**

Using the PET scanner in genetic studies, Dr. Mann and Dr. Parsey seek to understand the role of specific genes in the development of major depressive

Top: a normal brain; Bottom: the brain of an Alzheimer's patient showing increased presence of beta amyloid.

illness, and determine whether specific treatments may work for people according to their genetic makeup.

Current treatment for depression includes a range of antidepressant medications, each of which may need to be taken for 4 to 8 weeks before its effects on an individual can be determined. If one medication doesn't work, the patient must then try another. "But for a depressed person, even a week feels like forever," states Dr. Mann. Moreover, untreated major depression is the main cause of suicide. "With suicide the third leading cause of death among young people and the 11th leading cause of death in the U.S. in adults, the treatment of depression is a very important thing." Now, results from PET scans may help predict which patients will respond to which antidepressant drugs.

In this study, the team uses PET scans in combination with a panel of genetic tests from blood samples to gather data from participants. Patients in the study receive comprehensive evaluations and drug treatment at no cost.

Evaluations of depressed or bipolar patients, or even patients who have had an episode of depression in the past but are currently feeling well, include:

- PET scans of the serotonin system in the brain,
- MRI (while patients are off medication), and
- Measurements of key genes in the serotonin system.

"Sensitivity to stress can be measured by the level of expression of the serotonin transporter gene. People who have low levels of expression of this gene and are exposed to adversity are more likely to suffer depression than people who have higher levels," says Dr. Mann. The researchers have found that certain changes on the PET scan and specific serotonin gene variants predict who will recover with treatment. However, they are still establishing which combinations of genes and serotonin PET scans are the best predictors. "In time," Dr. Mann predicts, "we expect these scans and lab tests to become part of clinical practice."

Looking to the future, Dr. Mann suggests that, because it can show how much of a drug is needed to bind to specific targets, "this new use of PET also has the potential to accelerate the development of new drug treatments." PET scanning can determine the lowest dose of medications required to act on the targets of their action in the brain. This can help physicians determine the dose range required for optimal benefit and the fewest side effects, Dr. Mann explains. "Before PET was available, we had to do dose-finding clinical studies. Not only did they take a great deal of time, but they followed the principle of determining the maximum dosage of the drug that could be tolerated without troublesome side effects. Now we can use PET to determine the least amount of drug to be effective and avoid a lot of side effects."

The use of PET may help researchers to:

- **Detect disease before symptoms occur.**
- **Predict how patients will respond to particular therapies.**
- **Speed the development of new drugs.**

Drs. Mann, Parsey, Oquendo, and colleagues have developed methods using Positron Emission Tomography (PET) for visualizing how the brain responds to serotonin. These techniques allow further study of mood disorders and the effects of treatment. Some of these studies include:

- **Neurobiology of Depression and Antidepressants,** funded by National Institutes of Mental Health, $3 million. Dr. Mann, Principal Investigator.
- **Familial Pathways to Early-Onset Suicide Attempts,** funded by National Institutes of Mental Health, $2.5 million. Dr. Mann, Principal Investigator.
- **Psychobiological Predictors of Suicidal Behavior in MDE (Major Depressive Episodes),** funded by National Institutes of Mental Health, $1 million. Dr. Mann, Principal Investigator.
- **Biological Predictors of Treatment Response,** funded by the National Institutes of Health, $2.7 million. Dr. Parsey, Principal Investigator.
- **Imaging of Serotonin Transporters in Depression,** funded by National Institutes of Mental Health, $1 million. Dr. Parsey, Principal Investigator.

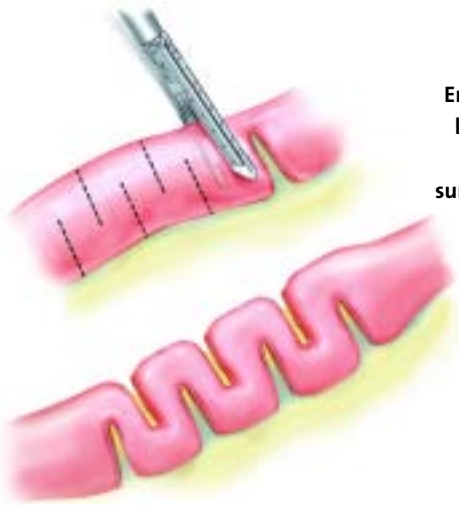
For referrals or more information, please contact Drs. Mann, Parsey, or Oquendo: 212.543.6774.

STEPping Forward

Surgeons Test New Surgery for Short Bowel Syndrome

With every advance in medicine, the thrill of discovery also brings a new set of challenges to meet and questions to resolve. For doctors treating short bowel syndrome, the advent of an important surgical treatment, the STEP procedure, is no exception.

Short bowel syndrome is a rare but serious condition that mainly affects newborns and young children. Because of either disease or required surgery, children with this syndrome are left with a shortened small intestine. The loss of intestinal function leaves them unable to digest food or grow as they should. Children with short bowel syndrome may be able to take some food by mouth, but sometimes long-term intravenous nutrition can be necessary. While this intravenous nutrition provides life-saving supplemental calories, it is highly complex and carries significant risks in the long-term. The most serious risks include infection, clotting of major veins and, in some cases, liver failure. These risks spurred a Boston physician to develop an innovative way to lengthen the bowel through a novel surgical procedure.



Serial Transverse Enteroplasty (STEP) can lengthen the bowel in some patients. The surgeons make multiple incisions into a short, dilated segment to create a longer, thinner segment of intestine. Although the new segment is initially a zig zag in shape, it becomes straight as it heals.

Nancy Heim

Described just three years ago, Serial Transverse Enteroplasty (STEP) can both lengthen and taper the small intestine in some patients. During the procedure, a short segment of the intestine is carefully cut and reshaped into a longer, thinner segment. The longer, thinner intestine is thought to function more efficiently and lead to better absorption of food. "This can be an important component in an overall plan for intestinal rehabilitation," says **Robert A. Cowles, MD,** *Assistant Professor of Surgery* at Morgan Stanley Children's Hospital of NewYork-Presbyterian.

In light of the success of the procedure in children, some physicians are beginning to broaden the use of STEP to other patients. "The use of STEP is changing," explains Dr. Cowles. But because the procedure is so new, surgeons have not been able to fully sort out which patients will benefit the most, and for whom it may be inappropriate. Dr. Cowles is now tracking outcomes and working to establish clear definitions as to optimum application of the STEP procedure. "It would be easy to apply STEP inappropriately," Dr. Cowles states.

Patients with dilated, shortened intestine are carefully selected as candidates for the STEP procedure. After the procedure is performed, their nutrition is carefully monitored and adjusted. Patients may take nutrition intravenously (into a central vein of the body), by mouth, or through a tube into the stomach or intestine *(enterally)*. As intestinal function improves and more calories are absorbed by the intestine, the amount of intravenous nutrition is reduced. "The final goal is to completely free these children from intravenous nutrition," Dr. Cowles explains. "We encourage patients to take at least some food by mouth, because it actually stimulates growth of the intestine. In cases where advancing oral nutrition is difficult, we recommend placement of a tube into the stomach for more certain delivery of nutrients to the intestine."

In determining eligibility for a potential candidate, the multidisciplinary Intestinal Rehabilitation and Transplantation team uses strict criteria in determining who may be a candidate for the procedure, including shortened intestinal length, dilation of intestine, and lack of severe liver disease.

When employing a new technique, it is important to be creative, but safe, in its applications. For example, the team recently performed what is thought to be the first STEP procedure in a child with short bowel syndrome who had already received a liver transplant. This child's liver failure, caused by long-term intravenous nutrition, initially made him a poor candidate for the STEP procedure. After the liver transplant, Dr. Cowles' team considered the STEP procedure to be safer and an important part of the child's overall intestinal rehabilitation plan. Similarly, in 2004, the team performed one of the first STEP procedures in a newborn baby with a congenital blockage of the intestine.

continued on page 9

ADDITIONAL TRIALS
in the Department of Surgery

BREAST CANCER
- Development of a new drug to treat breast cancer by blocking RAGE.

CANCER
- Immunotherapy, or tumor vaccines, to treat metastatic melanoma.
- Study of GM-CSF, a drug to reduce the growth of tumors in people with colorectal cancer.

DIABETES
- Therapies to help the immune system.
- Islet (pancreas) cell transplantation.

ENDOCRINE DISORDERS
- Outcomes after bariatric (weight loss) surgery.
- The relationship between hyperparathyroidism and cardiovascular disease.

HEART DISEASE
- Robotic surgery.
- Surgical treatment of atrial fibrillation.
- Minimally invasive cardiac surgery.
- Surgery for congenital heart disease.
- Heart transplantation.
- The effects of left ventricular assist devices (LVADs) in patients with heart failure.
- Alternative anticoagulants for cardiopulmonary bypass.
- Stem cells to repair the heart.
- Basic studies on vein grafts.
- The effects of cardiopulmonary bypass.
- Innovative methods of repairing the mitral valve.

Blocking TUMOR GROWTH

The quest to conquer cancer is undoubtedly one of the holy grails for scientists today. An array of research projects, including many at NewYork-Presbyterian Hospital, are devoted to the development of diagnostic tools, medical therapies, surgical techniques, new vaccines, tricks to strengthen the immune system, and other weapons against this formidable enemy.

Scientists now know that the process governing the growth of blood vessels (angiogenesis) plays an important role in the growth of cancerous tumors. Researchers have sought ways to inhibit the process by targeting specific growth factors. Such work has proven a highly promising strategy so far, and is the focus of continued research by **Jessica Kandel, MD,** *Associate Professor of Surgery* in the Institute for Cancer Genetics and *Director,* Charles Edison Laboratory for Pediatric Research.

Eight years ago, Dr. Kandel, Darrell Yamashiro, MD, and colleagues at the Pediatric Tumor Biology Laboratory were the first to describe the way experimental pediatric tumor growth could be suppressed by blocking a molecule called Vascular Endothelial Growth Factor, or VEGF, from performing its natural job. Their laboratory research provided key preclinical data about an antibody to VEGF, which is the basis of the drug now called Avastin. Approved by the FDA in 2004 for adults with colorectal cancer, Avastin is now gaining use in the treatment of lung and breast cancer.

The year 2004 also marked the first phase I trial of Avastin for children with solid tumors, conducted internationally by the Children's Oncology NCI cooperative group under Principal Investigator **Julia Glade Bender, MD,** *Assistant Professor* in the Division of Pediatric Oncology. The Phase I trial was completed this September, and paved the way for more widespread evaluation of this new therapy in children with refractory cancers. "Avastin has been shown to extend the lives of adults with metastatic colon cancer, and it is hoped that the same kind of survival advantage will be seen in children," says Dr. Kandel. Phase II studies of Avastin in children will begin later in 2006. "This is a very exciting example of bench to bedside research," she says.

Dr. Kandel's current focus in the laboratory is to understand how tumors adapt to blockade of VEGF. "Avastin is an effective therapy for some time," according to Dr. Kandel. In patients with colon cancer who do not benefit from other treatments, Avastin may extend their lives by an average of two years. "It is not a cure, however. Tumors eventually acquire resistance."

Understanding how tumors adapt to blockade of VEGF may play an important role in the development of therapies for children with resistant cancers such as neuroblastoma, Wilms tumor, and hepatoblastoma. "As a pediatric surgeon and a researcher it's very exciting to see these new biology-based therapies becoming available to children," says Dr. Kandel.

For information about research on pediatric cancer, please visit www.babysurg.org/ca or call 800.543.2782.

Highlight on Translational Research

RAGE

Translational research is all the rage at Columbia University Medical Center. Not *all* the rage, perhaps, but work by the Division of Surgical Science on the Receptor for Advanced Glycation Endproducts (RAGE) represents a vitally important segment of translational research currently underway at this institution.

Kristin Bailey

'Translational research' refers to biomedical investigation that advances basic science, or laboratory research, to the realm of patient therapeutics. Successful evolution of translational research requires careful, deliberate choices about which areas of laboratory research are most likely to yield practical results. Studies of a molecule called RAGE have produced such success for **Ann Marie Schmidt, MD,** *Chief, Division of Surgical Science,* Columbia University Medical Center, and her team of investigators. After several years of basic research on the molecule, Dr. Schmidt and her colleagues have reached a point where applications of this research appear likely to impact the treatment of cancer, heart disease, Alzheimer's disease, diabetes, and a host of immune-related disorders.

Dr. Schmidt's work on RAGE goes back to the 1990s, when she was conducting laboratory research on problems with blood vessels in people with diabetes. Her team made the basic discovery that sugar-modified proteins (called Advanced Glycation Endproducts, or AGEs) bind to endothelial cells (cells located on the interior surface of blood vessels), and that one particular receptor – RAGE – sends messages through cells that promote inflammation. In diabetics, inflammation contributes to serious complications including atherosclerosis, heart attacks, stroke, kidney disease, and retinopathy. "Inflammation is a key process in many lifelong diseases. RAGE does not cause diseases, but we found it is a player that perpetuates and amplifies them," says Dr. Schmidt.

In further study, Dr. Schmidt's team was surprised to learn that many inflammatory molecules (such as amyloid beta in Alzheimer's disease) interacted with RAGE. This observation gave her and **Shi Du Yan, MD,** *Associate Professor of Clinical Pathology,* an important clue that RAGE might have biological effects (such as worsening the damage caused by increased levels of amyloid-beta peptide that accumulate in the brains of people with Alzheimer's disease) and might be a worthwhile target for treatment. "It changed our view because it broadened the potential impact from just diabetes to other conditions," explains Dr. Schmidt.

Having moved from the test tube to studies on endothelial cells, Dr. Schmidt's team then designed studies of RAGE in animal models. They found that blocking the receptor markedly reduced inflammation in both large and small blood vessels. "Blockade of RAGE clearly reduced complications," Dr. Schmidt recounts. "The animals still had diabetes, tumors, and heart disease, but when RAGE was blocked, they had substantially less disease." Her team continues to study RAGE to determine whether blocking the molecule has long-term effects, and to further understand

Current research on RAGE at Columbia University Medical Center

- **Breast cancer:** Kathie-Ann Joseph, MD
- **Injury to blood vessels in diabetic patients:** Shi-Fang Yan, MD, Ravi Ramasamy, MD, and Ann Marie Schmidt, MD
- **Islet cell transplantation in diabetes:** Kevan Herold, MD, Raphael Clynes, MD, and Ann Marie Schmidt, MD
- **Liver regeneration:** Jean C. Emond, MD
- **Colon cancer:** John D. Allendorf, MD

Future studies will investigate whether blocking RAGE may:

- Protect blood vessels in people with diabetes;
- Reduce other complications of diabetes including kidney disease, heart disease, and wound healing;
- Treat Alzheimer's disease;
- Delay the progression of liver disease;
- Reduce the growth of cancerous tumors;
- Enhance the treatment of rheumatoid arthritis, multiple sclerosis, amyotrophic lateral sclerosis, and other diseases.

the physiological role of the receptor.

Meanwhile, their robust findings in animal studies have provided a foundation for clinical trials in people, and in conjunction with Transtech Pharma, the team developed a receptor blocker. Grants by the National Heart Lung and Blood Institute and the Juvenile Diabetes Research Foundation are supporting continued study of the biology of RAGE, its role in causing type 1 diabetes, and its role in complications of types 1 and 2 diabetes. Phase II trials are now testing whether drugs to block RAGE are safe and effective in people with Alzheimer's disease and diabetic neuropathy.

For more information, visit the Division of Surgical Science at www.columbia-surgery.org or call 800.543.2782.

STEP for Short Bowel Syndrome

continued from page 6

"The potential benefits of this new surgical procedure are exciting, and the Intestinal Rehabilitation and Transplantation team wants to be certain that it is being offered to as many children who may be able to benefit from it," says Dr. Cowles. "At the same time, it is important to continue to assess and improve the long-term outcomes of these chronically ill children."

For information about intestinal rehabilitation or the STEP procedure, please contact the Intestinal Rehabilitation team at 800.543.2782.

Advancing Treatment of Vascular Diseases

continued from page 3

angioplasty and stent procedures, whereas even five years ago, they would have had open surgery.

Their findings of safety and efficacy are leading to widespread changes in practice throughout the nation. "These studies are already having an impact at the national level in formulating public policy regarding screening," says **K. Craig Kent, MD,** *Chief, Division of Vascular Surgery,* NewYork-Presbyterian Hospital. "For example, this year, the federal government is approving cost reimbursement for screening for abdominal aneurysms for patients at high risk."

The ZILVER® trial provides an example of how NewYork-Presbyterian Hospital trials are extending the use of a valuable technique to treat new areas of the body. This clinical trial is investigating the first paclitaxel-coated stent for arteries in the legs. While drug-coated stents have been proven to prevent restenosis (narrowing) of the arteries of the heart, this is the first stent to be tested in the leg. "Preliminary results suggest that there are differences between the leg and coronary arteries, so the stent must be studied in the leg. Ours is the only study in the U.S. to investigate this," states **Nicholas J. Morrissey, MD**, *Bicampus Director of Clinical Trials, Assistant Professor of Surgery* at Columbia University College of Physicians and Surgeons/Weill Cornell Medical College, and Principal Investigator of this multi-center trial. NewYork-Presbyterian Hospital is the leading institution among approximately 20 participating in the ZILVER® study.

Dr. Morrissey acknowledges that conducting research at two university campuses presents unique challenges – especially in navigating through double the required regulatory processes. He is enthusiastic about the strength of the vascular program, however. "Our faculty are recognized as world leaders in vascular intervention. As a result, NewYork-Presbyterian is chosen for many of the most cutting-edge trials in the world," he explains. "Even if patients may not be eligible for a particular study, they can be assured that our doctors are top in their field."

To learn more about clinical trials in the Division of Vascular Surgery, please visit www.columbiasurgery.org or call 800.543.2782.

Biological Markers in **Breast Cancer**

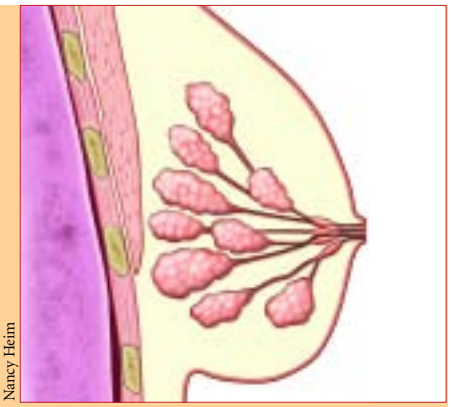
African American women have the highest mortality rates for breast cancer compared to other women, and although they do not develop breast cancer as frequently as white women, African American women face a 32% higher risk of dying from the disease than other women in the U.S. – even when they have access to excellent health care. Are behavioral, physiological, or genetic differences between populations responsible for this disparity? Tumor biology may hold some of the answers, according to **Kathie-Ann Joseph, MD, MPH,** *Assistant Professor of Surgery* at NewYork-Presbyterian Hospital/Columbia University Medical Center. In her clinical practice and research efforts, Dr. Joseph is seeking new strategies to reduce disparities between African American women and others diagnosed with breast cancer.

This study will determine whether there is a difference in estrogen receptor status between African American and white women with ductal carcinoma in situ (DCIS), and if so, whether that difference impacts recurrence and survival rates.

It has been well documented that among women diagnosed with invasive breast cancer, which can become deadly unless treated early, tumors are estrogen (ER)-negative in 40% of African American women, compared to 23% in white women. ER-negative tumors are associated with a worse outcome and an increased risk of recurrences – and they are not responsive to tamoxifen, which is an antiestrogenic therapy. Yet because tamoxifen was developed before the role of hormone receptors was identified, early studies of its effectiveness overlooked this important factor. And while physicians now routinely test ER status in women with invasive breast cancer, ER testing has not been routine practice for women with ductal carcinoma in situ (DCIS), or cancer located just in the cells lining the milk ducts of the breasts.

Dr. Joseph is now working to determine whether ER-negativity also plays a parallel role in DCIS. Like invasive breast cancer, DCIS may be ER-positive or ER-negative. If the tumors of African American women with DCIS are found to be frequently ER-negative (as they are in invasive cancer), this discovery will have important ramifications for the diagnosis and treatment of DCIS.

"Women who have DCIS are at an increased risk of developing invasive cancer later in life. Many hospitals still do not test the tumors of patients with DCIS to see whether they are ER-positive or negative, however. If we find that a high proportion of African American women are ER-negative, routine testing really needs to become the standard of care. It also means that researchers will need to develop other treatments besides chemotherapy and radiation, strategies that are not hormonally dependent." she states.
In the DCIS study, Dr. Joseph is collaborating with several other New York hospitals to compare tissue samples from African American women with those of white women. About 160 samples, half from each population, will be analyzed to determine the rate of ER-negativity in the two populations. She will also investigate whether other biological markers associated with worse prognosis, such as P21, BCL2, and Her-2, may be predictors of tumor recurrence and survival rates.



Nancy Heim

Ductal carcinoma in situ (DCIS) refers to cancer of the cells lining the milk ducts.

Left untreated, DCIS may begin to spread into the breast tissue surrounding the ducts, becoming invasive breast cancer. Although only some women with DCIS will develop invasive breast cancer, it is not possible to predict who will develop this more serious form.

More information about breast cancer and DCIS research is available at www.breastmd.org or at 800.543.2782.

Thymosin Beta-4 and Chronic Wound Healing

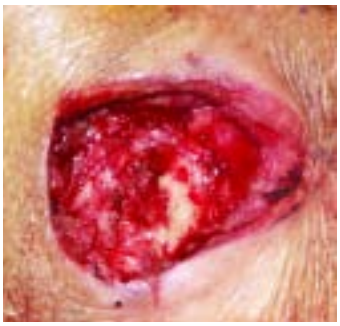
First human trial tests thymic hormone in pressure sores

About three million people in the U.S., primarily elderly and bedridden, suffer from chronic pressure sores ("bedsores") that do not heal. These kinds of infections can result in loss of limbs or, in some cases, even death. Because they require such long-term care, the cost of treating just one pressure wound can range from $14,000 to $50,000.

When a chronic wound occurs, it is because the normal process of healing has been disrupted. Many factors may be responsible for such interruption, including infection, systemic causes such as diabetes, and the use of certain medications such as corticosteroids.

Standard treatments for pressure sores and diabetic ulcers include agents to debride them (remove dead tissue), topical agents such as antimicrobials and enzymes, and various types of dressings. Other options include treatment by Vacuum-Assisted Closure or surgery. But even with these advanced strategies, the recurrence rate for chronic wounds remains high. What is needed is a way to help the body heal once infections develop.

NewYork-Presbyterian Hospital/Columbia University Medical Center is addressing this challenge in a study on thymosin beta-4, a naturally-occurring protein that can reduce inflammation and help wounds to heal. "Thymosin beta-4 is a major activator of actin, which improves the process of wound healing," says **Mark A. Hardy, MD**. Dr. Hardy is *Auchincloss Professor of Surgery* at Columbia University College of Physicians and Surgeons, and *Director of Islet Transplantation* at NewYork-Presbyterian Hospital/Columbia University Medical Center.



Thymosin beta-4, originally isolated from the thymic gland, can now be produced synthetically. NewYork-Presbyterian/Columbia is currently studying whether it plays a role in improving the healing of chronic wounds such as the one shown above.

In collaboration with Alan Goldstein, PhD, Dr. Hardy was the first to test new synthesized thymic hormones in 1968. Since then the hormones have been studied by several groups in adult patients with cancer, children with mucocutaneous candidiasis, and now in the healing of chronic wounds. "As a surgeon, I have had a long-term interest in finding ways of helping to speed up wound healing," says Dr. Hardy.

Although thymosin has not proven as successful in treating cancer as researchers had hoped, studies have found that it does improve the healing of chronic wounds. Initial tests on pressure sores in animal models found that thymosin is active in several wound healing processes, according to **June K. Wu, MD,** *Assistant Professor of Clinical Surgery* at Columbia University College of Physicians and Surgeons, and Co-Principal Investigator with Dr. Hardy. The next phase of the current study will be among the first to test thymosin beta-4 in people with pressure sores.

The thymosin beta-4 trial, sponsored by RegeneRx Biopharmaceuticals, Inc., is a randomized, double-blind, placebo-controlled study. About 20 patients will be enrolled at NewYork-Presbyterian/Columbia, and three-quarters of these will receive topical thymosin for their chronic wounds. The safety of three doses will be evaluated in this phase of study. NewYork-Presbyterian/Columbia is one among four participating institutions.

"Finding an agent that can promote healing of chronic wounds, reduce the time it takes for them to heal, or reduce the rate of recurrence of

continued on page 14

ADDITIONAL TRIALS

in the Department of Surgery

INTESTINAL FAILURE
- Changes in the nervous system after bowel resection.

KIDNEY DISEASE
- Immunosuppressant drugs for patients undergoing kidney transplantation.

LIVER DISEASE
- New treatments for metastatic liver cancer.
- Basic mechanisms in liver transplantation.

LUNG DISEASE
- Endobronchial Valve for Emphysema Palliation Trial (VENT), a minimally invasive alternative to lung volume reduction surgery (LVRS).

MINIMALLY INVASIVE SURGICAL TECHNIQUES
- A new mesh device to repair hernias.
- Study of virtual simulator training on outcomes after laparoscopic surgical procedures.

VASCULAR DISEASE
- Minimally invasive alternatives to stroke prevention.
- Thoracic aortic stent graft, a minimally invasive treatment for patients with thoracic aortic aneurysms.
- Synthetic vein grafts and arterial bypass grafts.
- Outcomes in peripheral vascular disease.

WEIGHT LOSS (bariatric) SURGERY
- LAP-BAND®, a minimally invasive surgical procedure.

WOUND HEALING
- Laboratory research on why chronic wounds do not heal.
- Identification of genes that inhibit wounds from healing.
- New treatments for chronic wounds.

Glossary

Aneurysm – ballooning of a blood vessel to a size that is twice its normal diameter. Aneurysms develop when weaknesses in the aortic wall succumb to the constant pressure of rushing blood and begin to stretch outward.

Angiogenesis – the process involving the formation of new blood vessels from pre-existing vessels. Angiogenesis is a normal process in growth and in wound healing, but it is also involved in the transition of tumors from a dormant state to a malignant state.

Arterial occlusive diseases – diseases that involve blockages of the large arteries. Common causes include atherosclerosis (hardening of the arteries), inflammation, and stenosis.

Balloon angioplasty – A procedure in which a catheter is inserted into a narrowed artery. A tiny balloon at the tip of the catheter is inflated to clear the blockage and widen the artery.

Beta amyloid – a protein that is the main component of amyloid plaques in various neurological disorders, most prominently Alzheimer's disease.

Biomarker or Biological marker – A physical trait, such as a body chemical or DNA, used to measure the course of a disease.

Cardiac output – the volume of blood that the heart pumps each minute.

Carotid endarterectomy – a surgical procedure to remove blockages from the inside of the carotid artery.

Carotid stenosis – narrowing of the carotid artery caused by fatty deposits. Carotid stenosis can lead to transient ischemic attacks (TIAs, or "mini-strokes") or strokes.

Clinical – Relating to the treatment of a patient or to the symptoms or course of a disease.

Congenital – refers to disease that is present at birth (as opposed to acquired).

Endothelial cells – the inside lining of the blood vessels throughout the circulatory system.

Endovascular – referring to a surgical treatment in which a catheter containing miniature instruments is inserted under the skin into a blood vessel.

Enteral – referring to the intestine. Enteral nutrition may be delivered to the intestine through a tube into the stomach.

Heart failure – inability of the heart to pump enough blood through the body. There are numerous causes and types of heart failure.

Intestinal rehabilitation – multidisciplinary therapy including nutrition, medicines, surgery, and possibly transplantation, to treat short bowel syndrome.

Intravenous – through a vein. Intravenous nutrition is delivered through a central vein of the body.

Metastatic cancer – cancer that has spread from an original site to other sites in the body.

MRI – Magnetic resonance imaging, also called magnetic resonance tomography (MRT), is a method of imaging the body using strong magnetic fields and non-ionizing radiation. MRI provides far better contrast resolution (the ability to distinguish the differences between similar tissues) than CT scan.

Neurotransmitter – a chemical substance that transmits nerve impulses, or messages, from one cell to another.

PET – positron emission tomography – a method of imaging that detects metabolic or chemical activity in the body. In contrast, CT scans (computed tomography, or computed axial tomography – CAT) show anatomical structures. For example, a PET scan would show a tumor's increased sugar uptake, while a CT scan would reveal its size and density.

Pressure sore – Also called decubitus ulcer or bedsore, a chronic wound occurring in people confined to bed for long periods of time.

Refractory – resistant or unresponsive to treatment.

Resistance – ability of a disease to withstand attempted treatment by a therapy.

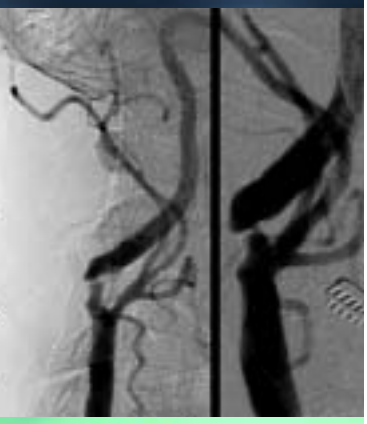
Restenosis – literally means the reoccurrence of stenosis (which is abnormal narrowing of an artery or other blood vessel).

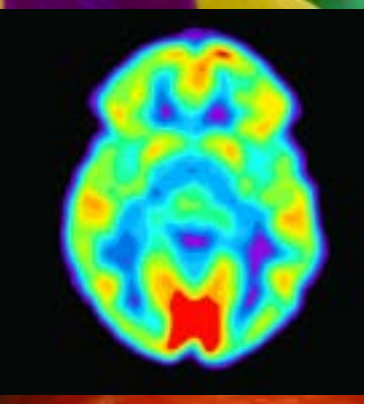
Serotonin – a neurotransmitter that plays an important part in conditions including depression, bipolar disorder, anxiety, migraine headaches, and others.

Short bowel syndrome – a serious illness in which the intestine is shortened, either by disease or necessary surgery. Patients with short bowel syndrome are unable to digest food properly.

Thymosin – A hormone secreted by the thymus gland that stimulates parts of the immune system.

Vascular – related to the blood vessels.





Clinical Trials – Terms and Definitions

Basic research – done in the laboratory, basic research involves studying how cells work, how they communicate, how they know what to do, and what conditions and drugs make their functions more or less efficient. Scientists who conduct basic research test new treatments in animals to find out if they might be helpful or harmful to people.

Clinical research – Treatments with the most promising laboratory results move from laboratory and animal studies into the clinical trial stage. In clinical trials, scientists apply their discoveries to humans, testing new drugs, devices, or innovative therapies in selected patients. Carefully conducted clinical trials are the safest way to evaluate potential medical treatments, assessing their effectiveness and potential risks.

Cross-over trials – trials in which patients receive both the treatment and the placebo at different times, with careful monitoring of their responses to both approaches.

Double-blind trials – trials in which neither the patient nor the researcher knows if the patient is receiving the treatment or the placebo.

Exclusion criteria – Factors that do not allow someone to participate in a clinical trial.

IDE – Investigational Device Exemption – permission granted by the Food and Drug Administration to use a new medical device during a clinical trial.

Inclusion criteria – The factors that allow someone to participate in a clinical trial.

IRB – Institutional Review Board, an independent committee of physicians, statisticians, community advocates, and others. The IRB is charged with ensuring that all clinical trials within a given medical institution are ethical and that the rights of the participants in those trials are protected.

Open label studies – studies in which both the patient and the researcher know that the patient is receiving the treatment and not the placebo.

Placebo – an inactive substance or "dummy" treatment.

Prospective trials – trials in which patients are identified and then observed over time.

Randomized trials – trials in which patients are arbitrarily grouped into (typically) a treatment group and a control group (also called a *placebo group*). The control group receives either the current standard treatment or no treatment at all. The results of the control group are then compared with those of the treatment group.

Translational research – the evolution of basic research into therapies for patients. Translational research involves identifying drugs, devices, or treatments that hold promise; funding and conducting the development; and transitioning the therapy to clinical research.

Phases of clinical trials

Clinical trials are conducted in phases. Each phase of a trial has a different purpose and helps scientists to answer specific questions:

Phase I Trials – Researchers test a new drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

Phase II Trials – The study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.

Phase III Trials – The study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.

Phase IV trials – Post-marketing studies delineate additional information including the drug's risks, benefits, and optimal use.

While small, early phase trials may be conducted by individuals or small groups of physicians, larger trials are typically conducted by hospitals, pharmaceutical companies, or device manufacturers. If a therapy successfully passes through phase III trials, the FDA may approve it to be marketed to the public.

Biventricular Pacing for Heart Failure continued from page 2

heart's function without causing these problems," Dr. Spotnitz explains.

Dr. Spotnitz believes that biventricular pacing will prove valuable for acute heart failure after open heart surgery, and that it is preferable to standard pacing. "There is a great deal of potential benefit for patients with both acute and chronic heart failure, but this is not well understood and requires systematic study," he says. So far, data indicate that compared to standard pacing, biventricular pacing increases the heart's output by 10%.

Trial 2: In the second study, Dr. Spotnitz is testing the effects of optimizing the location of the lead wires on the ventricles, and the timing of the electric impulses they send to the heart. "Studies have shown that adjusting the timing and the precise location are very important factors in determining how well a biventricular pacemaker works. Its effectiveness can be greatly increased by optimizing these parameters." To assess these factors, Dr. Spotnitz is leading a randomized trial testing different combinations of lead placement and timing. "There is a dramatic difference between the worst combination and the best combination of site location and timing," explains Dr. Spotnitz. "In the initial, exploratory stage of this trial, patients' cardiac output more than doubled when these parameters were optimized." At this time, Dr. Spotnitz is working with the Food and Drug Administration (FDA) to obtain an Investigational Device Exemption (IDE) to move to the next phase of the study.

"Biventricular pacemakers help some patients dramatically, and some not at all. In those who are not helped, is it because of the wrong combination of site location and timing? Or were they not good candidates for this therapy?" Dr. Spotnitz believes that when these and other questions are answered in clinical trials and this understanding is incorporated into the manufacture of devices, the benefits for all patients with heart failure will be substantial.

To learn more about biventricular pacing for heart failure, contact Henry M. Spotnitz, MD at 800.543.2782.

Thymosin Beta-4 and Chronic Wound Healing continued from page 11

wounds, would have the potential to improve the lives of many disabled patients," says Dr. Hardy.

Based on the results of this phase of the trial, the investigators plan to expand the study to examine the effect of thymosin beta-4 on the rate of post-operative wound healing, and to study the mechanism of its activity. This could lead to the clinical application of this novel hormonal approach to the recovery of surgical patients whose wound healing is impaired by various diseases.

For more information about chronic wounds, please visit the Wound Healing Center at www.columbiawoundhealing.org.

healthpoints is published by Columbia University Department of Surgery as a service to our patients. You may contact the Office of External Affairs for additional information, to be added to our mailing list, and to request additional copies. Please call 1- 800-543-2782.

For physician referrals, please call
1-800-543-2782

Deborah Schwarz-McGregor, RPA
Executive Director,
Office of External Affairs
Executive Editor

M. El-Tamer, MD
Medical Editor

Sherry Knecht
Managing Editor

Tanya Krawciw
Creative Director

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

healthpoints
ALL THE POSSIBILITIES OF MODERN MEDICINE