Researchers in the Department of Surgery are conducting studies that one day may result in improved outcomes for many critically ill patients.

Their research is examining the best way to prevent the reactivation of cytomegalovirus (CMV) in the critically ill surgical patient. A common pathogen in the herpes virus family that remains latent until the host’s immune system is compromised, CMV can result in abnormal inflammation and scarring in the lungs of the critically ill, setting the stage for infectious complications and end-stage organ failure.

The research effort began 10 years ago, when Dr. Charles H. Cook, assistant professor of surgery in the Division of General Surgery and principal investigator of the research, noticed that critically ill patients could experience reactivation of cytomegalovirus.

Cook and his fellow investigators conducted clinical studies to determine when reactivation occurred, and at the same time, they developed a murine model of reactivation in the laboratory. “Using that model over the past eight years, we determined what triggers reactivation and what its consequences are,” Cook says.

“One of the things we realized when we were studying human patients was that if you had CMV, there was a high incidence of bacterial infection. It was unclear whether bacterial infection triggered reactivation of CMV or whether CMV led to bacterial infection, and there are clinical data that support both of those hypotheses,” he says. “Using the animal model, we showed that bacterial infection could trigger reactivation of the virus. That was our first breakthrough in trying to figure out the mechanisms of reactivation.”

Cook says the researchers recently completed a paper in which they answer the most important question: whether reactivation is a problem. “One area where the virus reactivates is in the lungs. One of the clues we had that this might be a pathologic problem is that patients who got the virus in the ICU tended to be on the ventilator longer, to be in the ICU longer, and to have a worse outcome than patients who didn’t have reactivation,” he says. “We found that reactivation of the virus causes abnormal inflammation and scarring in the lungs, and that if you prevent reactivation using drugs, you can prevent the damage.”

Cook says the current focus of the research is determining optimal drug doses and dosing regimens to prevent reactivation of the virus. At the same time, the researchers are investigating portions of the septic response, to examine the causes of reactivation. “So far, it looks like many of the smaller parts...” (See Reactivation on page 2)
SURGICAL ONCOLOGY

Trial comparing partial, whole breast radiation therapy

Investigators at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute are participating in a multicenter study examining whether partial breast radiation therapy is as safe and effective as whole breast radiation, following surgery for certain early stage breast cancers.

The study, a phase 3 clinical trial sponsored by the National Cancer Institute, is recruiting 3,000 women with early stage breast cancer who have had a breast-conserving lumpectomy procedure.

Studies have shown that whole breast radiation therapy, which is usually given after a lumpectomy to kill any cancer cells that might remain in the breast, reduces local recurrences and increases long-term survival.

However, in recent years, thousands of women in the United States have elected to receive partial breast radiation therapy, instead of whole breast radiation. Partial breast radiation delivers therapy only to the tumor site and a small area of surrounding tissue. Although early reports suggest the newer procedure is safe and well-tolerated, no large, long-term studies comparing the two therapies have been conducted until now.

Women who agree to participate in the trial will first have a lumpectomy to remove their tumor and then will be randomized to receive either partial or whole breast radiation.

Whole breast radiation typically requires daily clinic or hospital visits for five to six weeks, while partial breast radiation requires therapy twice a day for only five days.

Dr. Stephen P. Povoski, associate professor of surgery in the Division of Surgical Oncology, says a shorter period of therapy is advantageous to many women.

“Some women who need radiation treatment after lumpectomy opt for a mastectomy, because they don’t have the means to come in for weeks at a time for whole breast radiation, “ he says. “For them, partial breast radiation therapy may be a good alternative, although we still need to find out if it is just as good clinically as the conventional treatment.”

Women who are randomized into the partial breast radiation arm of the study will have either a small balloon device inserted within the lumpectomy site for administration of the radiation therapy or else focused radiation therapy limited to the area around the lumpectomy.

Povoski says that in addition to providing a shorter treatment period, partial breast radiation can minimize radiation exposure to the rest of the breast, heart, and lungs and may spare patients some of the typical side effects of treatment, such as skin irritation.

Reactivation

From page 1

of the bigger septic response will trigger reactivation,” he says.

Cook hopes to eventually conduct a clinical trial that would block reactivation in at-risk patients and study the impact on their outcomes. “That’s our ultimate goal. What we’re doing now is laying the groundwork,” he says. “These drugs are potentially toxic, and these patients are very sick, so we want to have a clear idea of the dosing that will be helpful.”

“We’re uncovering a completely new disease process,” he says. “There’s a huge body of knowledge that needs to be developed.”

The research is supported by a five-year grant from the National Institute for General Medical Science.

Cook has been a regular speaker at the International Cytomegalovirus Workshop. Last year, he was an invited lecturer at the Fourth World Congress on Trauma, Shock, Inflammation, and Sepsis, in Munich, Germany. In 2003, he received the Surgical Infection Society’s prestigious Joseph Susman Memorial Award, for the most significant research presented that year.

In addition to studying CMV in the setting of critical illness, Cook collaborated for several years with Charles G. Orosz, Ph.D., the late professor of surgery who headed the transplantation research program in the Department of Surgery until his death in August 2005. Their work examined the influence of CMV inflammation on transplant tolerance and the influence of transplantation on reactivation. Cook has assumed leadership of the National Institutes of Health grant supporting those studies.
**CARDIOTHORACIC SURGERY**

**Technique reduces risks of surgery for treatment of esophageal cancer**

Ohio State is one of only a few U.S. institutions offering the minimally invasive procedure

As part of a multicenter trial sponsored by the National Cancer Institute’s Cancer and Leukemia Group B (CALGB), The Ohio State University Medical Center is among only a few institutions in the United States offering a minimally invasive procedure for the treatment of esophageal cancer.

Called minimally invasive esophagectomy, the procedure gives surgeons a clearer view of the chest and abdomen than that offered by traditional open surgery. In clinical trials to date, the minimally invasive technique has reduced respiratory complications and pain and shortened hospital stays.

Using endoscopic instruments inserted through nine small incisions in the chest and abdomen, surgeons remove most of the esophagus, one-third of the stomach, and the lymph nodes near the esophagus through an incision in the neck no more than two inches long.

“People often ask how we do this without having to open the chest and abdomen,” says Dr. Abbas E. Abbas, assistant professor of surgery in the Division of Cardiothoracic Surgery and a specialist in the treatment of esophageal cancer. “Interestingly, we can see even better inside, because we have magnification and long cameras that can go to places a surgeon’s eyes just can’t see. It’s especially helpful to be able to see the regional lymph nodes, which are often very difficult to assess with open surgery.”

Conventional open surgery to treat esophageal cancer involves three large incisions, from 15 to 20 centimeters each, which provide surgeons access to the abdomen, chest, and neck. The traditional open procedure also includes spreading the ribs, which is not necessary when the minimally invasive technique is used.

“Esophageal cancer traditionally has been a very difficult cancer to approach with any means of intervention,” Abbas says. “The traditional large incisions brought significant postoperative pain and were often accompanied by respiratory problems. It’s hard for patients to breathe after surgery because of the pain.”

After removing the damaged parts of the esophagus, part of the stomach, and the lymphatics, surgeons reattach the stomach to a pouch at the top of the esophagus. The stretched stomach rests in the space left open by the removal of the esophagus and in effect becomes the patient’s new esophagus.

“The traditional large incisions brought significant postoperative pain and were often accompanied by respiratory problems.”

“Even though we use a minimally invasive technique, these patients are still undergoing a significant operation,” Abbas says. “They can’t have the same large meals as before, so we encourage patients to eat multiple smaller meals throughout the day.”

The CALGB, a national clinical research group founded to bring together clinical oncologists and laboratory investigators and develop better treatments for cancer, has defined the criteria patients must meet to undergo minimally invasive surgery in the trial and is compiling data on the results. However, Abbas says patients may elect to have the minimally invasive procedure at Ohio State without enrolling in the trial.

The American Cancer Society estimates that more than 14,000 new esophageal cancer cases are diagnosed annually in the United States. The disease is three to four times more common among men than women.
A recent study led by Chandan K. Sen, Ph.D., has demonstrated that reactive oxygen species at certain levels can support the healing of wounds, and specifically, that wounds can generate their own low concentration of hydrogen peroxide, which has a role in healing.

The study found that at the site of injury, cells of wound tissue convert oxygen to reactive oxygen species, triggering oxidation-reduction, or redox-driven mechanisms. Although excess levels of reactive oxygen species, such as those found during chronic inflammation, may impair healing, low levels aid healing.

The observation that the redox state of the wound tissue may influence healing outcomes could lead to consideration of a novel redox-based principle for wound therapy, says Sen, professor of surgery, vice chairman for research in the Department of Surgery, and lead author of a paper detailing the findings of the study.

The paper is available in the on-line version of Molecular Therapy, the journal of the American Society of Gene Therapy.

A key characteristic of problem wounds is that they are hypoxic, or suffer from poor oxygenation, which means too little oxygen is available to initiate the reactive oxygen-dependent healing processes.

“Proper oxygenation of a wound is a fundamental prerequisite,” Sen says.

Under conditions of sufficient oxygenation, wound-related cells generate small amounts of reactive oxygen products, including hydrogen peroxide, which at certain levels act as chemical messengers to support healing. The hydrogen peroxide in question is not the typical household strength three-percent solution, but a lower concentration of the compound. At the molecular level, the hydrogen peroxide sends a message needed to trigger angiogenesis, or the formation of new blood vessels, the scientists found.

The study provides the first direct evidence that low levels of hydrogen peroxide are enzymatically generated by the body as a wound heals in healthy tissue.

Problem wounds, however, may suffer from conditions that limit hydrogen peroxide production at the wound site. In these and similar cases in which the body can’t be counted on to heal itself, delivery of reactive oxygen species could provide a new basis for therapeutic exploration, Sen says.

“We’re saying that the body makes hydrogen peroxide at very minute dosages that act as a signal for repair,” he says. “An excess of hydrogen peroxide can be damaging, but if we can find an innovative approach to deliver low levels of hydrogen peroxide into wounds that are difficult to heal, that could be helpful.

“Basic science studies have identified hydrogen peroxide as a trigger that drives redox signaling. Redox-based strategies to heal problem wounds may be applicable to a large number of people suffering from chronic wounds, such as diabetics, the immune-challenged, and those suffering from chronic granulomatous disease,” Sen says.

He says the study establishes a new paradigm supporting the role of reactive oxygen species as a signal for repair in the healing process. The findings also underscore the critical need to ensure that wounds are sufficiently oxygenated.

Sen co-authored the study, which was supported by the National Institute of General Medical Sciences, with Sashwati Roy, Ph.D., assistant professor of surgery; Savita Khanna, Ph.D., research scientist in surgery; Kishore Nallu, research assistant in surgery; and Dr. Thomas K. Hunt of the University of California at San Francisco.
Surgery faculty participate in firsts at Ohio State, Children’s Hospital

Department of Surgery faculty last year participated in transplantation firsts at The Ohio State University Medical Center and at Columbus Children’s Hospital.

At University Medical Center, transplantation faculty and staff made possible one of the first paired kidney exchanges in Ohio.

The arrangement allowed two patients in need of kidney transplants, who had willing but incompatible donors, to exchange donor organs.

In the exchange, which took place in August 2005, a 24-year-old Gahanna man, who was not a compatible donor for his mother, donated instead to a 34-year-old Cleveland area man. At the same time, the Gahanna man’s 52-year-old mother received a kidney from the Cleveland man’s 32-year-old wife, who was unable to donate to her husband.

The match between the unrelated local and Cleveland families was discovered after each couple had been through the preliminary screening process at University Medical Center only days apart, according to Dianne Goodrich, pre-transplant coordinator.

Testing showed that although the Gahanna man and the Cleveland woman were not compatible matches for their intended recipients, successful matches were possible if everyone involved agreed to swap donors.

“It was truly a serendipitous opportunity,” says Dr. Ronald Pelletier, assistant professor of surgery in the Division of Transplantation. “The couples agreed to the exchange, and what was turning out to be a dead end for the recipients became a win-win for everyone.”

Goodrich says, “The similar blood types between these two couples stood out, and it just struck us as a logical match.”

The four surgical procedures began simultaneously and involved four different surgical teams in separate operating rooms. Three hours later, the donors and recipients were recuperating from their operations, which were termed successful by Pelletier, lead surgeon in the procedures.

The other surgeons who participated in the operations were Dr. Ronald M. Ferguson, professor of surgery and executive director of the Comprehensive Transplant Center at University Medical Center; Dr. Mitchell Henry, professor of surgery and chief of the Division of Transplantation; and Dr. Amer Rajab, assistant professor of surgery and director of pancreas and islet cell transplantation in the division. Paired kidney exchanges offer advantages to people waiting for donor kidneys, Pelletier says.

“The success rate between recipients and live donor transplants are much better than when using organs from deceased donors, and pairing up eligible and willing donors with compatible recipients is an efficient use of resources,” he says.

Children’s Hospital

At Children’s Hospital, OSU Surgery faculty in July 2005 performed the institution’s first lung transplant.

The patient, who received two lungs, was a 23-year-old Pickerington woman who had suffered from cystic fibrosis since the age of 11.

Dr. J. Terrance Davis, professor of clinical surgery in the Division of Cardiothoracic Surgery at Ohio State, and Dr. Mark Galantowicz, associate professor of surgery in the division, collaborated on the operation.

The lung transplant program at Children’s was certified last year by the United Network for Organ Sharing and the Ohio Department of Health and Human Services and was accepted into the Ohio Solid Organ Transplant Consortium.

Cystic fibrosis causes thick mucus to accumulate in the lungs and digestive tract. In the lungs, the disease results in infection, which ultimately destroys the organs. ℹ️


---

**SPREADS**

**PUBLICATIONS**


**PRESENTATIONS**


El-Assal O, Besner G. Heparin-binding EGF-like growth factor (HB-EGF) promotes intestinal restitution. Third International Symposium on Necrotizing Enterocolitis, Columbus Children’s Hospital, Columbus, Ohio, April 16, 2005.

Ellison EC. Fifty years in neuroendocrinology. Gastrointestinal Cancers 2005: Current Updates on State-of-the-Art Management, The Ohio State University Medical Center, Columbus, Ohio, Aug. 26, 2005.


Muscarella P. Management of local pancreatic cancer. Gastrointestinal Cancers 2005: Current Updates on State-
I N B R I E F

of-the-Art Management, The Ohio State University Medical Center, Columbus, Ohio, Aug. 26, 2005.


Satiani B. Medicare: full disclosure. The Ohio State University, Department of Anesthesiology, Grand Rounds, Oct. 5, 2005.

Satiani B. Non-invasive arterial testing in non-healing wounds. The Ohio State University, Wound Care Committee, Oct. 25, 2005.

RECOGNITIONS

Dr. Lloyd G. Brown, a third-year resident in the Division of General Surgery and a student in the master of medical science program, was selected Sept. 1, 2005 to receive the first James King Research Award.

Brown received the award for a presentation titled “Analysis of Interleukin-29 Signal Transduction in Immune Cell Subsets,” a research project he is pursuing under the supervision of Dr. William E. Carson III, associate professor of surgery in the Division of Surgical Oncology.

The award, which is named in honor of Dr. James King, the first Ph.D. graduate of the Department of Surgery at Ohio State, provides $2,500 for travel to a national meeting and the purchase of educational materials.

Dr. Ginny L. Bumgardner, a surgeon in the Division of Transplantation, was promoted in Oct. 2005 to professor of surgery.

The Division of Pediatric Surgery’s fellowship program in surgical critical care, headed by Dr. Brian D. Kenney, assistant professor of clinical surgery, recently received accreditation for five years from the Residency Review Committee of the Accreditation Council for Graduate Medical Education.

Dr. W. Scott Melvin, chief of the Division of General Surgery and director of the Center for Minimally Invasive Surgery, was promoted in Oct. 2005 to professor of surgery.

Also, Melvin was course co-director for a postgraduate course titled “Gastrointestinal Cancers 2005: Current Updates on State-of-the-Art Management,” which was held Aug. 26, 2005, at The Ohio State University Medical Center.

The bariatric surgery program at The Ohio State University Medical Center, which is headed by Dr. Bradley J. Needleman, assistant professor of surgery in the Division of General Surgery, was recently named a Center of Excellence by the American Society of Bariatric Surgeons.

IN THE NEWS

Dr. William B. Farrar, professor of surgery and chief of the Division of Surgical Oncology, was interviewed Sept. 15, 2005, by WOSU-AM, about a Harvard study examining a possible link between surgery and cancer recurrence.

Dr. Mitchell L. Henry, professor of surgery and chief of the Division of Transplantation, was interviewed Sept. 19, 2005, by WCMH-TV/4, about questions involved in face transplantation.

Dr. Peter Muscarella II, assistant professor of surgery in the Division of General Surgery, was interviewed Dec. 1, 2005, by WBNS-TV/10, and Dec. 2, 2005, by WTVN-AM, for a story about pancreatic cancer.

Dr. Bradley J. Needleman, assistant professor of surgery in the Division of General Surgery, was quoted Oct. 19, 2005, by the Columbus Dispatch, in a story about a study finding that obese Americans who undergo weight-loss surgery die more often than previously expected.


Dr. Ronald P. Pelletier, assistant professor of surgery in the Division of Transplantation, and Dianne Goodrich, pre-transplant coordinator, were quoted Aug. 24, 2005, by the Columbus Dispatch, in a story about a paired kidney donation between two unrelated couples at University Medical Center. On Aug. 25, 2005, Pelletier was interviewed by WBNS-TV/10, for a story on the kidney exchange.
INSIDE:

1 Investigator studying viral reactivation in critical illness

2 Trial comparing partial, whole breast radiation therapy

3 Technique reduces risks of surgery for treatment of esophageal cancer

4 Scientists identify new role for oxygen in wound healing

Mark Your Calendar

The 2006 World Robotic Urology Symposium

April 7–8, 2006
Wexner Center for the Arts
The Ohio State University
Columbus, Ohio

See the Center for Continuing Medical Education web site at http://ccme.osu.edu

For more information, call (614) 293-3576