Not Getting Burned

By Ellen Goldbaum

System helps prevent radiation-induced skin injuries

The threading of slender catheters and stents through arteries to deliver treatments to the heart, the brain and elsewhere in the body has produced nothing short of a medical revolution.

But these delicate procedures require that patients be exposed to continuous radiation that can last up to an hour or more, sometimes causing skin injuries that, in rare cases, develop necrosis (tissue death), requiring skin grafts.

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Now, University at Buffalo researchers, working with an Amherst, New York, startup company called Esensors, have developed a unique, real-time patient dose-tracking system, which lets physicians know when the accumulated radiation dose is approaching a dangerous threshold.

The system is designed to be used either as a retrofit with existing fluoroscopy machines or to be included in the design of new machines.

Funded by grants totaling $814,000 from the U.S. Food and Drug Administration under the Small Business Innovation and Research program, the team of researchers is completing a prototype that will be clinically site-tested prior to commercialization.

"Our system provides complete tracking of actual radiation levels on the skin, providing both instantaneous dose rate, as well as cumulative exposure," explains project director Daniel Bednarek, PhD, a researcher at UB's Toshiba Stroke Research Center, professor of radiology, and research associate professor of neurosurgery and biophysics in the School of Medicine and Biomedical Sciences.

Development of the system was spurred by a growing concern among physicians and by advisories issued by the Food and Drug Administration's Center for Devices and Radiological Health warning of occasional, but severe, radiation-induced skin injuries during prolonged, fluoroscopically guided invasive procedures.

"It can take a long time to insert a catheter into the brain and perform a complicated endovascular treatment, for example," notes Bednarek, who is also adjunct professor in the Department of Physics in UB's College of Arts and Sciences. "Patients undergoing such procedures sometimes develop erythema—redness—hair loss or even skin necrosis in the exposed area."

These effects can result whenever long fluoroscopic times are used during interventional procedures, such as coronary angioplasty, stent placement, radiofrequency cardiac ablation and vascular embolization.

"With the equipment that currently is being used, the physician can minimize the chance for burns by moving the X-ray source instead of keeping the intensity on one spot," says Darold Wobschall, PhD, professor emeritus of electrical engineering at UB and president of Esensors. "The problem is that the physician is concentrating on the surgery and with X-rays coming in, he or she would have to be keeping mental track of where the dose is occurring at the same time. Our system solves that problem."

Through electronic sensors, the system tracks the position of the X-ray gantry and patient table, and thus, the location of the X-ray relative to the patient to determine the radiation exposure at the patient's skin.

"The computer tracks the beam's location and intensity, presenting the

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—Daniel Bednarek, PhD

beam and the cumulative distribution of dose on the patient's skin as a color-coded graphic on a display screen," says Wobschall.

As the dose accumulates, the color on the display changes from green, which is acceptable, through yellow to red, which is a signal that the patient could be receiving too much radiation.

This visualization of the X-ray beam and its location with reference to a graphic model of the patient presents the physician with real-time visual feedback, allowing him or her to make the appropriate adjustments.

An added feature under development includes a visualization of the distribution and amount of X-ray scatter throughout the room, providing a way to gauge exposure for the physician and other health-care personnel who may be present.

The development effort for the computer graphic display was led by co-investigator Kevin Chugh, PhD, formerly a research scientist in UB's New York State Center for Engineering Design and Industrial Innovation (NYSCEDII).

Petru M. Dinu, a doctoral candidate in the UB Department of Physics in the College of Arts and Sciences, played a major role in developing the system at UB's Toshiba Stroke Research Center. BP

Breathing Easier

Study shows smokefree law works

By Deborah Pettibone

Indoor air quality in bars, restaurants and other hospitality venues in Western New York (WNY) has improved significantly since implementation of a comprehensive New York State law requiring almost all indoor workplaces and public places to be 100 percent smoke-free. Results of the indoor air-quality study conducted by researchers at Roswell Park Cancer Institute (RPCI) were published in the November 10, 2004, issue of the Centers for Disease Control and Prevention's (CDC) *Morbidity and Mortality Weekly Report.*

Baseline air-quality measurements were made before the law took effect in July 2003 at 22 hospitality venues in three WNY counties, including seven bars, six bar/restaurants, five restaurants, two bowling alleys, a pool hall, and a bingo hall. The urban and suburban venues ranged from small neighborhood bars to large bar and restaurant chains. Follow-up measurements were taken three months after the law took effect in the same establishments on the same day of the week, and at approximately the same time of day. An air monitor was used to sample and record the levels of respirable suspended particles (RSPs). On average, the levels of RSPs declined by 84 percent after the law took effect.

"This study demonstrates that a statewide law to eliminate smoking in enclosed workplaces and public places dramatically reduced the levels of secondhand smoke in a wide range of hospitality venues," says Andrew Hyland, PhD, Department of Health Behavior at RPCI and lead author of the study.

Secondhand smoke contains more than 50 carcinogens and is responsible each year in the United States for an estimated 3,000 lung cancer deaths and more than 35,000 coronary heart disease deaths among people who have never smoked. It also contributes to respiratory infections, asthma, sudden infant death syndrome and other illnesses in children.

"Hospitality workers are the occupational group most exposed to secondhand smoke, a public-health hazard that is entirely preventable," notes Hyland. "This study adds to the evidence that smoke-free policies protect employees and patrons from the health effects associated with secondhand smoke exposure." BP

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Technique revolutionizes lumbar spine surgery

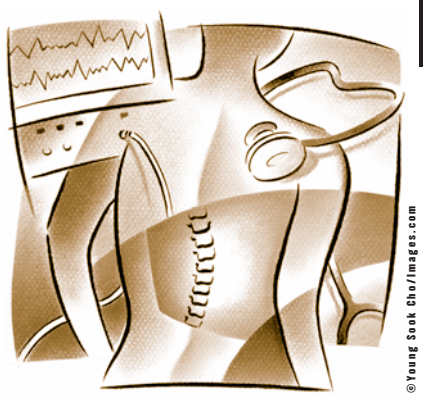
A Surgical First

Early this year, neurosurgeons in the School of Medicine and Biomedical Sciences performed the first minimally invasive spinal surgery in the U.S. using a new technique called axial lumbar interbody fusion (AxiaLIF ™) to stabilize the lumbar spine.

The procedure requires only a small incision in the back and allows patients to be ambulatory without pain just hours after leaving the operating room.

The first U.S. patient to undergo the new surgery said that two hours after the operation the pain in her back and leg was totally gone and that she was "just a little sore."

By Lois Baker



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"Lumbar spine surgery will never be the same," said L. Nelson Hopkins, MD, professor and chair of the UB Department of Neurosurgery, upon hearing of the patient's good results. "This begins a total revolution."

The new technique could be used for 90 percent of all fusion surgeries, Hopkins says.

Elad Levy, MD, UB associate professor of neurosurgery and radiology, performed the surgery on January 28 at Kaleida Health's Millard Fillmore Hospital. The patient was a 31-year-old woman who had a long history of back pain due to an injury. She had recently re-injured her spine, which resulted in debilitating pain in her back and legs that required her to take a leave from her bank job and to use a cane to walk.

Levy says the patient was an ideal candidate for the technology's U.S. premiere because she did not have arthritis or degeneration of the vertebrae, conditions often seen in the mostly older persons who require back surgery.

Typically spinal fusion surgery requires a 5-to-6-inch incision in the back, retraction of the back muscles and tissue in order to gain access to the surgery site, cauterization of blood vessels and generalized trauma to the entire spinal region, explains Levy. The patient usually spends several days in the hospital and several months in recovery.

Axial lumbar interbody fusion requires a 2-centimeter incision just to the left of the tailbone. Instruments needed to perform the procedure are threaded internally along the spine to the surgery site by following a guide wire. Miniaturized scrapers remove torn and diseased disk material and tiny drills create the spaces to insert screws that stabilize the spine.

For the right patients, the procedure could be done on an outpatient basis, Levy says.

The technique was developed five years ago by an interventional radiologist who founded a company called Axial Med, now Trans1 Inc. The first trials on cadavers took place at UB's Toshiba Stroke Research Center in 2000.

The first surgeries were performed in Brazil, where 35 patients have been operated on since the technique was introduced there in 2003. The Food and Drug Administration (FDA) only recently approved the procedure for use in the U.S.

"Dr. Hopkins has developed the premiere model for minimally invasive surgery centers in the U.S., so it's fitting that the first surgery took place in Buffalo," notes Rick Randall, president and CEO of Trans1 Inc. "This surgery was the first step in the validation of this unconventional approach to spinal surgery. This is going to be standard practice in the future." BP

Tissue-Engineered Blood Vessels

Potential for use in heart bypass surgery

Researchers at the University at Buffalo have developed a process in which cells are used to construct new blood vessels, opening the door to growing new blood vessels for procedures like coronary bypass surgery.

By Ellen Goldbaum

They describe their work in a paper published online in the American Journal of Physiology—*Heart and Circulatory Physiology* on October 14, 2004.

The small-diameter tissue-engineered blood vessels (TEVs), developed and implanted in sheep, exhibited the strength and resiliency necessary for implantation after just two weeks in culture, to date the shortest development time for artificial vessels that have functioned successfully. The TEVs functioned well in vivo for 15 weeks after implantation.

The UB researchers constructed the vessels by embedding vascular smooth-muscle cells isolated from sheep umbilical cords into fibrin, the essential clotting ingredient in blood. The fibrin gel matrix then was shaped into cylinders; after only two weeks, the tissue thinned down to approximately half a millimeter and they could then be implanted.

"We have shown that fibrin-based vessels can be implanted in vivo, remain patent and support blood flow rates for 15 weeks," says Stelios Andreadis, PhD, associate professor of chemical and of biological engineering in the UB School of Engineering and Applied Sciences. Andreadis was co-author on the paper with Daniel D. Swartz, PhD, research assistant professor, and James A. Russell, PhD, professor, both in the UB Department of Physiology and Biophysics in the School of Medicine and Biomedical Sciences.

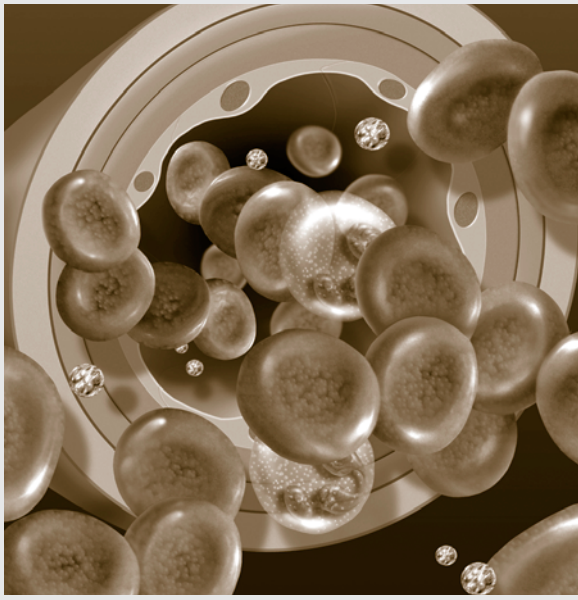
The tissue-engineered blood vessels exhibited blood flow rates and reactivity similar to those of native vessels.

"It's not a stretch to extrapolate that these TEVs could remain functional in the long term because the animals presented no adverse effects," says Andreadis.

Even more critical, the scientists say, the TEVs performed like native vessels 15 weeks after implantation, when the animals used in the research were sacrificed. They exhibited excellent 'remodeling,' producing collagen and elastin, and had increased their mechanical strength by more than a factor of three.

"These are the first tissue-engineered vessels to show long-term viability without clotting—a key problem with small diameter vessels—and with no adverse effects observed from the material we used," reports Andreadis. "Before implantation, the inner walls of these TEVs are coated with endothelial cells to mimic the composition of native tissue and prevent thrombosis."

After implantation, he notes, the fibrin gel was completely undetectable, an important outcome since some materials in other systems have degraded into toxic byproducts.



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The TEVs also exhibited not just mechanical strength, but the critical ability that native vessels have to constrict or dilate in response to their environment.

"We put our TEVs through rigorous testing," he says, "and we found that they are very reactive. We have developed vessels that dilate or constrict mechanically in response to chemical compounds. That's how native vessels adapt to changing flow rate."

Because of this property, the vessels may have additional applications as model systems for studying how mechanical forces act on the blood vessel wall.

They also may have application as toxicological models for in vitro testing of how vasoconstricting or vasodilating drugs affect blood vessels, Andreadis adds.

The research was supported by grants from UB's Interdisciplinary Research and Creative Activities Fund and by the Women's and Children's Hospital of Buffalo. A patent application has been filed on the tissue-engineered vascular vessel and the method for making it. BP

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By Lois Baker

Clean Teeth, Healthy Lungs

Oral health protects elderly from pneumonia

Helping nursing home patients brush their teeth or dentures does more than freshen breath, increase comfort and prevent gum disease: Physicians now have evidence that good oral health in institutionalized elders may help protect them from contracting potentially deadly pneumonia if they are hospitalized.

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This understanding is based on a University at Buffalo study in which researchers used molecular genotyping to match respiratory pathogens from the lungs of eight patients who developed hospital-acquired pneumonia with pathogens collected from their dental plaque when they were admitted to the hospital.

The study, which was reported in the November 2004 issue of the journal *Chest,* "is the first to establish unequivocally a link between dental hygiene and respiratory infection," says Ali A. El-Solh, MD, MPH, associate professor of medicine in the UB School of Medicine and Biomedical Sciences and first author on the study.

"Further research is now needed to determine the type of therapeutic intervention and the frequency of oral care required to reduce the risk of pneumonia in institutionalized elderly," he adds.

Earlier research, including studies conducted at UB, showed that the same types of bacteria commonly found in dental plaque often are present in those with respiratory diseases. However, the current investigation is the first to show that pathogens found in a patient's mouth at admission are genetically identical to pathogens found later in lung fluid following a diagnosis of hospital-acquired pneumonia.

The study population was composed of 49 nursing home residents who were admitted to the intensive care unit of Erie County Medical Center and required a respirator. The researchers omitted patients who had pneumonia when admitted or who developed pneumonia within 72 hours; had a low platelet count or blood-clotting disorders; had received antibiotic therapy or been hospitalized within the past 60 days; needed immunosuppressive drugs, or had no teeth or dentures.

All study patients were assigned a dental-plaque score following an oral examination, and samples of plaque were collected to determine the types of bacteria present. Of the 49 patients, 28 had respiratory pathogens in their dental plaque samples and 21 did not.

Patients were watched closely for signs of pneumonia. Fourteen patients eventually developed the infection: 10 from the respiratory pathogen group, four from the no-pathogen group.

Fluid samples collected from those with pneumonia were assayed to determine the type of bacteria present. Results showed that of 13 pathogens isolated from lung fluid, nine were a genetic match to those recovered from the plaque of the corresponding patient.

"These findings indicate that dental plaque is a reservoir of respiratory pathogens that can cause pneumonia in hospitalized institutionalized elders," says El-Solh. "We need to investigate the relationship between the burden of dental disease and the incidence of respiratory events.

"In the meantime, nursing homes and other institutions housing frail elderly should be involved actively in improving daily oral hygiene of their residents and enhancing access to dental care," he recommends. BP

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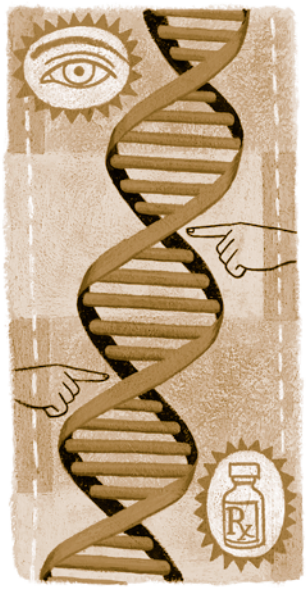
A GENE THERAPY METHOD that doesn't rely on potentially toxic viruses as vectors may be growing closer to the clinic due to in vitro research conducted by University at Buffalo scientists, the results of which were published in the January 11, 2005 issue of the *Proceedings of the National Academy of Sciences.*

The paper, which describes the successful uptake of a fluorescent gene by cells using novel nanoparticles developed as DNA carriers, demonstrates that the nanoparticles ultimately may prove an efficient and desirable alternative vector to viruses.

Nanoparticles As Vectors

Circumventing viruses in gene-therapy transfer

BY ELLEN GOLDBAUM



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Using confocal microscopy and fluorescent spectroscopy, UB scientists tracked optically in real-time the process known as transfection, including the delivery of genes into cells, the uptake of genes by the nucleus and their expression.

"We have shown that using photonics, the gene-therapy transfer can be monitored, tracking how the nanoparticle penetrates the cell and releases its DNA in the nucleus," explains Paras N. Prasad, PhD, executive director of the UB Institute for Lasers, Photonics and Biophotonics, SUNY Distinguished Professor in the Department of Chemistry in UB's College of Arts and Sciences, and a co-author of the paper.

"When the fluorescent protein was produced in the cell, we knew transfection had occurred," he says.

The work is important in light of the difficulties that have plagued gene-therapy human trials in recent years, including some fatalities that may have resulted from the use of viral vectors.

"Efficient delivery of the desired gene and substantial release inside the cell is the major hurdle in gene therapy," explains Dhruba J. Bharali, PhD, a co-author and postdoctoral researcher in the UB Department of Chemistry and UB's Institute for Lasers, Photonics and Biophotonics, where the work was done.

"Viruses have been used as efficient delivery vectors due to their ability to penetrate cells, but there is the chance they can revert back to 'wild' type," he says.

While non-viral vectors are safer, he notes that it is much more difficult to get them into cells and then to achieve the release of DNA once they do penetrate cells.

The advantage of the UB team's approach, he explained, is that unlike most other nonviral vectors, the DNA-nanoparticle complex releases its DNA before it can be destroyed by the cell's defense system, boosting transfection significantly.

The UB scientists also were able to use photonic methods to provide an unprecedented look at how transfection occurs, from the efficient uptake of nanoparticles in the cytoplasm to their delivery of DNA to the nucleus.

"By using our photonics approach, we can track gene delivery step-by-step to optimize efficiency," explains Tymish Y. Ohulchanskyy, PhD, the third co-author and post-doctoral research scholar at the institute.

The research team makes its nanoparticles from a new class of materials: hybrid, organically modified silicas (ORMOSIL).

"The structure and composition of these hybrid ORMOSILs yield the flexibility to build an extensive library of tailored nanoparticles for efficiently targeting gene therapy into different tissues and cell types," says Prasad.

The UB researchers now are collaborating on in vivo studies with colleagues from the UB School of Medicine and Biomedical Sciences to use their novel nanoparticles to transfect neuronal cells in the brains of mice. BP

This research was supported by the U.S. Air Force through its Defense University Research Initiative on Nanotechnology (DURINT) grant.