Profiles in Innovation

Research

DOWNSTATE 2009

Protecting the Brain
While Repairing the Heart page 14

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Albert Einstein, whose scientific discoveries rendered his name a synonym for genius, was a mediocre student in his earliest years. The explanation for this seeming paradox may be found in his own words: “I have no special talents. I am only passionately curious.”

It probably goes without saying that research scientists are driven more by curiosity than by any other human trait. Einstein cautioned, “The important thing is not to stop questioning...never lose a holy curiosity.” Yet for curiosity to yield results it needs endurance and nurturing. And that is where institutions like SUNY Downstate Medical Center come in.

SUNY Downstate has supported research in the advance of science, medicine, and health for 150 years, from the discovery of the glands named after one of Downstate’s founders, Dr. Alexander Skene, to the work in Downstate’s laboratories by the late Dr. Robert Furchgott that yielded him the 1998 Nobel Prize in Medicine. Dr. Furchgott recalled that his immense curiosity about the world began when as a child he attended nature study classes and became an avid shell collector and bird watcher. Yet Dr. Furchgott also noted a debt to the funding sources and the campus that made it possible for his lifelong pursuit of knowledge to bear fruit.

This issue of Profiles in Innovation is dedicated to our cutting-edge clinical research, which includes work on drug efficacy and safety in newborns; producing images of brain perfusion during open-heart surgery to help prevent cognitive loss; the problem of antibiotic resistance and the need for new drugs; the fatal danger of genital herpes to newborns and the search for a vaccine; racial disparities in cancer care; and cardiovascular disease in HIV-positive patients.

You will also learn of the leadership our campus has provided in disaster preparedness training; how lifesaving cervical cancer detection is being extended to the poor; and how Downstate is transforming the treatment of heart valve disease.

I think you will agree that “holy curiosity” is alive and well at Downstate.

Ian Taylor, MD, PhD
Senior Vice President,
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Cervical cancer is a largely preventable disease.

Pap smears, which assess cervical cells for signs of cancer or precancerous growth, have enabled doctors “to find lesions early, when they’re close to 100 percent curable,” notes gynecologic oncologist Ovadia Abulafia, MD. In fact, Pap smears and newer generation tests have all but eliminated cervical cancer in the industrialized world.

Except among the poor. Their limited access to medical care means they often miss out on cervical cancer screenings and the health benefits they provide. “Unfortunately, patients frequently come to us with cervical cancer that is in the advanced stages,” says Dr. Abulafia, a professor and chair of Downstate’s Department of Obstetrics and Gynecology. “They often haven’t had a Pap smear in ten years.”

That regrettable situation is also an important research opportunity. Though the disease’s prevalence in the United States is down steeply from the highs of the pre-Pap test 1940s — about 11,000 cases are now diagnosed annually, according to the National Cancer Institute — worldwide, cervical cancer remains the second-most common malignancy among women. Two hundred and eighty-eight thousand women die of the disease each year.

Dr. Abulafia has played an important role in researching cervical cancer screening and treatment, both as a principal investigator for the Gynecologic Oncology Group (GOG), a National Cancer Institute-funded cooperative clinical trials group, and as a former member of GOG’s cervical committee, which determines the standard of care for cervical cancer patients in the United States.

“What we know about gynecological cancers today is considerably more than what we knew 15 or 20 years ago,” he says. “And as a result, we’ve made significant progress in treating certain GYN malignancies, particularly cervical cancer.”

Dr. Abulafia is a strong advocate of the clinical trials system. “We offer participation in GOG trials to every patient who medically qualifies for a trial, regardless of ability to pay,” he notes.

Under his leadership, Dr. Abulafia and his colleagues have explored new types of cervical cancer screening, evaluating methods such as ThinPrep® (liquid-based cervical cytology), a more advanced Pap test. In fact, in a 2003 study published in the journal Gynecologic Oncology, Dr. Abulafia reported that ThinPrep® was more sensitive and accurate than the traditional Pap smear.

Dr. Abulafia has also pursued research into possible connections between HIV and cervical cancer. Because the vast majority of cervical cancers are viral in origin — caused by
persistent infections with carcinogenic strains of the human papillomavirus — and because HIV hinders immune responses, some in the medical community have been concerned that HIV-positive women may be at greater risk for precancerous cervical lesions and for cervical cancer itself.

Dr. Abulafia’s studies have tested whether cervical cancer screening methods are effective in HIV-positive women and whether a surgical technique called cervical conization can prevent progression to invasive cancer among HIV-positive women with precancerous cervical lesions.

“We found these methods were less effective in HIV-positive women than in healthy women, and those results emphasized the need for increased vigilance in testing HIV-positive women for cervical cancer,” Dr. Abulafia explains. “But now, with the widespread introduction of antiretroviral therapy for HIV-positive women, the incidence of both precancerous lesions and invasive cervical cancer has declined significantly.”

Dr. Abulafia has also collaborated with Downstate radiation oncologist Marvin Rotman, MD, in testing cervical cancer treatments that combine radiation and chemotherapy. (See Dr. Rotman’s profile on page 6.) One such trial found a 15 percent increase in five-year survival using the combined approach. “Our research with Dr. Rotman has enabled us to make significant progress in treating women at high risk for recurrent cervical cancer,” Dr. Abulafia says. “And we have vastly increased our knowledge about the complications and side effects of treatment.”

In fact, Dr. Abulafia says, “every GOG trial we participate in results in some important new knowledge, even if the trial proves the new treatment isn’t successful.”

Every trial we participate in results in some important new knowledge, even if the trial proves the new treatment isn’t successful.

With the conventional Pap smear method, cells can be obscured by blood, mucus, and inflammation.

The ThinPrep Pap Test method preserves the cells and minimizes cervical cell overlap with blood, mucous, and inflammatory cells.

Members of the Division of Gynecologic Oncology (from left): Wen-Ching Lee, PhD, Institutional Review Board administrator for GOG studies; Allison Wagreich, MD, senior gynecologic oncology fellow; Dr. Abulafia; Joyce McGuire, RN, clinical trials coordinator; Yi-Chun Lee, MD, gynecologic oncology division chief; Ghadir Salame, MD, junior gynecologic oncology fellow.

With the conventional Pap smear method, cells can be obscured by blood, mucus, and inflammation.

The ThinPrep Pap Test method preserves the cells and minimizes cervical cell overlap with blood, mucous, and inflammatory cells.

Number of U.S. women with invasive cervical cancer
Forty-five years ago, doctors, in order to protect cancer patients from radiation therapy’s low-energy beams, regularly covered them with rubber mats at the radiation site to reduce skin necrosis during treatment.

“The mat was about a centimeter thick, with little holes punched in it,” recalls Marvin Rotman, MD, a distinguished service professor of radiation oncology and chair of Downstate’s Department of Radiation Oncology.

In those days, the radiation beams used to kill cancer cells were not only much more diffuse than the pencil-thin beams used today, they also delivered 15 times less energy. Cancer patients were regularly subjected to disfiguring and intensely painful procedures that did little to improve their survival or quality of life. “It was a primitive enterprise back then!” Dr. Rotman recalls. “A young boy with Hodgkin’s disease and a bone lesion had a death sentence. Today, his chances of survival would be between 70 and 80 percent.”

As a researcher and clinician, Dr. Rotman has made significant contributions to the field of radiation oncology, utilizing ongoing support from the Radiation Therapy Oncology Group, a...
National Cancer Institute-funded clinical trials cooperative. He and collaborator Julian Rosenthal, MD, developed a number of new treatments using concomitant chemotherapy and irradiation. In treating certain cancers, radiation therapy also has another important benefit: administered “15 minutes to one hour after chemotherapy, there can be an almost synergistic cancer-killing effect,” Dr. Rotman explains. “It is often twice that of chemotherapy alone.”

Indeed, his research into concurrent chemo-radiation has significantly improved survival for patients with head and neck cancers, bladder cancer, soft tissue sarcomas, and gastrointestinal cancers that have spread to the liver. Dr. Rotman has also been instrumental in improving the treatment of carcinoma of the uterine cervix. He has transformed the treatment of melanoma of the eye, a rare form of ocular cancer. The American Society of Therapeutic Radiology and Oncology (ASTRO) recognized his pioneering work by awarding him its Gold Medal, the highest honor in the field.

“If there’s a theme to my work,” Dr. Rotman says, “it’s extending radiation therapy beyond palliation to cure disease and maintain organ function. Although, the truth is, we still have a long way to go.”

As a form of cancer treatment, radiation therapy offers unique benefits. “Using ionizing radiation, we can destroy cancer cells that can’t be seen with the naked eye,” Dr. Rotman explains. The technique can be particularly effective in eliminating micrometastases in lymph nodes, thereby helping prevent cancer’s spread, and in shrinking solid tumors. As a result, radiation therapy can allow for the removal of previously inoperable tumors, improve quality of life, and extend survival.

Increased survival is not the only goal of Dr. Rotman’s investigations, however. “I believe organ preservation is very important,” Dr. Rotman says. That belief guided his treatment approach to choroidal melanoma, a rare cancer of the eye.

Formerly, the disease had been treated with enucleation, or removal of the eye. But beginning in the mid-1970s, “I advocated for leaving the eye intact,” and treating the cancer with a temporarily implanted radioactive disk, Dr. Rotman notes. Almost 25 years later, a long-term, prospective trial found that the two approaches — Rotman’s and enucleation — led to similar survival rates. “It’s gratifying that this technique enables people to retain their eyes without jeopardizing their well-being,” Dr. Rotman says.

Dr. Rotman’s innovative techniques have advanced the science and provision of cancer treatment. “I look back with a sense of contentment,” he says, “and consider myself lucky to have contributed to radiation oncology’s life-saving potential.”
The racial disparities that exist in our country don’t disappear in the presence of cancer. In fact, the disease often highlights them. Black Americans — native-born African Americans as well as immigrants from the Caribbean and other parts of the world — suffer from the highest cancer death rates, with black men 35 percent more likely to die of the disease than white men, and black women 18 percent more likely to die than white women.

These disparities have many causes. One is that “the African American community doesn’t participate as widely in screening as some other communities,” explains hematologist/oncologist William Solomon, MD, a professor of medicine. “That can be for both economic and social reasons. Moreover, often, African Americans don’t have access to the same high-quality early detection and treatment services.”

Disparities by race are not limited to cancer survival, however. They continue as well in cancer clinical trials. In fact, a 2004 study published in the *Journal of the American Medical Association* found blacks and Latinos were one-third less likely than whites to participate in National Cancer Institute-sponsored clinical trials. This despite a consensus in the medical community that “the ethnic and racial make-up of clinical trials should reflect the patient population,” Dr. Solomon says. Without sufficient minority enrollment in clinical trials, researchers are unable to “conduct valid analyses of the intervention effect in these populations,” the National Institutes of Health has written.

At Downstate, 89 percent of oncology patients are African American or Caribbean American. Since October 2007, under Dr. Solomon’s director-
ship and with assistance from hematologist Olcay Batuman, MD, a professor of medicine, researchers and clinicians here have helped address the problem of racial disparities in clinical trial participation by offering patients unprecedented access to these medical studies. The effort is funded by the National Cancer Institute’s Minority-Based Community Clinical Oncology Program (MB-CCOP).

“The cancer trials we offer, and the state-of-the-art treatment that is part of those trials, are the same trials found at major cancer centers,” explains Dr. Solomon. “With this program, patients don’t have to go into Manhattan to enroll in a trial at Memorial Sloan-Kettering or New York Hospital. That fact benefits patients in Brooklyn, and it also benefits cancer research as a whole.”

Though oncologists in private practice sometimes encourage their patients to enroll in clinical trials, programs dedicated to increasing clinical trials enrollment at medical centers that are not dedicated cancer-treatment facilities are rare. In fact, Downstate is one of only 13 MB-CCOP sites in the United States, “and the only one in the Northeast,” notes Dr. Solomon, who, in 2008, was one of only 55 physicians nationwide to receive the Cancer Liaison Physician Outstanding Performance Award from the American College of Surgeons, the world’s largest surgeons’ organization. The award recognizes physicians “who go above and beyond the scope of their regular duties to improve patient care and provide direction to their hospital’s cancer program,” the organization notes.

With the MB-CCOP funding has been used to support the program’s outreach to local organizations. “Part of what we’re investigating is how best to collaborate with minority communities,” explains Dr. Solomon.

Working with Downstate’s Graduate Program in Public Health, the MB-CCOP has conducted surveys about attitudes towards clinical trials. “We’ve also met with various church groups and other groups in the area to discuss the services our program offers to patients,” Dr. Solomon says. The MB-CCOP staff emphasizes that the program’s trials are open to anyone, “regardless of immigration status and regardless of ability to pay.”

Among the services that Downstate’s MB-CCOP provides is “patient navigation,” a program in which cancer survivors help new patients access social services and negotiate their way through what is often a complex medical system.

In recent months, the MB-CCOP has begun enrolling individuals in cancer treatment and prevention trials, including one examining the efficacy of various smoking cessation techniques. Last year, it enrolled more patients than any other hospital in the country in a clinical trial testing the value of publications designed to aid patients after treatment.

“You can’t make progress in oncology without clinical trials,” Dr. Solomon notes. “And with the support of the MB-CCOP, we’re working to ensure that this progress benefits everybody.”
Heart Valve Disease: A Growing Problem

More than once, Jeffrey S. Borer, MD, has helped transform the treatment and diagnosis of heart diseases.

In the mid-1970s, working with colleagues at the National Institutes of Health, he introduced nitroglycerin as a treatment during heart attack. Later in the decade, in collaboration with physicists Michael V. Green, and Stephen L. Bacharach, Dr. Borer developed radionuclide cineangiography (RNC), a non-invasive imaging technology that revolutionized cardiac stress testing.

Today, Dr. Borer is chairman of Downstate’s Department of Medicine and chief of its Division of Cardiovascular Medicine. He is the editor-in-chief of the journal Cardiology, and, for more than 30 years, has been an advisor to the Food and Drug Administration, having chaired its Cardio-Renal Advisory Committee and its Circulatory Devices Advisory Panel. The latter advises the FDA on the approvability of such devices as catheters, pacemakers, implantable defibrillators, and heart valves.

It’s regrettable that heart valve disease never makes headlines the way other cardiac problems do.

As director of Downstate’s Howard Gilman Institute for Heart Valve Disease, he continues his pioneering work in an area that garners little public attention.

Heart valve disease remains one of cardiology’s vexing problems. Dysfunction in one or more of the valves can lead to heart failure, stroke, and sudden death from cardiac arrest. Yet, there is no effective treatment for the illness, save surgery. And much about the disease’s natural history remains unknown, making it difficult for doctors to know when best to intervene.

Dr. Borer and his colleagues, including clinical epidemiologist and Professor of Medicine Phyllis Supino, EdD; cardiologist, bioengineer, and Chief of Clinical Cardiology Edmund Herrold, MD, PhD; and molecular biologist and Research Professor of Medicine Daniel Catanzaro, PhD, have worked hard to address this paucity of medical knowledge. For more than 30 years, Dr. Borer’s team has documented the disease’s natural history. They have also explored its genetics and molecular biology. “The information we gather will enable us to better evaluate candidates for surgery,” he explains. “And, I hope, lead to new drug approaches to treatment.”

“It’s regrettable that heart valve disease never makes headlines the way other cardiac problems do,” Dr. Borer says. The illness is indeed newsworthy: Approximately 125,000 heart valve surgeries are performed each year in the United States, and 50 percent of people
over the age of 70 have some valve dysfunction. “As the population ages, valve disease is becoming a major public health issue,” Dr. Borer says.

Valvular heart disease has varied causes. Genetic variants are a common one, as is rheumatic fever. That disease is rare now in the United States, but quite common in the Caribbean, from which many of Downstate’s central Brooklyn neighbors hail. Among individuals with neither of those two risk factors, “there seems to be a genetic predisposition stimulated by certain environmental conditions,” Dr. Borer says.

To document the disease’s natural history, Dr. Borer and his colleagues have followed a cohort of almost 500 individuals with heart valve dysfunction. The team is not simply observing the disease process, however.

“We’re trying to determine what predicts poor outcomes, in order to define the best time for valve surgery,” Dr. Borer says. “In addition, we evaluate the process of functional recovery after surgery and examine what predicts death, morbidity, and other bad outcomes, such as heart failure.” In fact, a significant percentage of individuals who undergo surgical valve repair or replacement die suddenly of related causes within 10 years.

The team’s study has already determined that individuals with systolic hypertension — in which only the upper number in the blood pressure is elevated — and a type of heart valve disease called aortic regurgitation are three times more likely to suffer from heart failure or sudden death as individuals with aortic regurgitation alone.

Now, Dr. Borer, Dr. Supino and their colleagues are studying whether “poor exercise capacity before surgery predicts survival after,” Dr. Supino says. Such studies, Dr. Borer notes, “can teach us whether surgery is indicated and at what stage in the illness surgery should take place.”

Dr. Borer is also trying to answer these questions through research into valve disease’s underlying cellular and molecular biology. “We’re trying to find more accurate predictors of outcome than are available to us now with gross clinical studies,” he explains. “We’re looking for which genes are turned on and which are turned off, compared to normal,” Dr. Borer says.

“This research may enable us to find an abnormality that contributes to valve disease that could be beneficially altered with drugs or other non-surgical treatments.”

Such a possibility could reduce the likelihood of death and suffering from this hard-to-address illness, much in the way Dr. Borer’s research has transformed the diagnosis and treatment of heart disease in the past.

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**Prognostic Impact of Systolic Hypertension (HTN)* and Antihypertensive Medications In Patients with Chronic Aortic Regurgitation**

(a) All Patients n=80

(b) Patients with HTN n=30

*Systolic HTN > 140mmHg, **Antihypertensive drugs = ACE inhibitors (n=2), direct vasodilators (n=4), diuretics (n=7), combination therapy (n=3).
The advent, in the mid-1990s, of Highly Active Antiretroviral Therapy (HAART) has changed the nature of HIV infection. Rather than the short, harrowing, and fatal disease it was in the early days of the AIDS epidemic, HIV infection has become a chronic illness, with many individuals living for 20 or more years after diagnosis. Like many chronic illnesses, it includes a number of complications. One of them is heart disease.

In fact, today, cardiovascular disease ranks among the leading causes of death in HIV-positive people, says Associate Professor of Medicine Jason Lazar, MD, director of the University Hospital of Brooklyn’s program in non-invasive cardiology.

Building upon Downstate’s longstanding expertise in both HIV and cardiovascular medicine, Dr. Lazar and his team are pursuing the causes and potential treatments of heart disease in HIV-positive women. “Our job is two-fold,” says Dr. Lazar. “First, to identify the factors that raise cardiovascular risk for HIV-infected women, and then, quite simply, to find better ways to treat them.”

Dr. Lazar’s investigations are part of the multi-site Women’s Interagency HIV Study (WIHS), initiated at Downstate in 1993. WIHS is one of the world’s most comprehensive HIV studies; study sites have enrolled more than 3,000 participants since its inception.

The study examines all aspects of HIV disease in women. There are three groups of participants: HIV-positive women on HAART, other HIV-positive women, and healthy controls. The groups are socioeconomically matched. “With WIHS, we have an enormous database of biological and psychological information, as well as information about participants’ economic status and educational attainment,” says Dr. Lazar.

The fact that HIV-positive women are at increased risk of heart disease comes as no surprise to Dr. Lazar. “HIV
infection is associated with biological changes, such as inflammation and chronic activation of the immune system, which in other medical models are associated with increased incidence of heart disease,” he notes.

Indeed, among the study group’s HIV-positive women, Dr. Lazar’s team has documented a number of increases in heart-disease risk: a five-fold increase in cardiomyopathy (heart muscle weakness); higher levels of a heart stress-related biomarker called NT-pro-BNP, usually caused by HIV-positive women’s higher rates of Hepatitis C; and diminished dilating abilities in major blood vessels. Moreover, he observes, “our data confirm that poverty and low educational attainment more than double the risk of heart disease, just as they do in non-HIV-infected populations.”

The medical literature documents that HAART can increase cholesterol plaque build-up, a major contributor to heart disease. But HIV itself is an important cause of heart disease in HIV-positive women, Dr. Lazar has discovered. “Our studies show that high cholesterol caused by HAART is not related to cardiomyopathy,” he says. “Instead, the cause is HIV itself.”

Dr. Lazar has also found that HIV is responsible for the diminished dilating abilities of blood vessels in HIV-positive women. “HIV causes blood-vessel inflammation — vasculitis — and that vasculitis impairs the ability to dilate,” he explains. So-called progenitor cells in the bone marrow may also play a role in keeping blood vessels flexible.

In healthy people, progenitor cells help repair the linings of blood vessels, improving their ability to dilate under stress. HIV-positive women produce “greater numbers of KDR-positive progenitor cells and fewer numbers of CD34-positive progenitor cells” than HIV-negative women, Dr. Lazar has discovered. “These differences in progenitor cell production may explain some of the differences in dilation, as well as provide new insight into the process by which blood vessels repair themselves in general.”

Dr. Lazar’s work represents the best in the rapidly emerging field of translational research — the quick transformation of scientific discoveries into clinical applications. Indeed, at Downstate’s Cardiovascular HIV Affiliate Clinic, a heart-disease treatment program designed for HIV-positive patients, Dr. Lazar uses his team’s findings to optimize patient care.

“We’re altering treatment regimens to best protect our patients’ cardiovascular systems,” Dr. Lazar says. “We want to intervene before heart disease presents itself.”

Today, cardiovascular disease ranks among the leading causes of death in HIV-positive people.

Non-invasive recording of blood pressure from the radial artery (left) used to determine arterial stiffness and blood pressure in the central aorta (right) near the heart.

Non-invasive arterial blood pressure recording (top) and breakdown by mathematical technique into basic signal components (bottom).
In 2001, a study published in the *New England Journal of Medicine* confirmed what the medical community had known for years: open-heart surgery puts patients at significant risk for “long-term cognitive decline.” According to the authors, five years after surgery, 42 percent of the patients sampled had difficulties with memory, comprehension, speech, or problem-solving.

Though doctors speculate that these cognitive problems result from inadequate perfusion — blood circulation — in the brain during surgery, they don’t have the data to back their speculation up. “The monitoring of the brain,” says Daniel Lee, MD, an assistant professor of surgery and of biomedical engineering at Downstate, “is one of the last frontiers of surgery that hasn’t had much in the way of breakthroughs.”

Until now, that is. With funding from the National Institute of Neurological Disorders and Stroke, a division of the National Institutes of Health, and the New York State Department of Health, Dr. Lee is using imaging technology pioneered by Randall Barbour, PhD, a professor of pathology and biomedical engineering,
that enables the surgical team to view in real time brain perfusion during open-heart procedures. Wilson Ko, MD, who served as Downstate’s chief of cardiothoracic surgery until August 2009, also collaborated in the ongoing clinical trial.

If the device works — and early results suggest that it does — it will allow researchers to correlate risk factors that impede brain perfusion with later cognitive outcomes (Figure 1). “With this technology,” says Dr. Lee, “we may eventually be able to prevent brain damage during open-heart surgery — or any major surgery that affects blood flow to the brain.”

The device is based on diffuse optical tomography (DOT), a medical imaging technology Dr. Barbour began developing at Downstate 20 years ago. DOT utilizes a computer interface that reads near infra-red light as the light scatters through body tissue.

According to Dr. Barbour, who is the principal investigator of the study, more than 1,200 peer-reviewed papers have been published worldwide on the new imaging technique in the past five years. While the technology may one day have many medical applications, it appears to be particularly useful in visualizing changes in the quantity of blood flowing through tissue, and in how well oxygenated that blood is.

For the operating room, Drs. Barbour and Lee have designed a device that employs dozens of compact light sources and detectors, each only two or three millimeters in diameter, placed in contact with the scalp by means of headgear that resembles a shower cap (Figure 2). It is placed on the patient’s head and, during surgery, permits computerized readouts of perfusion in the brain. The device’s small size enables its use in operating rooms, where it would be impossible to employ bulky imaging equipment such as magnetic resonance imaging machines.

In addition to providing important information during surgery, it may also help Dr. Lee’s team pinpoint the causes of cognitive decline related to open-heart surgery. Doctors speculate that possible causes include blood pressure levels, red blood cell levels, and the placement and stabilization of numerous cannulas or tubes during surgery. (Some of this tubing diverts blood flow from the heart to a heart-lung machine during surgery.) By recording brain perfusion levels during surgery and later correlating those with post-operative outcomes, the researchers hope to discover how each of these factors affects patients’ cognitive abilities.

As the group’s technology evolves, it may allow the operating room team to correct during surgery conditions that can lead to later brain damage. “It might also be beneficial to do these scans before surgery,” says Dr. Barbour, “to identify those who may be at risk in ways that you otherwise could not anticipate. With this information, the surgical team could be better prepared to intervene.”

This new technology may have a tremendous impact on patients’ lives, as well as on society as a whole. Nearly 700,000 individuals undergo open-heart surgery each year in the United States alone. It could, the researchers believe, usher in a new era in open-heart surgery, one in which the brain is protected while the heart is repaired.

**FIG 1.** The color images depict a mathematical function, developed by Dr. Barbour and his research group, related to the amount of oxygen delivered to the brain by the blood stream. They are overlaid onto conventional MR images (gray) of the head. The larger the number, the better the oxygen supply and the redder the image. The patient who showed post-surgical cognitive decline (left) had less oxygen delivered to the brain than the patient who did not show any decline (right).

**FIG 2.** The “shower cap” headgear, showing several of the locations that are available for positioning light sources and detectors on the scalp. The cap shown also can hold both electroencephalography and infra-red light probes at the same time.
The genital herpes virus, Herpes Simplex-2 (HSV-2), can seem, misleadingly, harmless. Most people infected with the virus show no symptoms at all. If they do, those symptoms are often easily overlooked.

Yet, HSV-2 infection has a dangerous side. People infected with the virus are two to three times more likely to contract HIV when engaging in unprotected sex; they are more likely to transmit HIV as well. In individuals with compromised immune systems, HSV-2 infections can also lead to life-threatening pneumonia, brain inflammation, and liver damage.

The most pernicious consequence of all occurs when newborn babies passing through the birth canal are exposed to the virus by mothers who became infected during the final trimester of pregnancy. Each year, approximately 4,000 infants in the United States are infected this way, and a significant number of them die.

“Even with early diagnosis and early treatment,” says William McCormack, MD, distinguished teaching professor of medicine and obstetrics/gynecology, and director of Downstate’s Infectious Disease Division, “there can be severe neurological sequelae — mental retarda-

**Genital Herpes Vaccine Could Save Lives, Young and Old**

If this vaccine is successful, we’ll be able to start putting a dent in both the big and small problems HSV-2 infection present.

Dr. McCormack and members of his research team (from left): Cathleen LaPreta, senior staff assistant; Lorraine du Bouchet, PA; Lynette DeMee, MS, laboratory technologist.
tion, cerebral palsy-type symptoms. It can be a devastating illness.”

And, potentially, a preventable one. That possibility may not be far off, due, in part, to the work of Dr. McCormack. For the last four years, he has spearheaded Downstate’s participation in a multicenter, Phase III clinical trial of an HSV-2 vaccine that had shown promise in earlier testing. (A Phase III trial is a large, double-blind, randomized controlled trial designed to test a new treatment’s efficacy.)

“With any luck,” Dr. McCormack says, “we will help bring an HSV-2 vaccine to the public soon. And we can start preventing the infection’s many, unfortunate consequences.”

To date, HSV-2 transmission has been particularly difficult to forestall. Eighty to ninety percent of people infected with the virus don’t know they have it. Even those who do, and follow medical advice to abstain from sex during herpes outbreaks, can nevertheless transmit the virus to their partners.

As a result, worldwide, 536 million people between the ages of 15 and 49 are believed to be infected with HSV-2, with more than 23 million new cases each year.

Overall, women are at slightly increased risk of developing the persistent infection than men — 55 percent to 45 percent. And it’s women who have participated in Dr. McCormack’s trial. “Early testing showed the vaccine offered no protection to men,” Dr. McCormack says, explaining the gender-specific nature of the trial.

Developed by pharmaceutical giant GlaxoSmithKline, the vaccine “contains a unique antigen found on the surface of HSV-2,” Dr. McCormack says. Earlier, smaller trials proved the vaccine was effective, though not perfectly so: one trial found protection rates of approximately 75 percent.

Dr. McCormack’s Phase III trial enrolled sexually active women who tested negative for both HSV-2 and HSV-1, the related oral herpes virus.

Depending upon which arm of the trial the women were enrolled in, participants received either the HSV-2 vaccine or a hepatitis vaccine, “so that the comparison group received something of value,” Dr. McCormack says. Three doses were administered over a six-month period, with two years of follow-up. Dr. McCormack and his co-investigators at other clinical sites tested for HSV-2 in participants’ blood and for genital herpes lesions. In total, approximately 8,000 women were enrolled at 50 sites across the country. The trial has been funded jointly by GlaxoSmithKline and the National Institute of Allergy and Infectious Diseases, a branch of the National Institutes of Health.

“The data collection is complete and now we’re in the process of analyzing that data,” Dr. McCormack notes. A decision on the vaccine’s efficacy is expected within two years.

“If this vaccine is successful,” Dr. McCormack says, “we’ll be able to start putting a dent in both the big and small problems HSV-2 infection presents.”
Bacteria evolve to overcome obstacles to their spread. That fact is part of their very nature. Indeed, in the late 1940s, only a few years after penicillin’s introduction to the United Kingdom, approximately half of the staphylococcus (staph) infections there developed a resistance to the world-changing drug.

These days, multidrug-resistant (MDR) bacteria can “outwit” almost any of the antibiotics doctors use to treat them. Several of these bacteria have taken up residence in hospitals, unfortunately. In these healthcare settings, they put at risk some of the most vulnerable patients — infants and elders in intensive care units, immuno-compromised individuals already weakened by chemotherapy or disease.

Accurate statistics about death rates from hospital-acquired infections are difficult to come by. But “patients who get these bugs have very high mortality rates,” notes infectious disease specialist John Quale, MD, an associate professor of medicine. In one study, patients with one type of MDR bacterium — Klebsiella pneumoniae — had a three-fold greater risk of death compared to patients with a non-MDR form of the infection.

Whether those high mortality rates result from MDR infections themselves or “from the fact that these patients are very sick to begin with” is still unclear, Dr. Quale says. But a dramatic rise in the prevalence of MDR K. pneumonia infections in New York City hospitals from 2001 through 2006 highlighted the need for research into enhanced surveillance, detection, and infection control measures.

Dr. Quale and his colleagues hope to outsmart multidrug-resistant bacteria by finding their Achilles’ heel in the enzymes and proteins they produce.

Dr. Quale (seated) and his collaborators David Landman, MD, associate professor of medicine, and Simona Bratu, MD, assistant professor of medicine.
For several years now, Dr. Quale, has been collaborating with Simona Bratu, MD, assistant professor of medicine, and David Landman, MD, associate professor of medicine, to explore the molecular biology of antibiotic resistance in Klebsiella pneumoniae and another MDR bacteria, Acinetobacter baumannii. These are two of the world’s most prevalent and dangerous hospital-acquired infections.

The group, which is funded by the National Institute of Allergy and Infectious Diseases, a division of the National Institutes of Health, has two goals: to uncover the primary causes of antibiotic resistance in these two MDR bacteria and to identify new sites that antibacterial drugs can attack.

“To combat these infections, we really need new classes of antibiotics,” Dr. Quale explains. “But short of that, there are proteins and enzymes these bacteria produce that could be inhibited. We’re looking for the Achilles’ heel of the bacteria.”

In hospitals, MDR bacteria linger on surfaces and on infected patients, spreading through some of the most mundane types of contact. “In the intensive care unit,” Dr. Bratu explains, “a staff member might touch a patient who has the infection or pick up the germ by touching a patient’s bed.” That staff member might then pick up a chart at the nurse’s station, touch a phone, a computer or an IV pole. Through those points of contact, “another staff member can spread the bacteria to a different patient,” she explains. The fact that patients can harbor the infection but have no symptoms – and that clinical cultures cannot be relied on to identify patients who are infected – adds to the difficulty of control.

The research and clinical staff at Downstate have developed infection control protocols for intensive care units that, in one study, have more than halved Klebsiella infections. As documented in an article in the May 2009 issue of Infection Control and Hospital Epidemiology, an aggressive program that includes contact isolation, daily cleaning of environmental surfaces and patient-related items, education, and a team effort involving nursing and infectious disease staff can produce significant results.

But further limiting the spread of K. pneumoniae and A. baumannii requires research into the fundamental causes of their resistance.

One of the causes, the group has discovered, is beta-lactamase, “an enzyme that eats up some of the penicillin-type medications before those drugs can kill the bacteria,” Dr. Quale explains. Also under examination is the function of porins, “little pores in the cell membrane that allow antibiotics to get inside.” In MDR infections, porins’ function may be compromised in some way. Moreover, adds Dr. Bratu, “some of the bugs have what are called efflux pumps. When an antibiotic gets inside the cell, the efflux pump renders it ineffective by pumping the antibiotic back out again.”

The group is also measuring gene expression in the two MDR bacteria, in an effort to understand how gene regulation plays a part in antibiotic resistance and how its manipulation might enable new types of treatment.

“We need new drugs,” Dr. Quale says. “Our research can lay the groundwork for creating them.”
Disaster Preparedness

Getting Ready for the Unthinkable

Pandemic flu. Chemical leak. Terrorist attack.

Disasters like these require a special type of medical expertise, a special type of planning — so much so that New York City’s Department of Health and Mental Hygiene (DOHMH) has mandated that each of the city’s acute-care hospitals appoints an emergency preparedness coordinator.

At University Hospital of Brooklyn (UHB) that position has been ably filled by Michael Augenbraun, MD, a professor of medicine. Dr. Augenbraun collaborates on emergency preparedness activities with Bonnie Arquilla, DO, Downstate’s director of disaster management and an assistant professor of emergency medicine. Together, they have developed innovative disaster-preparedness programs that can serve not only UHB’s central Brooklyn neighborhood, but, through replication by other hospitals, the larger city, and indeed, the wider world.

With support from DOHMH’s Fund for Public Health in New York, Drs. Augenbraun and Arquilla have created protocols for mass screening and triage, delivering critical care, and controlling infection during a public health emergency. They’ve designed and conducted drills to help hospitals, churches, and schools throughout the city prepare for disasters. And now, they are sharing their expertise with medical centers and universities in the developing world.

“Hospitals are called upon to do such vital work during disasters that implementing these programs successfully is central to mitigating a disaster’s impact,” Dr. Augenbraun says, “that implementing these programs successfully is central to mitigating a disaster’s impact and guaranteeing the best possible outcomes.”

One of the keys to emergency preparedness is coordination among area healthcare providers. When Drs. Augenbraun and Arquilla took up the task of readying UHB for disasters, “one of the first questions we asked ourselves was, How do we create a coordinated response among medical providers in our neighborhood?” Dr. Augenbraun recalls.

The pair quickly developed a network of area hospitals — UHB, Kings County Hospital, Kingsbrook Jewish Medical Center, and Kingsboro Psychiatric Center — to participate in joint disaster-preparedness activities. Together, these hospitals have collaborated on at least 18 drills in the last seven years, each one modeling responses to possible disasters such as subway explosions and toxic chemical leaks.
“Last summer, we ran a drill with 350 volunteer ‘patients’ to test our protocols for a pandemic influenza,” Dr. Augenbraun explains. One of the group’s goals was to ensure that “infected” and “uninfected” volunteers were kept apart, to avoid further infection.

“We learned a lot about what we can anticipate,” Dr. Augenbraun says. For instance, institutions “may underestimate the need for space in case of a large number of patients,” Dr. Augenbraun says. “The drills have helped us refine our protocols.”

Another of Dr. Augenbraun and Dr. Arquilla’s accomplishments is the development of disaster response protocols for hospitals. Their manual, “Children in Disaster: Hospital Guidelines for Pediatric Preparedness,” is likely the first of its kind in the nation. The handbook is available for free online, and details, among other things, the pharmaceuticals hospitals should keep on hand, psychosocial interventions that might aid children, and security and tracking procedures for pediatric patients.

“I’m proud that the manual is accessible to any hospital that wants to use it,” says Dr. Augenbraun, who is also developing a guide to the disaster-related needs of the geriatric population.

The team’s influence has spread beyond New York City to the developing world. Dr. Arquilla has been collaborating with officials in South Africa to organize disaster preparedness protocols for the upcoming 2010 soccer World Cup there. She also consults regularly with medical officials in India. “The collaboration with South Africa is new,” Dr. Arquilla says. “But in my longstanding work in India, I’ve learned how healthcare workers can better handle large crowds and communicate with large numbers of patients.”

“What we’re doing,” Dr. Augenbraun says, “is creating a larger safety net. That net will enable hospitals to fulfill their roles as healthcare providers at the times when they are needed most.”
Neonatal newborns and premature infants in neonatal intensive care units (NICUs) are subject to a host of painful procedures: intubation, heel sticks, blood draws, and intravenous lumbar punctures, to name just a few. These babies may also experience significant pain as a result of their underlying medical conditions.

Pain is not just a quality of life issue for these sick children. Ongoing pain is associated with an increased likelihood of death in NICUs.

Unfortunately, “there is very limited analgesia available to newborns,” observes neonatologist and pharmacologist Jacob Velasco Aranda, MD, PhD, a professor of pediatrics and head of Downstate’s neonatal unit. In fact, only three drugs are used to manage pain in infants — acetaminophen (Tylenol), morphine and fentanyl — and both morphine and fentanyl carry with them significant risks: respiratory depression, and, in some cases, death. “Managing pain safely and effectively is one of the major issues we face as neonatologists,” says Dr. Aranda, who is one of a handful of experts in the country on drug efficacy and safety in newborns.

He is also a pioneer in his field, having made a number of important discoveries that have led to improved survival and health outcomes. One of those, about the use of caffeine for the treatment of apnea in premature infants, has led to sizeable decreases in both mortality and illness. A 2007 study in the *New England Journal of Medicine* found that among severely premature newborns — those with birthweights between 500 to 1250 grams — the administration of caffeine increased survival from 53.8 to 59.8 percent. Caffeine-treated babies were also 40 percent less likely to develop cerebral palsy and almost 12 percent less likely to experience developmental delays.

“Caffeine stimulates the mechanism in the brain that controls breathing,” Dr. Aranda explains. “And, of course, breathing is crucial to survival. But appropriate breathing and adequate ventilation are also essential for proper neurological development, which is probably why we see fewer cases of cerebral palsy and developmental delays in caffeine-treated babies.”

Today, Dr. Aranda, who maintains an academic affiliation with Wayne State University in Detroit, leads a multi-site clinical trial aimed at expanding analgesia options for newborns. The trial emerged from the planning process of the Pediatric Pharmacology Research Unit (PPRU), a National Institutes of Health-funded network of 13 university pediatric departments that explores pharmacological questions relevant to children. Through Dr. Aranda’s Wayne State affiliation, Downstate has become the only PPRU site in New York City.

The trial will examine codeine’s effects as a painkiller in newborns and explore how factors such as genetics, ethnicity, and age may determine how individual infants respond to the drug. “Codeine is easy to administer,” Dr. Aranda says, “so it could be a great addition to our therapeutic arsenal.”
“Children — babies especially — react to drugs differently than adults do,” Dr. Aranda says, explaining the need to test codeine on infants. The trial, funded by the National Institutes of Health’s National Institute of Child Health and Human Development, is titled “Absorption and Metabolism of Oral Codeine in Mechanically Ventilated Neonates.”

“The questions we’re asking are very simple ones,” Dr. Aranda notes. The first is whether newborns can absorb codeine at all. They may simply eliminate it from their systems. “The second question is,” he says, “If they do absorb it, can they activate it metabolically? Because codeine itself is not the active drug. The active drug is morphine, which is metabolized from codeine by two enzymes called CYP2D6 and UGT2B7.”

Though morphine doses used in previous clinical trials are associated with an increased risk of death among pre-term babies, Dr. Aranda believes codeine will not present similar risks because it is absorbed less efficiently.

To answer these questions, Dr. Aranda and his fellow investigators will administer a single dose of codeine orally and test for the drug and its metabolites in the babies’ urine and blood. To gauge the painkiller’s effectiveness, they will also study babies’ facial expressions and tongue movements.

Dr. Aranda’s study will examine whether genetic variations that control CYP2D6 and UGT2B7 expression “explain why some kids who are in pain get a drop of morphine and they’re very happy, and other kids, with the same disease and severity, get high doses of morphine and they’re still crying,” he says. In the future, such genetic information could lead to more individualized pain management.

Dr. Aranda also hopes to determine the role an infant’s age plays in codeine’s efficacy. “Newborns, notoriously, don’t express CYP2D6 and UGT2B7,” he notes. “But with this study, we may be able to discover at what age a premature infant begins to express these genes and whether a baby born at term expresses them earlier than a pre-term baby,” Dr. Aranda explains.

The hopes for the study are high. “There’s a lot of heartache in the NICU,” Dr. Aranda says. “But if we can expand the safe pain management options available to these infants, we can improve their lives significantly while they are in the NICU, improve their health outcomes, and relieve their families’ stress at knowing their children are in pain.”
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