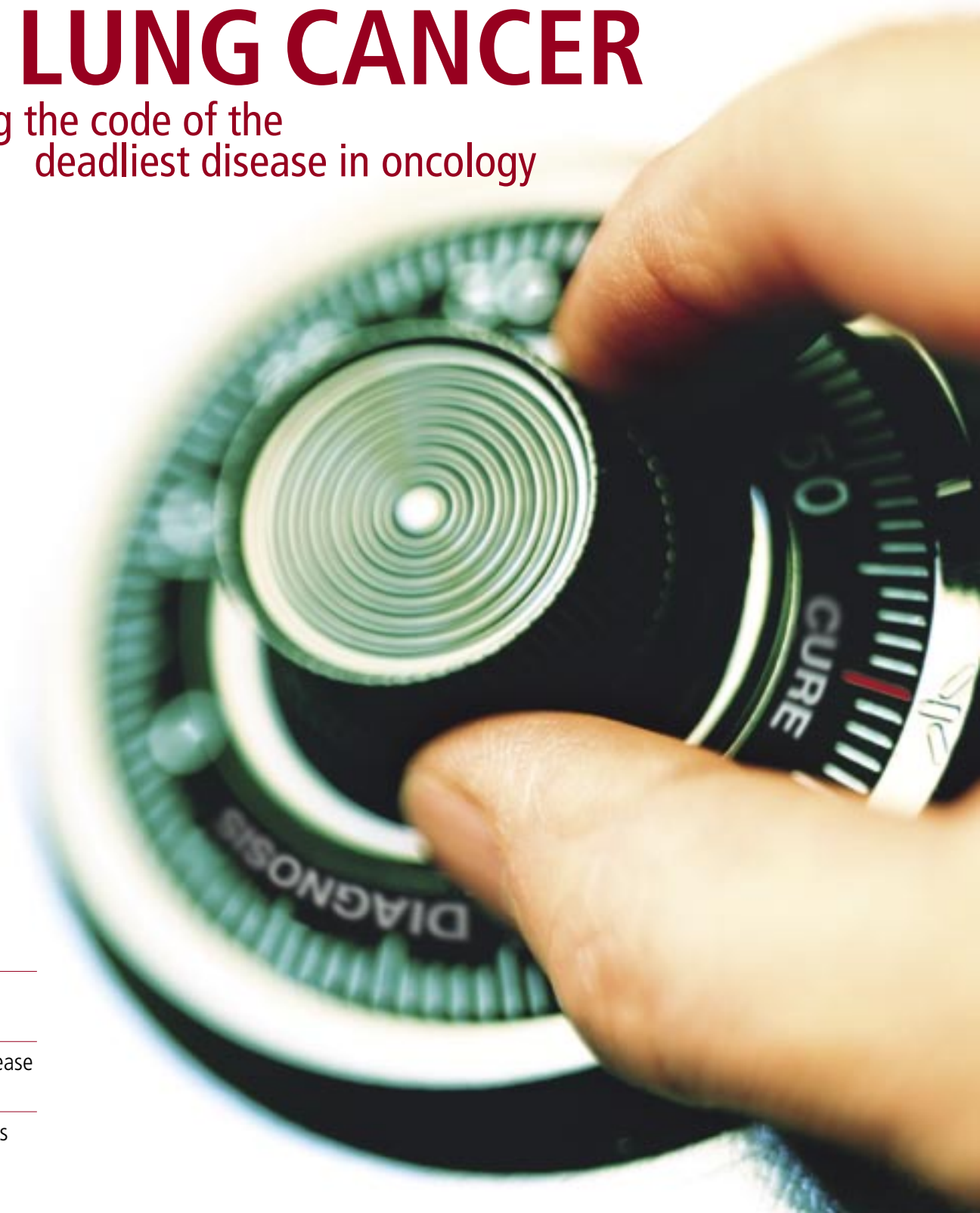
DukeMed MAGAZINE

VOLUME 5
ISSUE 1
SPRING/SUMMER 2005

ADVANCES IN RESEARCH, EDUCATION, AND PATIENT CARE AT DUKE

LUNG CANCER

Cracking the code of the deadliest disease in oncology



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Setting the direction of Duke Medicine

As my first year as chancellor for health affairs at Duke draws to a close, I am prouder than ever to be part of this institution. The reason is not simply Duke's excellence in patient care, medical education, and biomedical research—that much was clear before I arrived. What has impressed me greatly, as I have come to know Duke better, is its refusal to rest on its laurels. This is an institution unafraid to question the status quo and take bold action to do what it does well even better.

It is in this spirit of self-improvement that Duke Medicine has engaged in a strategic planning process to chart our course for the next several years. In many meetings over many months, our physician and nursing leaders, financial planners, strategists, and administrators from across the medical center and health system have applied their vast knowledge and experience to examine the challenges facing Duke Medicine, refine and prioritize our goals as an institution, and determine where best to invest our time, talent, and resources.

The challenges are great—a fact that will not surprise anyone familiar with today's health care environment. We must be prepared to respond to dramatic and rapid changes, such as a continuing shift toward ambulatory services, declines in federal and local government funding, new and expensive technologies that change how we diagnose and treat diseases, projected shortages in the health care workforce, and the fast-growing population of our home region.

At the same time, we must never lose sight of our fundamental missions in patient care, teaching, and research. We must always strive to provide the highest-quality, safest care to our patients, to produce health care providers well-prepared to meet the challenges of the future, to advance biomedical research and translate those advances into improvements in human health, and to address health inequalities at home and worldwide.

To address these challenges and priorities, we envision a model in which Duke Medicine is anchored by three major strengths: world-class research and academic programs in strategically targeted areas; excellent clinical services that are dominant in the region because they clearly differentiate Duke from its competitors; and a health system with superior, integrated, and easily accessible points of delivery within the local community.

For this model to succeed, the vast collection of hospitals, clinics, and other entities within the Duke Medicine community must work in close concert. We plan to enhance the alignment and integration of all our services, defining common operational and clinical standards in areas ranging from patient safety to information technology.

At the same time, we must continue to differentiate Duke by providing patient-centric care that is fueled by innovation. We must capitalize on Duke's inherent ability to not only think up new ideas, but translate them into treatments or services that will improve people's lives. This does not mean simply buying the latest technology, which is what many hospitals will do. At Duke, we can pioneer new understanding of the molecular basis of illness and methods to modify and change biological processes. We can develop approaches for educating tomorrow's practitioners to deliver innovative care. We can create opportunities to constantly develop new approaches for preventing diseases and treating illness in non-institutional settings.

We can do this because of the greatest and most irreplaceable asset we have at Duke Medicine: our people. As we progress through the planning process, I am constantly reminded that it is their intellect, their passionate pursuit of excellence in every area, and their compassion for the people we serve that will enable Duke Medicine to continue to offer its patients and its community "the future of medicine, delivered today."

VICTOR J. DZAU, MD
JAMES B. DUKE PROFESSOR OF MEDICINE
CHANCELLOR FOR HEALTH AFFAIRS,
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DUKE UNIVERSITY HEALTH SYSTEM

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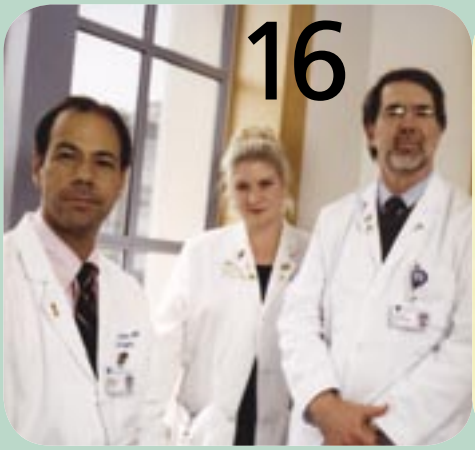


Lung cancer: Cracking the code

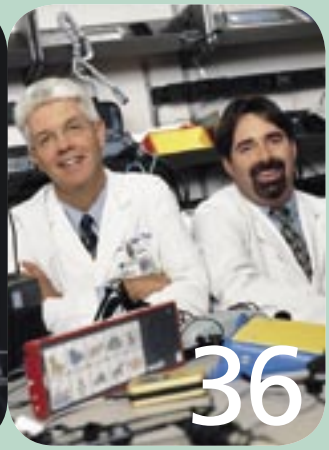
Making headway against the deadliest disease in oncology.

Taking away the power of the cigarette

Can researchers find a better way to help smokers quit?

A matter of life and limb

New ways to bypass peripheral artery disease.



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MEDICINE

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A distinguished past. A promising future.

Since the opening of our School of Medicine and Hospital in 1930 and School of Nursing in 1931, the people of Duke Medicine have striven to advance the quality and span of human life through innovation in clinical care and research, educate tomorrow's leaders in health care, meet the needs of the different communities we serve, and provide compassionate care to the poor and underserved. As we celebrate our 75th year and look to the future of medicine, Duke is proud to carry on these traditions upon which our success has been built.

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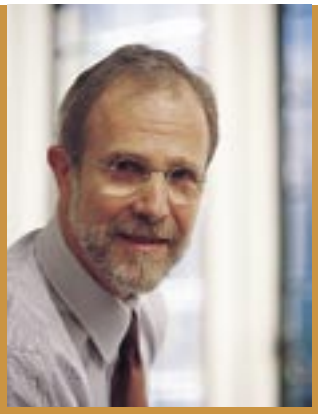

WILL MCINTYRE

from the dean

The fundamental unit of time in academic medicine is the decade

by R. Sanders Williams, MD
Dean, Duke University School of Medicine
Vice Chancellor for Academic Affairs

EARNING AN MD AT DUKE, as in other U.S. medical schools, requires four years. After graduation, certification within a specialty like Internal Medicine demands a further commitment of three years, and for those who continue on in a subspecialty—cardiology, for example—three additional years must be devoted to the task. Other specialties and subspecialties demand similar periods of time, give or take a year or two. Thus, it takes about a decade to prepare highly skilled practitioners of the medical arts, a principle that is generally understood and accepted.

A concept that is less well appreciated, I believe, is that the decade also should be considered as the fundamental unit of time in research. Trainees and young faculty tend not to think in these terms. Units of research time are typically approached in shorter intervals—a year for our third-year medical students, three to six years to earn a PhD, one to three year research fellowships, or three to five year cycles for competitive renewal of NIH grants. However, I urge those committed to life as an investigator to approach their research goals explicitly under the premise that ten years of focused endeavor are likely to be required to produce research findings of real merit and importance.

The history of scientific discovery suggests such an interval for the most notable advances, and in reviewing CVs one can usually discern about a decade of gestation for the finest contributions of the most successful investigators. In the 25 years of laboratory science I have enjoyed, my own trainees have heard this maxim so often that I suspect reading this anew in these pages may evoke some rueful eye-rolling. ("Look at this. He's at it again!") Nevertheless, those who have heeded this dictum have usually discovered for themselves the merits of this conceptual approach to research planning.

This year, I will have the privilege to be leading a fresh strategic planning effort for the Duke School of Medicine, which will coordinate with the other components of Duke Medicine (Health System, Private Diagnostic Clinic, School of Nursing) and of Duke University. In this context too, the decade as the fundamental unit of time in academic medicine emerges as an important principle. We are beginning the planning process by asking faculty, learners, and school leaders to imagine the school ten years hence, having advanced in specific ways each of us would find pleasing and exciting. We will be considering how that vision of success will be defined and measured, and those specific steps most likely to be required in the interval to promote that success. Such planning requires a quite different frame of mind than the common preoccupation with percentage changes in next year's departmental budget, fine-tuning of course content, or the like.

I urge those committed to life as an investigator to approach their research goals explicitly under the premise that ten years of focused endeavor are likely to be required to produce research findings of real merit and importance.

I am personally exhilarated to have this charge from Chancellor Dzau, and to rally my colleagues to come up with the fresh and creative thinking that will place our school in an even stronger position when the decade rolls around.

More PhDs, please

DUKE UNIVERSITY WILL SOON HAVE two new PhD programs: one in nursing and a graduate program (offering MS and PhD degrees) in medical physics.

The School of Nursing anticipates starting its program with four to five students in fall 2006. "The nation is in the midst of a critical shortage of nurses and that problem is compounded by the concurrent shortage of nursing faculty," said Dean Catherine L. Gilliss, DNSc. "Duke's new PhD program in nursing will prepare nurses to become university-based teachers of nursing and to conduct studies that will lead to important improvements in patient care."

The Medical Physics graduate program will be an interdisciplinary effort involving the graduate school, the School of Medicine, and the Pratt School of Engineering. The field combines the study of physics, math, computer science, and engineering to solve real-world problems in medicine, especially in areas such as diagnostic imaging, radiation therapy, and molecular imaging.

Duke's newest doctoral degree programs aim to alleviate national shortages of nursing faculty and medical physicists.

"Because we have 30 faculty who are world-class medical physicists, and because the U.S. produces only a fraction of the medical physicists needed today, it was clear that we had an excellent opportunity to make a mark with a new graduate program," says program director James Dobbins, PhD.

Duke's program begins this fall and will involve up to ten master's degree students and four PhD students each year.

Care comes home

THE OLD BUNGALOW at 815 Broad Street hasn't lost its homey feel, even though its dining room and bedrooms have been converted into examining rooms.

The home was recently transformed into the Walltown Neighborhood Clinic, a convenient place for local residents to obtain primary care services regardless of their ability to pay. Located near a city bus stop and the low-income Walltown neighborhood that flanks Duke's East Campus, the clinic opened in January and has served a steady stream of patients since.

A partnership between Duke, Walltown Neighborhood Ministries, and Lincoln Community Health Center, supported by a grant from The Duke Endowment, Walltown Neighborhood Clinic hopes to repeat the success of the Lyon Park Clinic in Durham's West End in bringing affordable, accessible health care to the community. That clinic opened in 2003 in a similar partnership between Duke and Lincoln. It recently expanded so more patients can be seen.

For more information, call 919-419-1254.

Waste not

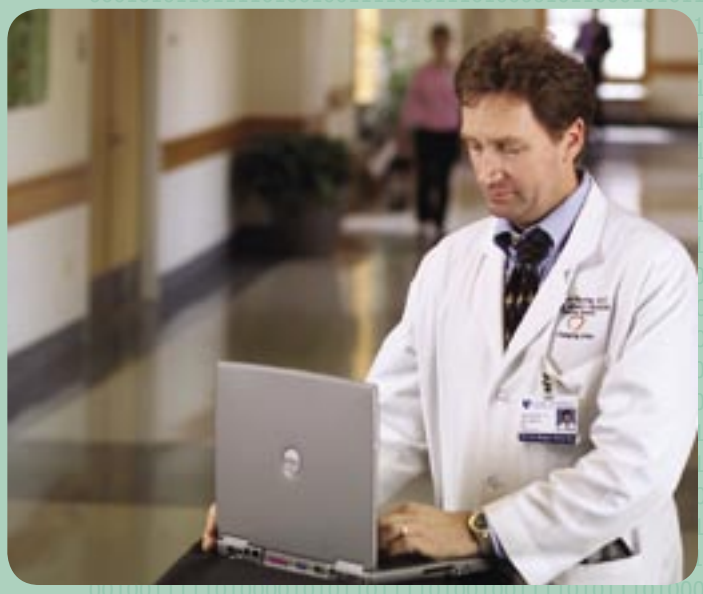
OVER THE PAST FIVE YEARS, Duke University Hospital has reduced its output of biohazardous waste by more than one million pounds—thanks mostly to switching from disposable synthetic surgical gowns and linens to reusable linens. "We just decided that was a lot of stuff to be sending to the landfill," says Barney Branch, director of sterile processing. The new linens, which can be re-sterilized after every use, are now used just about everywhere except the Eye Center, since minuscule cloth fibers are verboten in its hermetically sealed operating rooms.

At an average disposal cost of 28 cents per pound, the waste reduction has also saved over a quarter of a million dollars, according to SRI/Surgical Express, Inc. The company recently presented Duke with its EcoSense Award in recognition of the accomplishment.

In April Duke adopted an institution-wide environmental policy that aims to make the university a national leader in implementing environment-friendly management and practices. Learn more at www.duke.edu/sustainability.

Goodbye to old-fashioned orders

THE DAYS OF HAND-SCRIBBLED orders are nearing their end at Duke University Hospital. After years of planning, Duke's Computerized Physician Order Entry (CPOE) system will be available at every adult patient bedside by early this fall, allowing physicians to send medication and test orders straight to the lab or pharmacy with a few clicks of a mouse.



Efforts to introduce Computerized Physician Order Entry systems have flopped at some hospitals, but leaders say Duke's adoption has gone "much more smoothly than expected" thanks to extensive input from clinicians. "The system has been so well thought out that even old dogs like myself can catch on quickly," says cardiologist Michael Blazing, MD (pictured).

Hospital leaders began to explore CPOE back in 2000, realizing its potential to improve patient safety. Over half of all medical mistakes are associated with ordering errors—wrong medicine ordered, wrong dosage calculated, failure to note possible allergies or drug interactions, and so forth. CPOE eliminates many simple errors such as those associated with illegible handwriting or inaccurate transcription of verbal orders. But it also goes far beyond that to provide clinical decision support. It can automatically recommend drug dosages, alert physicians of drug allergies or interactions based on information in the patient's online medical record, prompt physicians with evidence-based guidelines for care, and provide up-to-date medical information, among other features. With its built-in intelligence, CPOE has been shown to cut serious medical errors by anywhere from 55 to 80 percent.

Still, adopting CPOE isn't quite the no-brainer it would seem. Even today, only an estimated 10 percent of U.S. hospitals have fully implemented CPOE systems.

"They're big and complicated, and require lots of resources to implement properly," says Duke University Health System's Chief Information Officer (CIO), Asif Ahmad. "And not just financial resources. Using computers for physician order entry is a huge cultural change, and it takes an incredible effort to make sure it is implemented in a way that helps, rather than hinders, physicians."

At some other major hospitals, CPOE systems have proved so user-unfriendly that clinicians successfully lobbied to boot them out. Duke's own CPOE adoption took longer than expected. Choosing the system took nearly two years and the input of more than 100 physicians, notes hospital CEO William Fulkerson, MD. The final choice was McKesson's Horizon Expert Orders system, but it couldn't be plugged in right off the shelf; Duke's CPOE team has spent months integrating it with Duke's existing clinical information systems. "The team always kept the focus on making the system an intuitive tool for clinicians, and on doing everything possible to ensure patient safety," said CPOE program director Leslie Mackowiak.

The team worked with clinical leaders to preload the system with hundreds of customized order sets that outline standard care for specific diagnoses based on Duke practices and the latest evidence-based guidelines. While physicians can always choose to override the suggested orders, "Order sets help physicians access key information quickly, ensure that what they order is complete, and reduce the chances of forgetting something," says clinical content manager Jimmy Tcheng, MD.

The final product debuted at four patient beds in September 2004; after an initial pilot in the Heart Center, CPOE has steadily been introduced on one unit after another, preceded by extensive staff training. In January, Duke announced that it had formed a strategic partnership with McKesson to provide and distribute evidence-based clinical content, documented processes for best practices, and transferable knowledge for use with McKesson's CPOE product, enabling other hospitals to more rapidly adopt the system. Hopefully Duke's experience will benefit others, says Associate CIO Mike Russell, MD. "The reception of CPOE has been overwhelmingly positive here. The implementation is going much more smoothly than anyone predicted, thanks to incredible support and participation by hospital faculty and staff plus a great deal of hard work by the CPOE team."

JOHN MAKELY / THE BALTIMORE SUN

Embracing the unexpected

WHETHER WORKING AS A RINGSIDE DOCTOR in Baltimore or planning for his new position as vice chancellor at Duke, Nobel laureate Peter C. Agre, MD, reveals himself to be a man who follows his passions, trusts his instincts, and is determined to do the right thing.

Ask Vann Bennett to tell you something most people don't know about Peter Agre, and he doesn't hesitate. "Peter is probably the only Nobel laureate who was once a fight doctor," says Bennett, MD, PhD, the James B. Duke Professor of Cell Biology and Agre's close friend since medical school.

Apparently Agre, as a young researcher at Johns Hopkins, developed romantic notions about boxing after reading a few too many Hemingway novels and got himself a gig moonlighting as a ringside doctor at Baltimore fights. "It was pretty intense," Bennett recalls. "Once, in the middle of a highly contested fight, a boxer was knocked out of the ring by a blow to the chest. Peter thought he didn't look well and stopped the fight. There was a huge outpouring of rage—tons of money had been bet, and there were five thousand people yelling at Peter to let the fight continue. I thought he'd need police protection. But he made the right call. It turned out the boxer had a collapsed lung, so Peter probably saved his life."

Tending to tough guys may not be exactly what one would expect of a distinguished laboratory scientist like Agre [pronounced OG-ray], who won the 2003 Nobel Prize in Chemistry for discovering the long-searched-for mechanism by which water passes through cell membranes. But then Agre is a surprising guy all around. He speaks some Norwegian and Russian, is married to a direct descendant of Pocahontas, and swims a mile at noon every day. He made his seminal discovery of the aquaporin protein in an Alexander Fleming-like fashion—by paying attention to a mystery substance that could have been easily overlooked—and reportedly responded to the news that he had won the Nobel Prize by saying, "In chemistry? What the hell do I know about chemistry?"

"Peter is deceptively smart," says Bennett. "He's brilliant, but doesn't have to show it off to people. He's amazingly accomplished, extremely ethical, and has very strong social and humanistic values. It's a great package that you don't often find in scientists at that level."

Agre's new role at Duke has been custom-designed to suit his particular blend of scientific brilliance and social conscience. As vice chancellor for science and technology, a position he assumes July 1, Agre will help guide the development of biomedical research at Duke as well as make broad contributions to society as a public spokesman for science (see page 46). *DukeMed Magazine* recently chatted with Agre about his passions and his plans as vice chancellor.

How has winning the Nobel Prize changed your life?
It's been wonderful—and a little crazy. I delivered 105 lectures last year! Honoring all the requests for my time has become impossible, but I do plan to contribute to science in new ways, and the Nobel provides a sort of bully pulpit for that. Otherwise I don't think it's changed me much. I always say my dog doesn't love me any more and my family doesn't love me any less.

You've been courted by many leading institutions, including the National Heart, Lung, and Blood Institute and the Mayo Clinic. Why did you finally decide to leave Johns Hopkins for Duke?
I have a long history with Duke—some of my closest friends were here when I was a hematology/oncology fellow at UNC, and our daughter Claire graduated from Duke in 2002. I'm also very impressed with the recent leadership renaissance. I met [chancellor] Victor Dzau last year and we hit it off immediately. You have a new president, Richard Brodhead, a new dean of Arts & Sciences, George McLendon, and a new chairman of medicine, Pascal Goldschmidt, who's a close personal friend. And my best friend, my roommate from medical school, is Vann Bennett. These are impressive individuals whom I enjoy personally and that meant more than anything else.

One of your roles at Duke will be to serve as a public ambassador for science. Why is this important?
There's a real need in this country for people to have a more sophisticated understanding of science. People often make up their minds about issues like stem cell biology or global warming without actually knowing the facts. If someone doesn't want to be enlightened it's very difficult to make much progress. But a lot of people in the U.S. simply haven't taken the time to try to understand what's going on—and the media coverage can be pretty superficial. If people want to understand science, we should make it accessible to them.

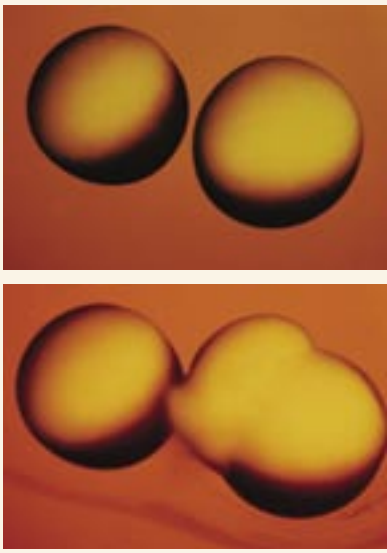
What are some of the issues you especially want to address?
I'm very interested in human rights. I just became chair of the National Academy of Science's committee on human rights, which looks out for academics around the world whom we feel are being unjustly imprisoned or persecuted. I also have a strong personal interest in improving science education in our schools. It's an area of crisis, and poses a real threat to America's leadership in science. Our children are not getting as much instruction as they need, and our science teachers are not getting the financial and emotional support they deserve.

Was your interest in improving education sparked by firsthand experience? We understand you were actually earning a D in high school chemistry before withdrawing from the class.
Actually, the teachers I had in public school in Minneapolis were wonderful. My woeful performance was due to my involvement in social concerns, including an underground newspaper, the Roosevelt High School Substandard. I'm sure if I had tried harder I might have gotten a C.

You'll also be moving your research lab to Duke?
Yes. I don't think it's feasible to maintain a big research lab given the number of requests and expectations of me at this point, but we will have a small lab focused on studying a few aspects of aquaporins that may play important roles in human disease processes. We're looking at possible ways one member of the aquaporin family might be useful in new treatments for malaria, how aquaporins are involved in maintaining blood sugar during starvation, and aquaporins in osteoclasts, which are cells that may be involved in osteoporosis.

Any parting words?
Well, I'm honored and thrilled to be joining the Duke family. You guys have a young university, you're forward-looking, and boy, will this be a great opportunity for Peter Agre!

Learn more about Peter Agre's work—and read his engaging autobiography—at nobelprize.org/chemistry/laureates/2003.



Exploding frog eggs confirmed Peter Agre's serendipitous discovery of aquaporins—the molecular aqueducts that transport water in and out of cell membranes. Agre first noticed the mysterious protein when working on unrelated blood studies, and designed an experiment to see if it was indeed the cellular water channel scientists had long been searching for. Sure enough, eggs injected with the aquaporin protein (bottom) readily soaked up water when placed in a bath, bursting within minutes, while untreated eggs remained stable.

The prizewinning discovery answered a question that had been "a major puzzle for over a hundred years," says Duke cell biologist Vann Bennett, MD. "The process by which cells handle water transport is fundamental to all forms of life, from plants' ability to survive drought conditions to animals' ability to form urine. The implications of his discovery are just enormous."

NSAIDs: Now what?

ONGOING CONCERNS about the safety of COX-2 inhibitors (coxibs) such as Vioxx (rofecoxib) has cast a pall over the entire class of nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2-selective and -nonselective alike. In April, along with "asking" Pfizer to remove Bextra (valdecoxib) from the market, the FDA requested labeling revisions for all prescription and nonprescription NSAIDs. In its announcement, the FDA noted that package inserts for prescription NSAIDs should include a boxed warning that highlights "the potential for increased risk of cardiovascular (CV) events and the well-described, serious, potentially life-threatening gastrointestinal (GI) bleeding associated with their use." In addition, the FDA asked manufacturers of over-the-counter products containing the NSAIDs ibuprofen, naproxen, and ketoprofen to provide more specific labeling information about the potential CV and GI risks and to remind patients to limit use of the medications as spelled out on the package, unless their physician says otherwise.

The coxib controversy serves as a reminder that every drug has side effects, and health care providers should consider the delicate balance of risk versus benefit when prescribing any medication, says David Pisetsky, MD, PhD, chief of Duke's division of rheumatology and immunology. "The coxibs were invented to have fewer GI side effects, and along the way we found that some of them had other side effects. So it's no longer a simple risk-benefit equation."

Moreover, it's difficult for health care providers to practice evidence-based medicine with these medications because there's very little hard data available. "Our system of drug development and post-marketing surveillance has failed to produce a solid estimate of the balance of risks and benefits for any patients taking chronic NSAIDs or coxibs," said cardiologist Robert Califf, MD, director of the Duke Clinical Research Institute, during a session at this year's American College of Cardiology meeting. "How can it be that, despite all the money spent on these drugs, we still can't tell the consumer what the balance of risk and benefits are for any of them?"

The coxib controversy serves as a reminder that every drug has side effects, and health care providers should consider the delicate balance of risk versus benefit when prescribing any medication, says David Pisetsky, MD, PhD.

Pisetsky points out that the adverse cardiovascular effects showed up in clinical trials among patients taking the drugs regularly for prolonged periods, whereas most people take them sporadically for, say, a headache, musculoskeletal pain, or dysmenorrhea. "So it's very difficult to get a grasp on the risk to this group of patients," Pisetsky says. He adds that the cardiovascular events observed in clinical trials were actually a small increase in a common problem. "Physicians in practice would probably not be able to detect the increase in their smaller population of patients."

The FDA Advisory Panel that met in February recommended, as a first-line NSAIDs therapy, the combination of naproxen and a gastric-acid-suppressing proton pump inhibitor such as omeprazole (Prilosec) to protect the gut. Califf agrees but suggests that NSAID alternatives, such as acetaminophen and topical therapies, should be considered. The COX-2-selective drugs should be avoided unless other strategies fail.

For his patients with osteoarthritis, Pisetsky advocates alternatives such as acetaminophen, an exercise regimen, and weight reduction, and notes that sometimes the patient's situation warrants cortisone injections or even joint replacement. "Of course, there's a risk with injections and with surgery as well so, again, the physician and patient need to assess the risks and benefits of any treatment." He notes that it's prudent for the patient to find the lowest dosage of NSAIDs that provides pain relief and to try to avoid taking them regularly on a long-term basis.

Since all therapeutics involves a balance of risk versus benefit, Califf adds that perhaps "First, do no harm" should be changed to "On average, do more good than harm."

Macular degeneration gene found

RESEARCHERS AT DUKE and Vanderbilt have pinpointed the first major gene that determines an individual's risk for developing age-related macular degeneration (AMD). This chronic, progressive disease—which affects as many as 15 million Americans—is the leading cause of visual impairment and legal blindness in the elderly.

A common variant of the gene, called complement factor H (CFH), explains approximately 43 percent of the risk of AMD among older adults, the researchers estimate. The team identified the disease-related gene after screening 182 families affected by AMD and 495 other individuals with the condition.

"This gene opens the door to a whole new understanding of the factors that contribute to this disease," says the study's senior author, Margaret Pericak-Vance, PhD, director of the Duke Center for Human Genetics. "The finding may ultimately lead to new methods for identifying those at high risk for macular degeneration and suggests new pathways for drug development."

AMD causes progressive impairment of central vision, explains ophthalmologist Eric Postel, MD, head physician for the Duke AMD genetics research team. It can leave people unable to perform everyday activities such as driving, reading, writing checks, and recognizing faces. Available therapies usually can only stall disease progression: none can effectively reverse the course of the disease.

Further studies of CFH and the cellular components with which it interacts might lead to a rapid increase in understanding of the biology of the disease, the researchers add. That information, in turn, should allow scientists to advance on new treatments and preventive therapies.

The researchers reported their findings in *Science* (published online March 10, 2005, in *Science Express*).

Discovering a new cancer drug

DUKE COMPREHENSIVE Cancer Center scientists have discovered a potential new drug that inhibits its destructive cell signals that drive the growth of one-third of all cancers. The scientists showed they could block the growth of cultured colon cancer cells using this new compound, called cysmethynil.

Their finding, reported in the March 22 *Proceedings of the National Academy of Sciences*, is the first step toward developing a new class of anti-cancer drugs that block the Icmt protein from activating uncontrolled cell growth, a hallmark of cancer, according to Patrick Casey, PhD, a Duke pharmacologist and cancer biologist.

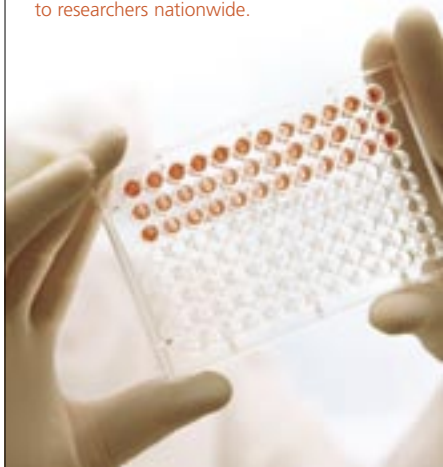
Moreover, says Casey, their discovery is the first to emerge from the Duke Small Molecule Screening Facility (see sidebar).

"This is the first selective small molecule inhibitor of Icmt, a protein that has been shown to be an important player in keeping a cancer-causing gene called 'Ras' turned on inside cells," says Casey. When the scientists tested the compound's ability to inhibit Ras function in living cells, they found it blocked the ability of colon cancer cells to grow independently in soft agar, a typical test of the cancerous potential of cells.

"The next step is to test cysmethynil in animal models," said Casey. "We don't know how the compound will be metabolized in living animals, but we are encouraged by our initial results." Duke University has filed a patent application for cysmethynil, Casey says, and intends to shepherd it through the first steps of drug development by testing the compound in animal models of cancer.

The research was supported by a grant from the National Institutes of Health (NIH) and a Howard Hughes Medical Institute predoctoral fellowship to Casey graduate student Ann M. Winter-Vann, the first author of the study.

Duke's new Small Molecule Screening Facility houses a library of more than 13,000 compounds available for screening promising drugs with potential to fight cancer and other diseases. Using automated robotics, the facility provides the kind of drug discovery capability usually available only to pharmaceutical company scientists. The facility is a finalist for one of six $9-million NIH grants that will create a national network of publicly accessible small molecule facilities and make them available to researchers nationwide.



Among the unusual cases Duke specialists have come across was this foiled attempt to swallow an aluminum packet full of heroin.
Used with permission from Gastrointestinal Disease, An Endoscopic Approach (eds. Benjamin S, DiMarino A), 2002, Slack, Inc., Thorofare, NJ.

"You swallowed *what*?"

WHEN IT COMES TO CASES of mistakenly swallowed objects, gastroenterologist John Baillie, MB, ChB, and pediatrician Michael Skinner, MD, have seen it all: doll's eyes, safety pins, even a fork. So they had plenty of stories to share with the producers of *You Swallowed What?*, a documentary that aired this spring on Discovery Health Channel. We recently asked Baillie to tell us more about his adventures with foreign bodies.

? What's the weirdest thing you've ever seen someone swallow?

Let's see, I saw a 10-year-old child once who had swallowed a Pez dispenser shaped like Goofy—that was probably the weirdest. Crucifixes are another odd item that we come across on occasion.

? How do you decide what to remove and what to let, er, pass through?

Movement is what we look for. Daily x-rays show whether an object is moving smoothly through the digestive tract. If we don't see movement, then it's time to go in after it. That's when we grab our foreign body kit, which is a suitcase filled with three-prong grabbers, little fishing nets, baskets, and other specialized instruments.

? What object has been the most challenging to remove?

A surprisingly common object, a chicken bone, is what really stands out in my memory. We were preparing to remove the bone, which had perforated the esophageal wall, when we noticed something pulsating. Closer inspection revealed that the bone had actually punctured the left ventricle of the heart, so rather than removing the bone, we sent the patient to surgery.

? How are you finding life as a reality TV star?

You know, for 20 seconds of airtime, I've actually had quite a few patients and colleagues comment on the show. And while the lucrative book offers haven't been pouring in, it does make for good cocktail party conversations.

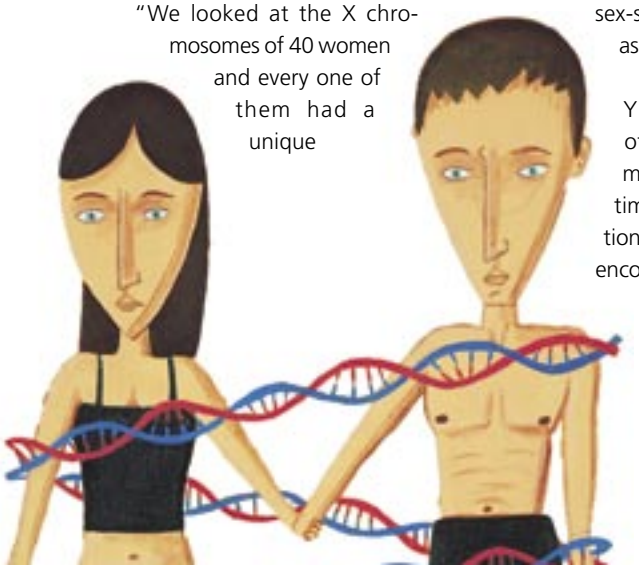
For continuing education…

Baillie and Duke colleagues Michael Byrne, MD and Robert Mitchell, MB, BCh, recently published an overview of medical management of ingested foreign bodies for primary care physicians. The article is available online at www.emedmag.com/html/pre/gic/consults/051503.asp (or just visit our Web site, dukemedmag.duke.edu, for a direct link).

The X factor

THE FIRST COMPREHENSIVE survey of gene activity in the X chromosomes of women has revealed an unexpected level of variation among individuals, according to researchers at Duke's Institute for Genome Sciences & Policy (IGSP) and Penn State.

"We looked at the X chromosomes of 40 women and every one of them had a unique pattern of gene expression," said Huntington Willard, PhD, IGSP director and senior author of the study. "That variation is completely unique to women. The X chromosomes of males are all the same in this regard."



Such genomic differences may help explain sex-specific traits in complex disease, as well as normal gender differences, he said.

In mammals, males have one X and one Y chromosome while females have a pair of X's. Many genes on the male Y chromosomes have been lost over evolutionary time, leaving it with fewer than 100 functional genes. In contrast, the X chromosome encodes more than 1,000.

Researchers have long known that genes on one copy of the female's X chromosome are switched off, a modification known as X inactivation that was originally thought to completely silence the genes on the second X chromosome. In the late 1980s, however, the first evidence came to light that some portion of those genes remained active. The new work extends that earlier finding to the full set of X-linked genes, and further reveals that individual women exhibit extensive differences among them with respect to X inactivation, Willard said.

The findings also highlight key differences between female and male genomes. "We now know that 25 percent of the X chromosome—200 to 300 genes—can be uniquely expressed in one sex relative to the other," Willard said. "In essence, there is not one human genome, but two—male and female."

The scientists reported their findings in the March 17 *Nature*. In the same issue, they and more than 250 other researchers also reported the complete DNA sequence of the human X chromosome.

Spotting Rocky Mountain spotted fever
(and its spotless cousin)

IF YOU'RE DRIVING on the autobahn toward Austria, cruising at more than 100 mph, something very unusual would have to occur to cause your wife to try to get out of your speeding car. But that's exactly what happened the day Lloyd Michener, MD, and his wife, Gwen Murphy, PhD, arrived in Europe three summers ago. Murphy became disoriented with a high fever and began reaching for the door latch. By the time Michener raced Murphy to the emergency room in Salzburg, she was losing consciousness.

"The Austrians are very conservative medical treaters," says Michener, chair of Duke's Department of Community and Family Medicine. "They were going to watch her and see what happened. But a frantic husband—me—urged them to go ahead and give her antibiotics."

The doxycycline saved his wife's life. Before leaving North Carolina, Murphy, an avid hiker and gardener, unknowingly had contracted ehrlichiosis—a tick-borne disease, sometimes called "spotless Rocky Mountain spotted fever," that attacks small blood vessels throughout the body. When Murphy reached the hospital, she was already "within an hour or two of dying," says Michener. She recovered fully, but not before spending a week in the ICU with multiple pulmonary embolisms, liver failure, and heart failure.

As the weather heats up in North Carolina, so does concern over Rocky Mountain spotted fever (RMSF) and its spotless cousin, ehrlichiosis. The Tar Heel state sees more cases of RMSF than any other locale in the nation and three times as many as the next closest state. Ehrlichiosis, which has identical deadly effects and similar symptoms to RMSF, was first identified just 20 years ago, and may be increasing in frequency.

The diseases appear in suburban areas where residents have close contact with the outdoors and in warm climates where ticks can thrive longer—all factors that make North Carolina ripe for cases, says Duke infectious diseases expert Daniel Sexton, MD.

The good news is that almost all patients with either RMSF or ehrlichiosis have an excellent chance of recovery if treated early with antibiotics, says Sexton.

But knowing when to treat can be tricky. Physicians often overlook the illness because it is notoriously difficult to diagnose; in its early stages, it can "masquerade as any one of a number of benign diseases, including a variety of viral illnesses," says Sexton. And doctors cannot depend on the telltale presence of a rash. In one of 10 cases, patients with RMSF have what Sexton calls "spotless fever," where a rash either isn't noticeable or doesn't show up at all. Up to 90 percent of ehrlichiosis cases present without a rash, and in many patients the rash may be delayed in onset.

"For an individual patient who presents with a nondescript illness, the odds are not very high that they're going to have spotted fever," says Sexton. "The trick is to suspect and treat those with a tick-borne illness, and not to treat everybody who ever has a fever in North Carolina with an antibiotic."

Sexton recommends factoring in not just symptoms such as high fever, headache, and, in more than half of cases, gastrointestinal complaints, but also the time of year, whether a tick bite is known or likely, and how many days the illness has been present before making a judgment.

"It's a complex equation," he said. "But doctors should all realize that if a person becomes sick in an area where spotted fever or ehrlichia are common, if it's spring or early summer, and if the illness has been going on for a number of days and is getting worse, treatment for the possibility of RMSF or ehrlichia is generally a good idea."

> The Tar Heel state sees more cases of RMSF than any other locale in the nation and three times as many as the next closest state.

Is it RMSF?

1. Does the patient have an unexplained high fever?
2. Does the patient present from spring through early autumn?
3. Does the patient have a rash?
4. Has the illness been present and worsening over a few days?
5. Is a tick bite known or likely?

Consider RMSF or ehrlichiosis if 1 and 2 are true. Initiate treatment if 1 and 2 are true AND one or more of 3, 4, or 5 are also true.

Rx for heart: Work out, chill out

EXERCISE AND STRESS management can not only reduce depression and distress in heart patients, but can also improve physiological markers of cardiovascular health, according to a major Duke study.

The Duke trial enrolled 134 patients with stable heart disease and randomized them to one of three groups—exercise, stress management, or standard medical therapy. Patients who received the behavioral treatments showed a nearly 25 percent improvement in vascular endothelial function—comparable to that achieved in drug trials. Patients who received exercise training or stress management also had improved baroreflex sensitivity (abnormally low baroreflex sensitivity is associated with worse outcomes in heart patients). Furthermore, in a subgroup of patients who had stress-induced wall motion abnormalities (WMAs) before treatment, those receiving behavioral treatment also had lower WMA scores after treatment than patients receiving usual care.

"These findings add additional support for the use of non-pharmaceutical approaches to treating patients with heart disease," said Duke medical psychologist James Blumenthal, PhD, lead author of the study published in the April 6 *JAMA*.

JOEY BENTON / SALISBURY POST

Psychiatrist Richard Weisler vividly remembers the rotten-egg odor of hydrogen sulfide that emanated from the asphalt terminal and hot-mix plant in Salisbury, North Carolina, where he grew up. Years later, he and other researchers have discovered a possible link between airborne chemicals and an increased suicide rate in the community.

Study suggests link between contaminants, suicide in NC community

A team of researchers from Duke, UNC, Clean Water for NC, and the NC Depression and Bipolar Support Alliance (DBSA) helped in a Blue Ridge Environmental Defense League (BREDL) study that recently reported a threefold increase in the suicide rate in two Salisbury, NC, neighborhoods between 1994 and 2003. In 2003 there were 128 suicides per 100,000 individuals, roughly 10 times the statewide average.

The neighborhoods, home to 1,561 people, are downwind from a liquid asphalt terminal, a contaminated former petroleum tank farm, and an asphalt hot-mix plant, which also contained a contaminated cleanup site where the NC Department of Transportation had dumped solvents used to test asphalt.

A 2001 state estimate put the average maximum hydrogen sulfide level in a large part of the area at 215 parts per billion (ppb). The newly revised, but not yet implemented, NC 24-hour hydrogen sulfide standard is 86.2 ppb.

The researchers made the hypothetical link between hydrogen sulfide and suicides based on biological plausibility, noting that the chemical affects brain neurochemistry as a direct gaseous neuromodulator that potentially affects mood states and the psychological stress response. The study team reported that the asphalt terminal and plant also released other neurotoxic compounds such as benzene, chlorinated solvents, and carbon disulfide, among others. Carbon disulfide has been linked to personality changes, mood disorders, and suicides.

In addition, "Some research suggests that asphalt and highway workers exposed to asphalt-solvent fumes show an increase of suicide rates and brain cancers," says study author Richard Weisler, MD, an adjunct professor of psychiatry at Duke. The incidence rate of primary brain cancers in these neighborhoods from 1995 to 2000 showed an increase about 6.4 times greater than expected for the population, he says.

Weisler, co-author Sheila Singleton of the NC DBSA, and Rowan County health officials worked with the Centers for Disease Control and Prevention to begin implementing a psychoeducation and referral program for area residents, as well as educational programs for area health and mental health providers. Weisler and Singleton also helped area residents form a mental health support group.

Further studies are planned, and significant action has already been taken, says Weisler, but reducing potentially toxic exposures from the plants and safe cleanup of the solvent and petroleum contaminated area sites will be crucial.

"We do not know with scientific certainty that the area suicides are linked to hazardous chemical exposures, but we know enough to recommend that it is not worth taking any more chances on the potential association," he says.

The roots of depression

Duke researchers have discovered a genetic defect linked to major depression, a condition affecting nearly 20 million Americans. The finding could lead to the first diagnostic test for genetic predisposition to depression.

The team identified a defective gene that generates a mutant version of the enzyme tryptophan hydroxylase-2 (TPH2), which controls production of the brain chemical serotonin. Abnormalities in serotonin levels are considered a key contributor to major depression and other neuropsychiatric disorders. Cells expressing the mutant enzyme produced approximately 80 percent less serotonin than cells with the more common form of the enzyme, the team found.

In a screening of 350 patients, the researchers found that more than 10 percent of those with unipolar major depression carried the abnormal gene, compared to no patients with bipolar disorder and one percent of those who had not been diagnosed with either disorder.

Patients with depression who carried the abnormal gene also showed resistance to treatment with selective serotonin reuptake inhibitors (SSRIs), a class of drugs that includes paroxetine (Paxil), sertraline (Zoloft), and fluoxetine (Prozac). In addition to its diagnostic use, the genetic marker might therefore also aid in identifying, in advance, those patients who will likely fail to respond well to SSRI therapy, according to senior author Marc Caron, PhD, a James B. Duke Professor of Cell Biology and member of the Duke Institute for Genome Sciences and Policy.

The researchers further suggest that this and other variants of the gene might explain such paradoxical adverse reactions to SSRI treatment as suicidal behavior and SSRI-exacerbated mania and psychosis.

The Duke team reported its findings Dec. 9, 2004, in the early online edition of *Neuron*.

Colonoscopy beats the alternatives—for now

Colonoscopy does a better job detecting colon polyps and cancer than "virtual" colonoscopy with CT scans or air contrast barium enema (ACBE) X-rays, according to a Duke study published in the Jan.1 *Lancet*.

In fact, the study's Data and Safety Monitoring Board recommended ending the trial early because the accuracy of colonoscopy so clearly superseded that of other tests in the study (see chart). But Duke radiologist Erik Paulson, MD, a study co-author, points out that CT technology and patient preparation techniques for CT colonography have advanced considerably since the study was designed in 2000. "I'm certain these improvements will result in better sensitivity. There's no doubt CT colonography will play a role in screening," Paulson says.

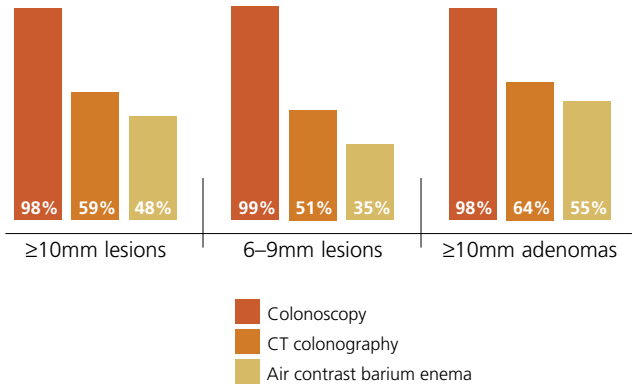
He points out that, unlike colonoscopy—in which a flexible tube containing a light source and camera is inserted through the rectum and into the colon—CT colonography is non-invasive, does not require sedation, and enables patients to return to work immediately following the test.

Of the three imaging methods studied in 614 patients, ACBE had the highest rate of false-positives and the lowest sensitivity. A high rate of false-positives is problematic because detection of lesions that are not really there will lead to additional tests, increased costs, and the possibility of complications, says lead author Don Rockey, MD.

Paulson says the Duke study is the first to show virtual colonoscopy is more sensitive than ACBE. "Should CT colonography replace air contrast barium enema? I think the answer should be yes," he says.

It was recommended that the trial end early because the accuracy of colonoscopy so clearly superseded that of other tests in the study.

SUCCESS AT DETECTING COLON POLYPS IN PATIENTS



Why it's important to iron your genes

IRON DEFICIENCY is the most prevalent and severe nutritional disorder worldwide, affecting more than 2 billion people. Its symptoms range from anemia, fatigue, weakness, and cognitive deficits to serious heart complications and developmental disorders, and low iron levels can even influence the development of hereditary blood disorders, Parkinson's disease, and certain cancers.

More than 80 genes start to malfunction when people don't get enough iron, the essential nutrient abundant in foods such as red meat and spinach.

But just how iron deprivation makes the body go haywire wasn't well understood until recently. In a study reported in the Jan. 14 *Cell*, Duke researchers demonstrated for the first time that iron-starved cells preserve the little iron they possess by shutting down the major iron users in order to maintain the cell's essential functions. "Iron deprivation actually reprograms the metabolism of the entire cell," says Dennis J. Thiele, PhD, professor of pharmacology and cancer biology. "Without this nutrient, there is a complete reorganization of how cellular processes occur."

Thiele and colleagues demonstrated in yeast cells that iron deprivation dramatically reduced the activity of more than 80 different genes. Some of these genes are known to be vital in generating energy, copying the cell's genetic code, and protecting the cell from free radicals and aging. The effects of others are unknown, meaning that iron deprivation may cause even more side effects than currently recognized. Thiele says the discovery could aid in the diagnosis and ultimately the treatment of serious disorders caused by low iron levels.

Reaching out to the young in heart

WHEN YOU'RE A MAJOR referral center treating patients with one of the most common birth defects—congenital heart problems—you're bound to be busy. Sometimes a bit too busy, as Duke's Pediatric Cardiology Service found recently when it faced one of the downsides of bustling business—a problem with access. Several recent initiatives will help ensure that more patients can be seen more quickly, says division chief John Rhodes, MD.

"Our patient load has been expanding in every area—cardiac cath, echocardiography, electrophysiology, outpatient clinics, inpatient admissions, and surgeries—and it's increased about 25 percent in recent years," Rhodes explains. "To meet the demand, we've recently hired six new faculty, who are all well trained and great people."

The service staffs about a dozen outreach clinics each month in several North Carolina cities. But the goal is to place full-time pediatric cardiologists in communities large enough to support one, Rhodes says; he's already found one for Raleigh, and another will soon hang out his shingle in the Fayetteville area. "Raleigh is clearly a good-sized city, but, surprisingly, Duke's Angelo Milazzo is the only pediatric cardiologist in the community," he says.

Along with holding general pediatric cardiology clinics, the service offers several "super-subspecialty" clinics that focus on children with hyperlipidemia, pulmonary hypertension, and single-ventricle or other complex congenital malformations, as well as adults who have congenital heart problems. "We also offer some super-subspecialty procedures in the areas of cardiac catheterization, cardiac MRIs, and electrophysiology [for children with arrhythmias]," Rhodes adds.

Last fall, the service initiated a new access model that offers appointments within seven days, notes nurse practitioner Bronwyn Bartle. "And we offer same-day access on weekdays when the referring physician feels the patient should be seen immediately."

The service also works closely with expectant parents whose unborn child has been diagnosed with a heart defect and will be delivered at Duke. "Our pediatric cardiovascular surgeons perform more than 300 operations a year and have special expertise in many of the complex defects that need to be corrected soon after birth," Bartle says. "We will be seeing a lot of these parents, so we want to get to know them before birth and prepare them for what's to come."

"It's a very exciting time to work here at Duke," Rhodes says. "And although I realize I'm not being objective, I think that treating kids with heart disease who really need our care is one of the important jobs in the world."

For information, e-mail heartline@duke.edu or call 919-681-2916; for appointments call 919-668-4000; for referrals call 919-684-8111 and ask for the pediatric cardiologist on call.

Pre-op screening… and then some

"TO SAY THAT BETH SAVED my life is not an overstatement," says a patient whose rare disorder was discovered by nurse practitioner Beth Owen (right) during a routine screening.

The middle-aged woman was one of dozens of patients seen in Duke's preoperative screening clinic that day. But she turned out to be one in a million—or one of three in a million, to be exact.

The woman had come in before her scheduled surgery to remove a potentially cancerous pancreatic tumor. As Owen examined the patient, however, she began to suspect that her problem might be of a different nature, based on such subtle clues as the woman's arthritis, hypertension, and most of all an unusual physical appearance that reminded Owen of pictures in her nursing textbooks.

An endocrine consult confirmed Owen's suspicions: the woman had acromegaly, a serious disease in which the pituitary gland produces too much growth hormone. Sometimes triggered by tumors on the pancreas or pituitary gland, acromegaly can cause enlarged hands and feet, a protruding forehead and jaw, and a host of other problems both cosmetic and systemic. The disorder is diagnosed in only three out of a million people a year, and is notoriously easy to overlook—although it can be treated. Today, thanks to her sharp-eyed caregiver, Owen's patient is in much better health.

Diagnosing rare diseases isn't exactly what one would expect of a preoperative screening clinic, but medical director Ron Olson, MD, says the clinic team have come to expect the unexpected. "We do one of the most comprehensive preoperative assessments around," he says. The clinic's nurse practitioners and physician assistants see almost every patient scheduled for surgery at Duke, and may spend anywhere from half an hour to an hour or more with each one, taking a history and conducting an examination. "The medical system is so fragmented today that this may be one of the few places patients are looked at as a whole, especially if they haven't seen a primary care physician in a few years," says Olson.

As a result, clinic staff often spot health problems that have gone undetected or unmanaged. While there are the occasional dramatic discoveries—as when a patient scheduled for breast surgery had an abdominal mass that turned out to be ovarian cancer—the staff more often finds common conditions like asthma, COPD, hypertension, and diabetes. These can usually be treated in the clinic to get them under control before surgery, Olson says. In addition to coordinating care as needed, the clinicians also talk to the patient in depth about the perioperative experience, and clerical staff make sure the anesthesiologist and surgeon have the information they need.

"We do everything we can to optimize the patient for surgery," Olson says. "And it's great when we can help them improve their health for the long term as well."

"The medical system is so fragmented today that this may be one of the few places patients are looked at as a whole, especially if they haven't seen a primary care physician in a few years," says Ron Olson, MD, medical director of Duke's preoperative screening clinic.

THOMAS D'AMICO, MD
Cuts recovery time in half with minimally invasive surgery

Cracking the code of LUNG

JENNIFER GARST, MD
Advocates awareness of dangers of lung cancer for women

JEFFREY CRAWFORD, MD
Conducts trials of new therapies

CANCER

BY MINNIE GLYMPH

Why are women more susceptible to lung cancer than men?
Why do different people respond differently to the same therapy?

As researchers begin to tease out genetic mutations linked to lung cancer and design targeted therapies in response, there's growing hope for people diagnosed with the deadliest of cancers. Duke's crack team of lung cancer specialists is leading the push to discover new treatments—and offer better care to patients with lung cancer today.

LUNG CANCER

THE LUCKIEST DAY OF DANNIE WOODRUM'S LIFE—if one can call such things lucky—was the morning in 1998 when her lung collapsed. The 32-year-old mother of three had gone to bed early the night before, convinced by her aching chest that she was coming down with the flu, and woke up in excruciating pain. "I jumped out of bed screaming, 'I'm having a heart attack!'" she recalls. "I was crying so hard. It was like a knife going through my chest over and over."

But it wasn't a heart attack. Nor was it the pneumonia two different hospitals diagnosed her with over the next couple of weeks. It also wasn't linked to the severe allergies Woodrum had been told she had a year earlier, when an allergist evaluated the wheeze that had been pestering Woodrum for months and sent her home with a prescription for Claritin. It was only after her primary care physician referred her to a pulmonologist that Woodrum learned the truth: she had lung cancer.

She traveled from her South Carolina home to Duke for evaluation, and was diagnosed with stage II squamous cell carcinoma—relatively good news: the cancer had begun spreading from her lungs, but so far had infiltrated only the surrounding lymph nodes. Thoracic surgeon Thomas D'Amico, MD, performed minimally invasive surgery to remove the tumor, and ended up pulling Woodrum's entire deflated lung out through the three-and-a-half-inch incision.

"Dr. D'Amico told me I was lucky," says Woodrum, who is cancer-free today, eight years after her surgery and subsequent chemotherapy and radiation therapy. "Even though the tumor was still pretty small, because of where it was it blocked my airway and made the whole lung fall. If that hadn't happened I could have gone on for several years without knowing what was wrong, and I would have died."

Woodrum's assessment sounds bleak, but it's not unfounded. Lung cancer is the deadliest disease in oncology. While advances in screening and treatment have dramatically improved survival in many other types of cancer in recent years—prostate, breast, colon, non-Hodgkin's lymphoma—efforts to extend the lives of lung cancer patients have been less successful. None of the available screening tests has proven effective in saving lives, and because most people are diagnosed only after lung cancer has reached an advanced, incurable stage, the five-year survival rate is just 14 percent.

While overall survival rates have only inched up, there's been a sea change in demographics. The incidence of lung cancer in men has been steadily dropping for years, but cases among women climbed 60 percent from 1990 to 2003. Lung cancer surpassed breast cancer as the leading cancer killer of women in 1987, and now kills more women than breast and ovarian cancer combined. While the spike largely reflects the growing number of women smokers over the last few decades, many of the women diagnosed with lung cancer today quit smoking long ago. And the fastest-growing subtype of lung cancer, bronchioloalveolar carcinoma (BAC), occurs most frequently in young women who never smoked at all—for reasons that are unclear.

But perceptions of who gets lung cancer have lagged behind reality, says Duke oncologist Jennifer Garst, MD. She thinks that may be one reason why Woodrum's ailment was misdiagnosed time after time—the possibility simply wasn't on anyone's radar screen. "Even physicians are shocked when young women get lung cancer," Garst says. "When people think of lung cancer they think of older men who have smoked cigarettes all their lives, and that's not necessarily the case any more. We don't know whether it's due to environmental factors or an estrogen link or something else, but women are at higher risk than men for developing tobacco-induced lung cancers, even with lower total exposure to tobacco. They tend to get cancer at an earlier age, and they're also more likely to develop non-smoking-related adenocarcinomas."

At Duke and other cancer centers nationwide, physician-scientists are beginning to tease out why women and certain other groups of people are more susceptible to lung cancer than others—and why different people respond differently to the same therapies. As the answers begin to emerge, they are helping clinicians extend life for both men and women with lung cancer at last.

A BANNER YEAR FOR BREAKTHROUGHS

Last year, at the annual meeting of the American Society of Clinical Oncology, Canadian researchers generated great excitement by presenting a study showing that the experimental epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) Tarceva (erlotinib) extended survival by an average of two months in patients with advanced-stage non-small-cell lung cancer (which comprises 80 percent of all lung cancer cases). Two months may not seem like a lot—but for patients with less than six months to live, it's a significant advance. Tarceva was the first drug in this class proven to extend life for lung cancer patients.

the EGFR mutation, and the results used to select their therapy.

"This is the first time in lung cancer treatment that we've ever been able to direct therapy based on a biologic feature of a tumor," says Crawford. "It's a paradigm shift in how we manage patients."

The finding is hopeful even for people without EGFR mutations, adds cancer researcher Michael Kelley, MD. "I don't think there's going to be a single cure for lung cancer, especially for smokers, because they have all kinds of genetic alterations in their cells," he says. "This research is exciting because it proves that by understanding the specific genetic defects in tumor cells, we can design targeted drugs to address those defects."

> **Right now we** just give everyone a standard course of chemotherapy, which is sort of like giving everyone penicillin. Sure, some people will respond, but not everyone—and if people are resistant, doctors have to figure out which drug will work for them."
>
> —David Harpole, MD

"It was a breakthrough trial," says Duke medical oncologist Jeffrey Crawford, MD. "This was the first time an EGFR-inhibitor showed a clear survival benefit across a broad range of patients." In fact, a similar, FDA-approved agent that targeted a different part of the EGFR pathway, Iressa (gefitinib), disappointed clinicians in 2004 by failing to show an across-the-board benefit.

But what may be most intriguing about these drugs, says Crawford, is that they both work exceptionally well in women, Asian patients, and people who never smoked.

"Ever since these drugs were around we've realized that there's a subpopulation of patients who do dramatically well with them," says Crawford, who has led trials of the therapies at Duke. "This year we found out why—these patients have a particular mutation in the EGFR protein targeted by these drugs."

Duke is part of the nationwide clinical trials consortium that will be conducting clinical research to further document the benefits of EGFR inhibitors in that population. But the findings have already changed clinical practice. At Duke, patients who fit the profile are now tested for

GENETICALLY TAILORED TREATMENTS

David Harpole, MD, director of the Thoracic Oncology Research Program, is already searching for such defects. "Right now the only marker for lung cancer that we know of is the EGFR mutation," he says. "That's great if you're a non-smoking female of Asian descent, but it's not especially helpful for the other 90 percent of lung cancer patients. We're trying to find mutations that will help us create targeted therapies for everyone."

> This research is exciting because it proves that by understanding the specific genetic defects in tumor cells, we can design targeted drugs to **address those defects.**"
>
> —Michael Kelley, MD

Since 1996, Harpole has been collecting clinical data and samples of tumor tissue, blood, and bone marrow from patients undergoing lung cancer surgery at Duke (with their consent). The collection, housed in freezers in Harpole's laboratory, is now one of the largest consented lung cancer tumor banks in the world, with nearly 1,000 patients represented.

In his current study, Harpole has plucked samples from 100 patients who had surgery for early-stage lung cancer. Half of them survived and are considered cured of cancer, while the other half suffered early recurrences of the disease. Using advanced analysis techniques, Harpole is working with geneticists Joseph Nevins, PhD and Mike West, PhD of Duke's Institute for Genome Sciences and Policy to identify genomic biomarkers and with Vanderbilt University scientists to identify proteomic biomarkers associated with the patients' outcomes. The researchers will use the resulting data, along with the patients' clinical and pathologic information, to construct a model to predict how patients will fare after surgery.

Harpole has submitted a grant proposal to test the model on 250 additional patients in the database. If it works, the researchers will conduct a clinical trial in early-stage lung cancer patients undergoing surgery. Patients for whom the model predicts early recurrence will be randomized to receive either chemotherapy or the standard course of treatment, observation.

"There are risks and even deaths associated with chemotherapy," says Harpole. "We don't want to needlessly treat patients who are going to be fine without it. And for those who do need chemotherapy, we hope to identify biomarkers within their tumor that will help us select the most effective type of chemotherapy for them."

That line of research will benefit patients at more advanced stages of lung cancer as well, he says. "Right now we just give everyone a standard course of chemotherapy, which is sort of like giving everyone penicillin. Sure, some people will respond, but not everyone—and if people are resistant, doctors have to figure out which drug will work for them."

Women especially may benefit, he adds. "There are clearly differences in how lung cancer affects men and women. But there's no difference in treatment—and there probably should be. That's an issue we'll be looking at."

NEW APPROACHES TO SURGERY

Harpole's study will focus on stage IA patients, those with the very smallest tumors, for whom the benefits of adjuvant chemotherapy are uncertain. Until recently, in fact, it wasn't at all routine for any but advanced-stage lung cancer patients to receive chemotherapy—earlier-stage patients commonly had surgery only, and many radiation therapy patients did not receive chemotherapy.

Last year, though, two landmark studies demonstrated unequivocally that chemotherapy improves survival in stage IB to stage III lung cancer patients who have had surgery to remove cancerous tumors. "The results were dramatic," says Crawford, who led Duke's participation in one of the trials. "Our trial showed that survival rates increased from 69 to 82 percent after three years, and the other study showed an increase from 54 to 69 percent at five years. If you look at the magnitude of the benefit, it's greater than providing chemotherapy after breast cancer surgery."

Clinical practice has quickly adapted to bring patients the benefits of research, and Crawford says more patients are being treated with chemotherapy at earlier disease stages, whether after surgery or to shrink the tumor prior to surgery. At the same time, Duke researchers are working to improve existing approaches to chemotherapy—testing new drugs as well as novel combination therapies, in which chemotherapy is paired with agents such as Tarceva, dendritic cell vaccines, antibodies that target cancer cells, or Gleevec (imatinib mesylate), which may help chemotherapy or radiation therapy penetrate large tumors by improving intratumor blood flow. "As we're developing less toxic chemotherapies and other targeted therapies, the vast majority of lung cancer patients are now receiving some type of adjuvant therapy," Crawford says.

But, points out surgeon Thomas D'Amico, patients have to be physically able to withstand the rigors of treatment. "Adjuvant therapy has only been proven beneficial if given within six weeks after

Could smokers one day pop a pill to prevent lung cancer?

IT'S A QUESTION RESEARCHERS at Duke and elsewhere are working to answer—even though not everyone is happy the question is being asked. "Some people say if you develop a strategy to prevent lung cancer, you might encourage people not to quit smoking," says Michael Kelley, MD.

But quitting is notoriously hard to do. And since tobacco smoke causes permanent genetic changes in the lungs, even people who have stopped smoking will forever have a higher risk of developing lung cancer. With 90 percent of lung cancer deaths related to smoking, interrupting the biochemical changes that lead to cancer could save tens of thousands of lives a year.

Kelley and his colleagues are trying a number of strategies to counteract carcinogenesis. In one study, the researchers tested a drug called oltipraz designed to stimulate the body's own detoxification agents. Unfortunately, Kelley says, "We found that in patients who smoked, we could no longer induce the body's own properties to repair damage, at least with this drug." They're hoping to conduct a similar trial using a less toxic drug, Sialor (anetholtrithione), which can be given in larger amounts.

The team is also testing agents that target other biochemical pathways involved in lung cancer development, such as the EGFR and COX-2 pathways. These trials in current and former smokers serve a dual purpose—researchers believe that the same drugs might be useful both for treating cancer and for preventing it. "We're looking at tumor shrinkage, and also at biomarkers that might tell us whether or not these agents will be useful for prevention," Kelley says.

For right now, though, "There's nothing I would recommend to people outside a clinical trial to prevent lung cancer—other than 'Don't smoke,'" Kelley says. "Pretty basic, but extremely hard to do—and that's a whole other story." (Read it on page 24.)

surgery," he says. "If someone hasn't fully recovered from surgery by then, they may not be ready to undergo toxic chemotherapy—and they could miss their window of opportunity."

Minimally invasive surgery, a specialty of Duke's thoracic surgeons, can help ensure that more patients can receive potentially lifesaving chemotherapy after surgery.

In a standard thoracotomy, surgeons make at least a foot-long incision around the patient's chest between the ribs, then use a retractor to spread the ribs open, "like parting Venetian blinds," says D'Amico. While the open surgery makes it easier to see and remove the cancer, the patient is left with cut muscles, pain, and often broken ribs. In contrast, minimally invasive thoracoscopic lobectomy, performed with the aid of tiny operating cameras, enables surgeons to remove an entire pulmonary lobe through an incision generally no longer than five centimeters. No retractor is necessary.

"Minimally invasive surgery is proven to preserve pulmonary function and result in less pain, less time requiring a chest tube, less inflammatory response, and a faster return to activity," D'Amico says. "In studies we've conducted, patients stayed an average of three days in the hospital after minimally invasive surgery, compared to six to seven days for traditional thoracotomy."

Despite the advantages, many hospitals don't offer the technically advanced procedure, which D'Amico admits is "hard to do and hard to teach."

"I feel like I'm still learning how to do it, and I've done over 500," he says. "It's not like operating on a gall bladder, where if you tear it it's OK because you're going to take it out anyway. If there's an injury to the pulmonary vessels pretty significant bleeding can occur, and you can't control that thoracoscopically—you will have to open the chest."

D'Amico and his colleagues have refined the technique by strategically placing the incisions to optimize visibility and reduce the chances that surgeons will have to revert to a full thoracotomy. The fact that Duke has four surgeons devoted exclusively to treating lung cancer patients has also enabled the team to gain extensive experience in the procedure, he adds. Today, over half of the 1,500 lung cancer surgeries performed at Duke each year are minimally invasive.

TREATMENT FOR LIFE

Only medical, radiation, and surgical treatments can cure lung cancer, but there's another treatment, often overlooked, that can dramatically impact a patient's quality of life—and even its quantity.

"What we call performance status—how healthy you are—directly impacts survival in this disease," says Jennifer Garst. "I personally think supportive care is as important as other types of active treatments."

That's particularly true in patients receiving chemotherapy. Now that chemotherapy is often used curatively,

The new face of lung cancer

Once considered a disease of male smokers, the deadliest of cancers is now striking women in record numbers. Dannie Woodrum, mother of three girls (pictured), was diagnosed at 32 and has since shared her story on ABC's *20/20* and in American and Latin American issues of *Glamour* magazine.

"People like Dannie who have survived lung cancer and want to tell people about it are extremely important," says Woodrum's oncologist, Jennifer Garst, MD. "It's such a deadly disease that we don't have a lot of people like that."

Garst and other scientists and caregivers are working to help raise awareness of lung cancer's dangers for women and increase research funding through WALC (Women Against Lung Cancer). For more information, visit www.4walc.org.

Having tremendous anxiety can be every bit as painful as physical pain. We work very hard to help people manage that, whether through anti-anxiety medications, meditation, or exercise such as yoga, which can also improve patients' breathing capacity."

—Jennifer Garst, MD

instead of just to extend survival, it's critical to protect patients' overall health from the ravages of therapy, says Crawford. "If a patient is receiving chemotherapy after surgery or radiation, and they get a fever or infection and die, that's tragic—particularly if they might have been cured."

He and his colleagues have developed and tested a number of protective agents that patients can receive along with chemotherapy to reduce such complications. These include white cell growth factors, such as Neupogen (filgrastim) and Neulasta (pegfilgrastim), which can prevent fever and infection, and erythropoietic agents that can reverse anemia by stimulating the growth of red blood cells. "Lung cancer patients can develop anemia from chemo or radiation treatments, the disease itself, or surgery and blood draws, and on top of that they frequently have other problems such as emphysema, where they need the maximum oxygen-carrying capacity they can muster," says Garst. "If one of those patients becomes anemic, they're not just going to feel a little fatigued, they'll feel really awful."

Weakness can also stem from weight loss and nutritional deficits, which can impact response to treatment and long-term survival. "A significant number of patients develop taste disorders, whether from radiation treatments that cause salivary glands to dry up or from chemotherapy, which can injure different sets of taste buds and create an imbalanced palate," says Garst. "Some patients even develop taste problems and anorexia before they are diagnosed—tumors may secrete something that causes taste alterations." She and Susan Schiffman, PhD, have studied the use of flavor enhancers to improve patients' appetites; Garst adds that she has anecdotally found Megace (megestrol acetate) to be effective. Because women experience more nausea after chemotherapy than men, Garst also often assigns them to gentler regimens or adds anti-nausea medications.

Psychological and spiritual support is also critical, Garst adds. "Having tremendous anxiety can be every bit as painful as physical pain," she says. "We work very hard to help people manage that, whether through anti-anxiety medications, meditation, or exercise such as yoga, which can also improve patients' breathing capacity."

Garst is currently working with pain specialist Francis Keefe, PhD, on a clinical trial evaluating whether patients' caregivers can help them manage pain and reduce anxiety by teaching coping skills. And the entire Duke thoracic oncology team places a priority on helping patients cope, Crawford says. "We have two assets that very few other cancer centers have—an extensive Cancer Patient Support Program and tremendous support from midlevel providers. The care burden for both patients and family is very high, their needs are very high, and to be honest, physicians just don't have the time to address all of those needs. Our physician assistants and nurse practitioners and other caregivers are really invested in helping patients cope with their day-to-day psychosocial and medical needs. That team approach has made a dramatic difference in the total quality of care we provide."

"Lung cancer is a deadly disease, and there are many situations in which we can't cure our patients," adds Garst. "But we can still care for them. That means supporting them, supporting their family, and giving them the best quality of life we can, for as long as we can." □

Duke's multidisciplinary team of lung cancer specialists, including thoracic surgeons, medical oncologists, radiation oncologists, pulmonologists, and other professionals, hold a joint clinic four times a week to offer patients integrated care. To make an appointment, please call 919-684-5621.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Taking away
the power of the cigarette

Can researchers find a better way to help smokers quit?

BY ANGELA SPIVEY
ILLUSTRATIONS BY PHIL BASS

What are cigarette smokers hooked on? You know the answer. Even tobacco companies concede that a cigarette is basically a delivery system for an addictive drug—nicotine.

But to a smoker, a cigarette is much more than that. A smoker craves not only nicotine, but all the tiny things he or she has unconsciously learned to associate with it—the feel of a lighter in a pocket, the smell of burning tobacco, the sensation of smoke in the throat. "A smoker who has smoked a pack a day for twenty years has inhaled a cigarette over a million times," says Robert Shipley, PhD, director of the Duke Stop Smoking Clinic. "Each time, they have associated that inhaling of a cigarette with something pleasurable."

Research shows that those associations are so strong that the cigarette's power lies just as much in its sensory effects as in the nicotine, says Jed Rose, PhD, research professor of biological psychiatry. Rose and colleagues conducted one study in which smokers were given several choices, including pressing a button to receive an IV dose of nicotine or taking puffs of a denicotinized cigarette, made of tobacco from which the nicotine had been extracted. In a 10-minute trial, the smokers chose to puff denicotinized smoke an average of six times, while they chose to receive IV nicotine only one time. "They preferred getting smoke without the nicotine over getting nicotine without the smoke," Rose says. "Which really flies in the face of what a lot of die-hard nicotine addiction theorists would have predicted."

Understanding the intricacies of addiction to cigarettes is key to helping smokers kick the habit—a goal that has proved frustratingly elusive for both the health care community and smokers themselves. Most current smoking-cessation methods are only mildly helpful, with overall quit rates falling below 15 percent after six months, Rose says.

Smoking-related illnesses kill 440,000 Americans every year.

Figuring out how to boost that success rate is the aim of Rose and other researchers affiliated with Duke's new Center for Nicotine and Smoking Cessation Research (Duke CNSCR). The center, an expansion and consolidation of Duke's nicotine research program, was funded in 2004 with $15 million in unrestricted money from Philip Morris USA. "This money is for us to use completely independently and freely to help develop the best treatments to help people quit smoking," says Rose, who directs the center. (As is Duke's policy with all awards, the researchers will publish research results without any review or approval from Philip Morris.) By learning more about the interactions between nicotine, the sensory and behavioral aspects of smoking, and smokers' beliefs about their habit, the center's scientists are developing better ways to help smokers quit.

TIMING IS EVERYTHING

The mainstay of smoking-cessation treatment is nicotine replacement therapy (NRT), which can help relieve some of the irritability, hunger, and other withdrawal symptoms that smokers feel in the first weeks of quitting. Patients who use NRT are more successful than those who don't. Initial quit rates on NRT are about 25 percent; without, 5 to 10 percent.

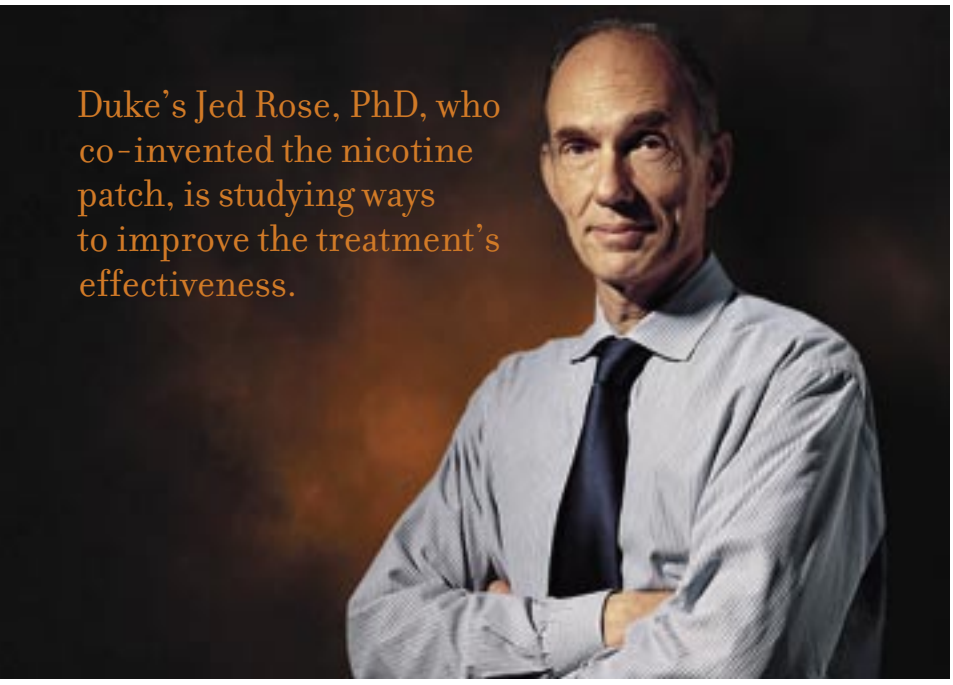
Recent research conducted by Rose, a co-inventor of the nicotine patch, suggests a simple way to modify NRT to dramatically increase those success rates. The modification helps NRT not only relieve withdrawal, but actually weaken smokers' dependence on the cigarette itself.

In one study, Rose had a group of smokers start using a nicotine patch on their target quit date, just as the labeling directs. Another group began the patch early—two weeks before they stopped smoking. Those who used the patch while still smoking were twice as successful at quitting.

Why? Using NRT and cigarettes at the same time appears to "devalue the experience of smoking," Rose says. If the physical need for nicotine is met by the patch, but the person still smokes, then each time he lights up, the cigarette itself provides less of a reward. Gradually, the smoker's body and brain learn not to associate cigarettes with pleasure. The cigarette loses some of its power.

Rose and clinical psychologist Joseph McClernon, PhD, have shown a similar effect in smokers who use both the patch and denicotinized cigarettes. Functional Magnetic Resonance Imaging (fMRI) of smokers' brains indicate that the treatment weakens the dependence on cigarettes. When smokers simply looked at smoking-related pictures (photos of lit cigarettes or of people smoking), fMRI scans showed a strong response in two areas of the brain. After two to four weeks of treatment with the patch and denicotinized cigarettes, new fMRI scans showed that the response to smoking-related photos had weakened; it was now similar to the response to neutral photos. "To their brains, these once-potent smoking cues now look similar to a stapler or a set of keys," McClernon says. This work has been submitted for presentation at the College on Problems of Drug Dependence in June 2005.

Rose is excited about these preliminary studies and is launching a larger study of 400 smokers to learn more. "It's shaping up to be a very exciting line of research that might be very close to entering future clinical practice," he says. So far, studies



Duke's Jed Rose, PhD, who co-invented the nicotine patch, is studying ways to improve the treatment's effectiveness.

Rose compares a smoker's addiction to a tree, and nicotine to water nourishing that tree. "The nicotine is playing an essential role in strengthening the habit of smoking," he says. "But what the smoker is stuck with in the end is this tree of a habit."

have not shown serious physical effects from smoking while on NRT, but the possibility of a nicotine overdose remains a concern in the minds of some. Rose's larger study will assess safety by varying smokers' use of regular and low-nicotine-yield cigarettes while on NRT, measuring their blood levels of nicotine, and monitoring for adverse effects.

TURBO-CHARGING THE NICOTINE PATCH

A novel drug, mecamylamine, may work in much the same way—by taking away the power of the cigarette. Clinical trials at Duke have shown that using mecamylamine and NRT together is more effective than using either drug alone. Mecamylamine is believed to block some of the brain's receptors for nicotine. The researchers suspect that, with mecamylamine blocking some of those receptors, and transdermal nicotine occupying others, there are few receptors left for the actual cigarette smoke to stimulate, so smoking a cigarette becomes less pleasurable. A Phase III clinical trial of a patch that contains both nicotine and mecamylamine has been completed, but more studies may be needed, Rose says.

Other work at Duke explores novel ways of delivering NRT. Eric Westman, MD, MHS, director of Duke's Smoking Research Laboratory, and Rose are testing liquid nicotine that smokers could add to soft drinks. "It's still early but it looks promising," Westman says. "One of the time-honored debates is, do you make nicotine replacements tasty, or do you make them a little bit aversive?" Westman believes that nicotine replacements should be palatable. "If the smoker has a decision between a cigarette with a taste that they like, or a nicotine-replacement product that tastes bad, they're going to go for the cigarette," he says. But, others fear "hooking people on cherry-flavored nicotine."

Nicotine replacements are designed for short-term use of one to three months. Their addiction potential is low compared to cigarettes, but some patients do find it difficult to stop using them. Long-term use of NRT is not ideal, Westman says, but the alternative—going back to cigarettes—is worse. "We know nicotine isn't harmless," he says. "But we have the understanding that nicotine by itself is less harmful than nicotine in tobacco." Doctors have to inform patients that the effects of using NRT for many years are unknown. But, Westman says, "I would rather have someone hooked on nicotine gum than still smoking."

MOTIVATING SMOKERS TO QUIT

The best therapies won't help until a smoker has committed to quitting. But it's difficult to get smokers to face that their habit puts them at risk. "People don't want to believe that bad things can happen to them," says Isaac Lipkus, PhD, of Duke's Cancer Prevention, Detection, and Control Research Program (CPDCRP). Lipkus is exploring strategies to help smokers think more realistically. For example, he's using spirometers, which are available in most hospitals, to measure lung function of college-age smokers and determine their "lung age." "We're trying to find out, if we tell college smokers that their lung age is greater than their chronological age, does that really affect their risk perceptions?" he says. "And if so, does that increase their desire to quit smoking?"

Most smokers have some conflicting feelings about their habit, and Lipkus is looking for ways to capitalize on that. He and his colleagues have found that teens and college students who express


Eric Westman, MD, MHS

More than 3,000 people a year die of lung cancer caused by secondhand smoke.

ambivalence about their smoking are more likely to say they want to quit. The researchers are experimenting with questionnaires, videos, and other methods that might help smokers face their feelings. "People don't want to feel torn or conflicted about things," Lipkus says. "But we want people to recognize their ambivalence and work through it so they will change their behaviors."

Other Duke research seeks to take advantage of "teachable moments"—times when the risks of smoking and benefits of quitting may be especially apparent. In the Family Ties study, led by


Isaac Lipkus, PhD

Lori Bastian, MD, smokers who have family members with lung cancer are invited to participate in a stop-smoking program. Participants receive free nicotine patches, a reusable family photo album filled with smoking-cessation materials, and a customized booklet that reinforces the emotional impact of their relative's diagnosis as a motivation for quitting. "Stress and coping theories suggest that a stressful event can motivate some individuals to examine and change their unhealthy behaviors," says Bastian. "By timing smoking cessation interventions to follow a loved one's diagnosis of lung cancer, we may be more successful in encouraging smokers to quit." Another ongoing study, led by Duke ob-gyn Evan Myer, MD, and CPDCRP researcher Kathryn Pollak, PhD, focuses on helping pregnant smokers quit (see Resources sidebar).

STRATEGIES FOR SUCCESS

Once smokers are ready to quit, they are more successful if they have a strategy for handling cravings. Arming smokers with a plan is a major part of the QuitSmart smoking cessation program, developed by Duke's Robert Shipley. In one study, 66 percent of smokers using QuitSmart were still smoke-free at six months, versus just 16 to 30 percent in four comparison treatments. The program uses multiple methods—gradually switching to low-nicotine cigarettes before the quit date, various forms of NRT, hypnosis, and behavioral treatment such as encouraging smokers to reward themselves.

"Smokers spend a lot of their life in the actual smoking ritual. Now they have time on their hands," Shipley says. "We want them to use that time not to clean the cupboard, but to do something to feel good—take a walk, a bubble bath—so they don't feel deprived, which could lead them back to cigarettes."

All these approaches—weakening the power of the cigarette, helping smokers face their risk for disease, and developing a plan for quitting—tackle not just the physical addiction to nicotine, but the smoker's emotional dependence on the whole habit. Shipley says that, for most smokers, giving up cigarettes is like giving up a good friend. "If a smoker is lonely, they smoke. If they're bored, they smoke," he says. "While you and I can see it as a false friend, to a smoker, day by day, hour by hour, it's been a very good friend to them." □

[Editor's note: Jed Rose has a financial interest in nicotine patches. Robert Shipley is president of QuitSmart Stop Smoking Resources, Incorporated.]

RESOURCES

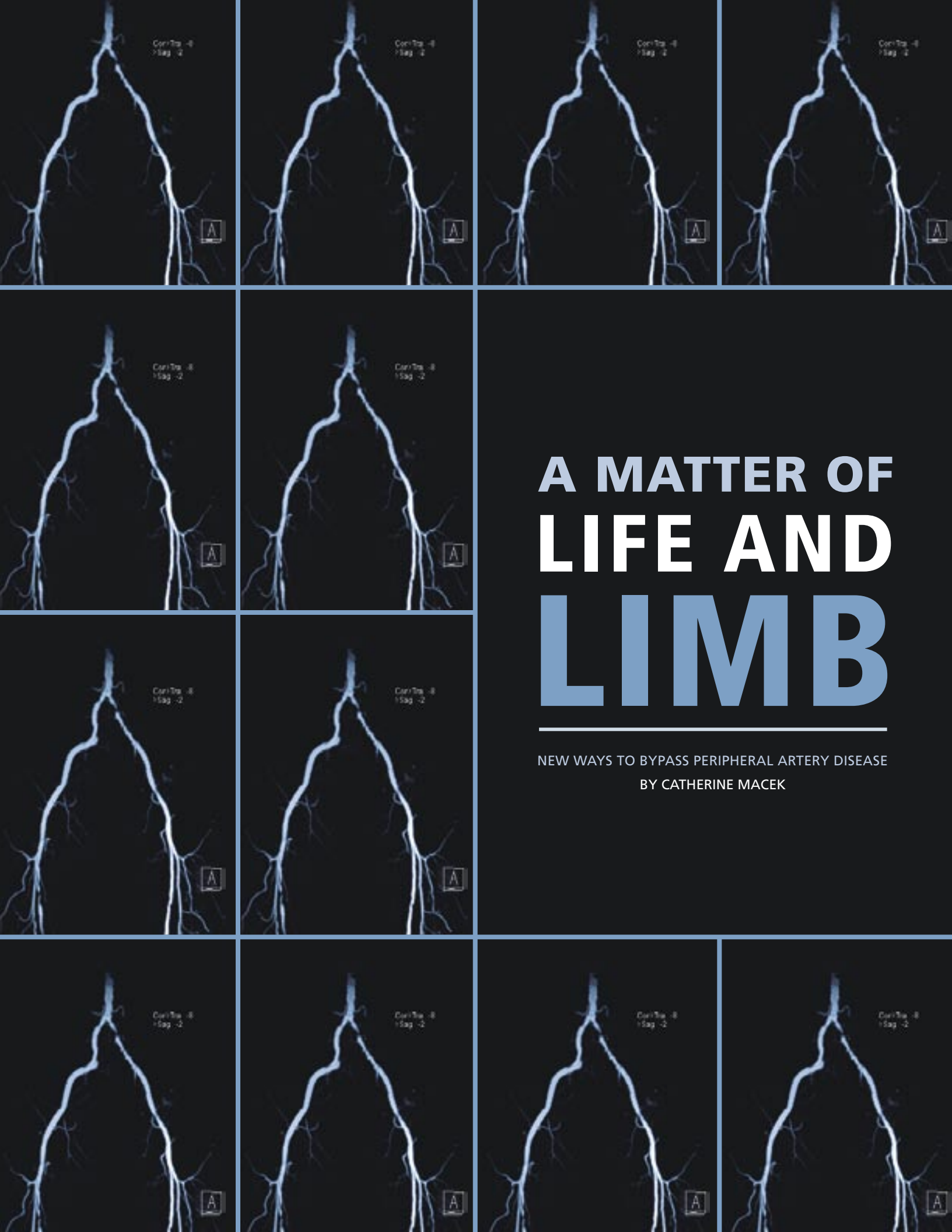
- The Duke Center for Nicotine and Smoking Cessation Research has offices in Durham, Charlotte, Raleigh, and Winston-Salem. Smokers interested in participating in CNSCR research projects can visit www.duke.edu/web/nicotine/subjects/index.html.

The best stop-smoking strategies now

Modifications to nicotine replacement therapy as well as novel drugs may soon give smokers a better chance of successfully quitting. But what can smokers do now?

- **TRY, TRY AGAIN.** It is common for smokers to make more than one quit attempt before succeeding for good.
- **TAKE ADVANTAGE OF THE MANY FORMS OF NICOTINE REPLACEMENT.** It's available in not only a gum and a transdermal patch, but a nasal spray, an inhaler, and a lozenge. Patients can combine various forms based on their needs. For instance, a patient could use the patch primarily but add the gum or inhaler when cravings strike.
- **CONSIDER HIGHER DOSES OF NRT.** A nicotine patch delivers 21 milligrams of nicotine a day, about the amount in one pack of cigarettes. But what about a smoker who smokes four packs a day? Such smokers may need higher NRT doses simply to relieve withdrawal. The FDA has not approved use of NRT in higher doses, but it has been found useful in the research setting, says Duke's Eric Westman, who coauthored a study that showed success with inpatient treatment with doses of up to 56 milligrams a day of transdermal nicotine for four days.
- **CONSIDER ZYBAN.** Zyban is a form of the antidepressant bupropion (Wellbutrin) approved for use in smoking cessation. Duke psychiatrist Kishore Gadde, MD, found in 1999 that the same compound also helps people lose weight. Although it's generally agreed that a 10- to 15-pound weight gain is worth it if a person is able to quit smoking, Westman points out, Zyban may be helpful for those who are particularly worried about gaining weight when quitting.
- **INCLUDE SOME FORM OF BEHAVIORAL THERAPY.** Telephone counseling has been shown effective for adults in several studies, says Duke psychologist Isaac Lipkus, PhD, as have printed materials tailored to smokers' specific needs, such as what to do when they're around friends who smoke.

- The Duke Addictions Program offers individual QuitSmart instruction. Call 919-684-3850 for details. For information on the QuitSmart Stop Smoking Program, please visit www.QuitSmart.com.
- For more information on the Family Ties study, which is currently enrolling smoking family members of end-stage lung cancer patients at Duke, call 877-485-9858 (toll-free) or e-mail stephanie.molner@duke.edu.
- For more information on the Baby Steps study of the effectiveness of nicotine replacement therapy in helping pregnant smokers quit, call 877-285-7050 (toll-free) or e-mail brouw001@mc.duke.edu.



A MATTER OF LIFE AND LIMB

NEW WAYS TO BYPASS PERIPHERAL ARTERY DISEASE

BY CATHERINE MACEK

Who among us hasn't experienced aches or pain in our legs

after a long walk or hours of gardening on our hands and knees? But when debilitating leg pain occurs after a short walk from the car to the store, it often signals a serious problem—atherosclerosis in one or more major arteries of the lower limbs. A condition once considered unique to the heart, atherosclerotic plaques can also form in the arteries in the legs, neck, kidneys, and even the intestines, restricting blood flow as they grow. When blockage occurs in the leg arteries, the most common site outside of the heart, it's known as peripheral artery disease, or PAD.

People with the hallmark symptom of PAD, intermittent claudication—leg pain precipitated by exercise that abates with rest—often consider the problem a normal sign of aging. Often they neglect to tell their physicians about the mobility-limiting pain, and the condition may progress unchecked to critical limb ischemia, with a high risk for gangrene and amputation. Moreover, PAD is often a harbinger of life-threatening cardiovascular events, notes cardiologist David Kandzari, MD, of the Duke Peripheral Vascular Disease Program. "People who have intermittent claudication, gangrene, or undergo amputations because of critical limb ischemia don't die from these conditions—instead, they die of myocardial infarctions or strokes."

Duke cardiologists established the Peripheral Vascular Disease Program in part because of widespread misconceptions about PAD. "Even some physicians believe we don't have a lot of therapy options to offer patients, so why bother to look for the disease," says cardiologist Brian Annex, MD, one of the program's founders, who conducts basic and clinical research on the condition. "We're trying to get an important message out—there is a lot we can do for these patients."

PINPOINTING PAD

It's estimated that more than 8 million Americans over age 40 have PAD. Most don't realize they have it because nearly 75 percent have no overt symptoms or mistake them for something else. "PAD is endemic in the Southeastern United States, but the signs, when they exist, are underrecognized by patients, and the condition is underdiagnosed by physicians," notes Annex. "At most, half of the people with documented PAD have the classic symptom of intermittent claudication. Others may have generalized fatigue or a feeling of heaviness in the legs and buttocks during activity, or have no symptoms at all."

One way to look for clues of PAD is by performing a thorough history as well as a complete physical exam of the legs and feet (which is especially important among patients with diabetes—see page 34). Signs of arterial insufficiency include a weak or absent pulse; arterial bruits; brittle toenails; shiny skin; hair loss; feet or legs that feel cool to the touch; sores and ulcerations that are slow to heal; numbness, lack of pain perception or other neuropathies resulting from chronic ischemia and in diabetes; and a delay in the return of normal skin color after the leg has been elevated for one minute. The most reliable noninvasive screening test, however, remains the ankle brachial index (ABI). The 15-minute test employs a Doppler stethoscope to determine the ratio of the systolic blood pressure reading in the ankle to that in the arm (obtained the traditional way). An ABI less than 0.9 is abnormal, and the lower the number, the greater the blockage—and the greater the risk of critical limb ischemia, heart attacks, and strokes.

Along with obtaining an ABI, vascular technicians at Duke often take segmental blood pressures at various sites on the leg and the toe and pulse volume recordings, which provide a qualitative assessment of blood flow. The tests are especially informative in patients whose arteries are calcified and hard to compress, resulting in artificially high blood pressure readings. Additional diagnostic tests that pinpoint the location and extent of the blockage include ultrasound, computed tomographic or magnetic resonance angiography, and X-ray angiography using contrast dye, which remains the gold standard for vascular imaging.

The risk factors for PAD parallel those for heart disease: diabetes mellitus, tobacco use, hyperlipidemia, and hypertension. The American Diabetes Association recommends ABI screening in everyone with diabetes over age 50, and a study of the prevalence of PAD in the August 10, 2004 *Circulation* suggested that other high-risk groups—the elderly, current smokers, African-Americans, and people with reduced kidney function—should also be considered for screening.

First-line treatment recommendations focus on a combination of behavioral and pharmacological interventions to improve the quality of life, prevent possible coronary and cerebrovascular events, and reduce the risk of limb loss.

KEEPING IN CIRCULATION

Physicians have a variety of tools to manage PAD once identified, notes Duke cardiologist James Zidar, MD, who oversees the Peripheral Vascular Program at the Duke Health Raleigh Cardiovascular Center. Patients seen in Raleigh or at the Southpoint Clinic in Durham are treated with "a team approach, so we can determine the best course of care for each patient," Zidar says.

As with heart disease, risk factor modification is key, says Anita Cook, a nurse practitioner and clinical coordinator with the program. First-line treatment recommendations include:

- Smoking cessation strategies and aggressive control of diabetes—paramount, because these two risk factors are most closely associated with PAD.
- Control of cholesterol levels—dyslipidemias are common in patients with PAD.
- Dietary modifications—eat a low-saturated-fat and low-cholesterol diet and lose weight if necessary.
- Good blood pressure control—to reduce

the risk of cardiovascular and cerebrovascular morbidity and mortality and because hypertension nearly doubles the risk of developing PAD.

- Antiplatelet therapy—to diminish the risk of blood clot formation, heart attack, and stroke, as well as slow the progression of PAD.
- Strategies to improve blood flow to the legs—with an exercise program for all and, for some, treatment with cilostazol (Pletal), a drug approved for intermittent claudication that promotes vasodilation and inhibits platelet aggregation.

NO PAIN, NO GAIN

Patients make great strides in improving their pain-free walking distances after only a few weeks of exercise training, which experts agree is the single most effective way to improve blood flow and reduce the incidence and severity of intermittent claudication. Duke physicians recommend a simple-to-follow plan in which patients walk until the legs hurt, rest until the pain stops, then continue the walk-rest cycle for 30 to 60 minutes at least three times a week. Supervised exercise programs work best, but currently most insurance companies won't reimburse for PAD rehabilitation programs (although many will for coronary artery disease rehab).

Why is exercise so effective? Researchers believe that exercising the legs stimulates angiogenesis, the growth of new blood vessels, but "We don't really know why it works," Annex says. "If we understood why, it would be much easier to make our treatments more effective." To address this question, Annex and colleagues at Duke have recently begun enrolling patients in the AMNESTI trial (Angiogenesis and Mechanisms of Exercise Training in PAOD [Peripheral Artery Occlusive Disease]). The NIH-funded study will include men and women randomized to either a three-month individualized exercise program conducted at home or a supervised exercise program at Duke's Center for Living. Using a variety of methods, the researchers will follow such markers as the growth of new blood capillaries, the occurrence of programmed cell death (apoptosis) within leg muscles, and the appearance of additional circulating vascular progenitor cells, which are responsible for blood vessel repair.*

ATTACK THE PLAQUE

In the case of disabling claudication or critical limb ischemia (with its specter of amputation), invasive measures to increase blood flow may be necessary. Depending on the location and severity of the blockage, options for revascularization include various endovascular procedures, such as percutaneous transluminal angioplasty (a.k.a. balloon angioplasty), often with stenting; a variant using a low-temperature balloon (cryotherapy); and plaque-excising atherectomy. For severely occluded arteries, surgery may be required to clear out or bypass the blockage, notes vascular surgeon Jeffrey Lawson, MD, PhD. PAD was traditionally the purview of vascular surgery before less invasive procedures became more common, Lawson adds, and he and fellow vascular surgeons Richard McCann, MD, John Gray, MD, and Mark Sebastian, MD, continue to offer PAD patients a host of medical therapies, surgical options, and stenting depending on the nature of the blocked artery and the patient's needs.

The SilverHawk plaque excision system, which received FDA approval in 2003, has become a popular alternative to angioplasty among Duke's interventional radiologists and cardiologists. The working end of the catheter used during the procedure contains a rice grain-sized carbide cutting blade, rotating at 8,000 RPM, that shaves and collects the plaque lining the artery.

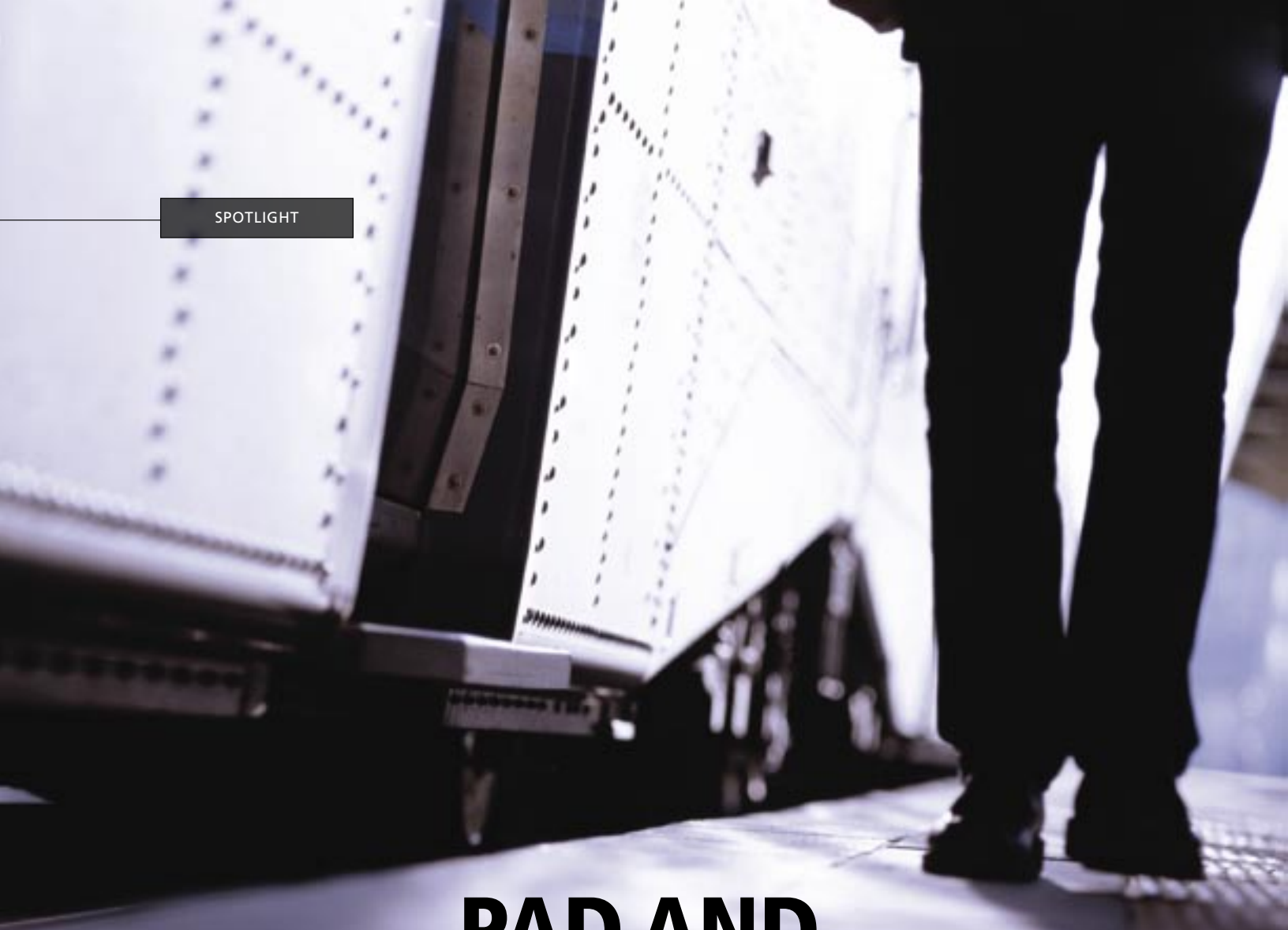
The ability to retrieve the conglomeration of fat and cells allows researchers to perform genomic and metabolic analyses on the harvested plaque. These studies offer the opportunity to learn more about pathophysiology of PAD, which is qualitatively different than coronary artery disease in many respects. For instance, stents coated with medications that inhibit restenosis (renarrowing of the vessel) work well in the coronary arteries but so far have been ineffective in the lower-limb arteries. Duke researchers are currently performing genomic and metabolic analyses of harvested plaque to see if patterns emerge that are associated with good or poor outcomes.


James Zidar, MD

Jeffrey Lawson, MD, PhD

Researchers in Lawson's lab conduct similar studies on arterial tissue har-

* For more information about the AMNESTI study, contact Leslie Kelly, recruitment coordinator, at 919-660-6739 or kelly045@mc.duke.edu.



PAD AND DIABETES

FREQUENT TRAVELING COMPANIONS

The complexity of their disease makes people with diabetes especially at risk for developing arterial insufficiencies in their lower limbs. The abnormal metabolic state that exists with diabetes adversely affects the vessels as well as the flow and coagulability of the blood; hyperglycemia also encourages platelets to aggregate. In addition, peripheral artery disease (PAD) in diabetics often develops in the vessels below the knee. The distal location—combined with the neuropathy and blunted pain perceptions that occur as diabetes progresses—means that these patients often don't experience the warning sign of claudication. Simply wearing poorly fitting shoes may lead to an ulceration that never heals, which can limit mobility and even progress to gangrene and amputation.

The American Diabetes Association now recommends screening for PAD in anyone with diabetes over age 50, notes Duke endocrinologist M. Angelyn Bethel, MD, since identifying the condition before it progresses is enormously helpful to offering effective treatments. Lifestyle changes, antiplatelet therapy, and aggressive treatment of risk factors such as hypertension and elevated blood lipids are especially critical in this population, she notes.

"In addition, all patients with diabetes should undergo a thorough annual foot exam by a health care professional, a quick and easy component of the physical exam that's often overlooked," Bethel says. "It provides a wealth of information of the vascular and neurologic status of these high-risk patients. In fact, I ask the nurses who work with me to have all patients with diabetes remove their shoes and socks as a visual cue for me to remember the exam and a cue for the patients to mention any problems."

These patients should also be instructed to examine their own feet on a daily basis. "That education also includes instruction on good skin and nail care and, occasionally, a referral to a podiatrist," Bethel adds.

Patients make great strides in improving their pain-free walking distances after only a few weeks of exercise training.


David Kandzari, MD

vested from feet amputated because of gangrene. They've already detected 60 different genes whose proteins are produced at higher- or lower-than-normal levels in the diseased tissue. They are also collaborating with biomedical engineering researcher Laura Niklason, MD, PhD, who is growing artificial blood vessels in her lab as a substitute for the plastic vessels now used in some bypass surgeries.

THERAPEUTIC ANGIOGENESIS—TWO STEPS FORWARD

One of the most promising treatments for PAD is therapeutic angiogenesis—promoting the growth of new, healthy blood vessels to increase blood flow to the legs. But growing blood vessels is no easy trick. It involves tinkering with the body's dynamic balance between angiogenic growth factors and angiogenic inhibitors, a complex sea of chemicals which regulate neovascularization during wound healing and pregnancy, for example, but can wreak havoc under pathological conditions, such as cancerous tumors and "wet" macular degeneration. Human-engineered angiogenesis also hasn't been terribly successful in the past; although animal studies showed that various growth factors had the capacity to increase blood vessel development, administering a single growth factor in early clinical trials had little or no effect on the blood-starved limb or heart.

Taking a different tack, Duke researchers have turned to finding ways to stimulate growth factor production in vivo. In one study, Annex and colleagues successfully jump-started vessel growth in rabbits with experimentally induced limb ischemia by injecting their legs with a gene-containing plasmid, a circular unit of DNA. The gene codes a protein responsible for activating other genes, including the one for vascular endothelial growth factor (VEGF).

Along with detecting significantly elevated blood levels of three forms of VEGF, the researchers found an increase in capillary density, cellular proliferation, and tissue perfusion in the plasmid-treated legs. The NIH has initiated the AVENGE (Activating Vascular Endothelial Growth Factor) clinical trial with the plasmid; Duke recently began its trial, which focuses on critical limb ischemia, says Annex (e-mail annex001@mc.duke.edu for information).

A second innovative treatment involves drafting vascular progenitor cells, a type of adult stem cell that secretes angiogenic growth factors and is responsible for developing blood vessels early in life and repairing them in adulthood. The pilot project, conceived by Lawson and former surgical fellow Michael Murphy, MD, begins with harvesting bone marrow from a patient with critical limb ischemia who has no other treatment options and sending it to the lab headed by Nelson Chao, MD, chief of the division of cellular therapies and head of the bone marrow transplantation program at Duke. There, the specialized progenitor cells are isolated; then Lawson injects them into the patient's calf at 41 sites. Two patients treated so far are doing very well, Lawson says. "In fact, both had feet ulcers that have healed, and there's evidence of improved blood flow in the treated legs of both patients." The researchers plan to enroll up to 25 participants in a trial of this cellular-based therapy. (For more information, contact Suzanne Finley at 919-681-6432).

STRIDING AHEAD

For all the clinicians involved with Duke's Peripheral Vascular Disease Program, promoting awareness and increasing the diagnosis of PAD is a top priority. Cook has already organized free ABI screening days for individuals with diabetes and others at high risk for PAD. The cardiologists offer an extensive outreach program that includes presentations to regional health care providers about PAD and related vascular diseases.

In addition, plans are in the works to establish a multidisciplinary vascular center to provide a single portal for patients and combine the efforts of diagnostic and interventional radiologists, vascular surgeons, cardiologists, neurologists, nurses, and vascular technicians—a prime example of Duke's commitment to invest in innovation.

"We plan to continue expanding our multidisciplinary approach to PAD and other vascular diseases at Duke, through research and by integrating conventional and experimental therapies," Annex says. "At the same time, we hope to raise awareness about the importance of recognizing and promptly treating this potentially devastating disease." □

For more information on the Duke Peripheral Vascular Disease Program, patients call 1-888-ASK-DUKE, physicians call 1-800-MED-DUKE.

Frank DeRuyter, PhD, and Kevin Caves

freeing VOICES

BY DENNIS MEREDITH

New technologies are giving a voice to people with communication disorders—with even more amazing advances on the horizon

Denise Carlson loves to visit with her grandsons, ages two and four, chattering with them about all the things that fascinate small boys. She joins friends in her local basket-making guild for lively discussions about their craft. And she enjoys catching up on the latest family news during frequent visits with her nine younger brothers and sisters.

She does all this despite having lost the physical ability to speak.

"I was diagnosed with bulbar palsy in July 2004," writes Carlson, a patient of Richard Bedlack, MD, PhD, in Duke's MDA/ALS Clinic. "I had started stuttering, followed by slow slurred speech. With a recent EMG test, I now display abnormal ALS symptoms. I cannot talk. I can make noise but nothing intelligible. I can write and keyboard now but I am losing strength in my left hand so it is a slow go."

Engaging and articulate in writing, Carlson has so far overcome the physical barrier that would otherwise cut her off from other people—thanks to a handheld text-to-speech computer prescribed by Duke's Assistive Technology Clinic.

"I love this gizmo," she declares. "I can adjust the speed of the voice for the ease of the listener. The touch screen feature is great with the recent hand weakness. I can store frequently used phrases. It offers suggested words using most used recognition. I'm still learning all the neat features."

It's been especially helpful for communicating with her grandsons, who are too young to read but are very responsive to her computerized voice, she writes. "This device has allowed me to stay interactive in a most positive way. My family knows I want it donated to the clinic when it is no longer a use for me."

FINDING THE KEY THAT FITS

For people trapped inside themselves by disease or disability, assistive technologies are the keys that unlock their ability to communicate. The need for these technological intermediaries is enormous: Approximately one in six people in the U.S. has a communication disability, and for over 2 million, the disability is so severe that they require a communication device or system to express themselves.

Carlson is one of some 21,000 patients a year seen by Duke's Division of Speech Pathology and Audiology. Each presents a unique case, says Frank DeRuyter, PhD, chief of the division within the Department of Surgery. "Our patients range in age from infants

Duke's Assistive Technology Clinic outfits patients with a range of ingenious devices to help them communicate, such as a hands-free computer mouse that works by tracking the user's head motions (this page) and a dual-switch mount that positions switches where a user can best activate them—whether it's with their hand, head, or foot (page 36).

to seniors, and have assorted communication difficulties that are associated with an entire gamut of disorders"—including multiple sclerosis, amyotrophic lateral sclerosis (ALS), autism, stroke, traumatic brain injury, Parkinson's disease, cerebral palsy, and other muscle diseases.

To meet such a broad clinical challenge, the clinic draws on scores of candidate devices to link patients with the world. A display room in the clinic contains an entire wall of shelves holding communication devices of every imaginable type. They include the most sophisticated handheld computers with keyboards of all sizes, whose screens can show letters, words, or symbols. And they include less complicated systems designed for patients with cognitive disabilities. Some devices employ switches that can be tailored to operate with the nod of the head or a puff of breath; others can be operated using strategies such as "scanning" or Morse code.

The diagnostic challenge is to match a patient to the appropriate technology, says rehabilitation engineer Kevin Caves.

"Once we get a referral, we use a questionnaire to gather background information about a patient—who they communicate with, things they've tried, and their physical abilities," he says. "We'll then evaluate their communicative and cognitive abilities, sensory abilities and limitations, and how they can move. From that we compile a list of features of devices that might be most appropriate—ranging from simple switch activation to letter-based or picture-based displays of different sizes. From that assessment, we identify an appropriate device and train them on it for a trial period."

Such matching is an enormously challenging task, emphasizes DeRuyter. He and his colleagues work in a world of multiple, changing targets—including progressive worsening of their patients' disorders, changes in their home and work environments, ever-advancing technology, even uncertainty as to whether patients will use the devices.

"We have not had a good understanding of how this technology is being used," says DeRuyter. "There have been several anecdotal reports about technology being abandoned, ending up in closets or just not being used after it's been prescribed."

. . . BUT WILL THEY USE IT?

To tackle such challenges, DeRuyter heads a six-institution Center for Assistive Technology Outcomes Research funded by a $2.3-million grant from the National Institute on Disability and Rehabilitation Research (NIDRR). The center seeks better ways to prescribe mobility and communication devices—from computers to wheelchairs—and to measure their effectiveness.

"When costly mobility or communication devices are prescribed—for example, a wheelchair can cost up to thirty thousand dollars—we want to ensure that it's going to be used," says DeRuyter. "We may find that a person is an appropriate candidate for a communication device, but they only communicate with a family member, and do so fairly well because they have shared a lifetime of experiences with that person. So they may not realistically need the device.

"We also want to understand whether the device is a short-term transition to another device. In that case, it would make more sense to rent or borrow the device instead of purchasing it."

The center is also developing handheld personal digital assistant (PDA)- and Web-based tools to capture outcomes data on the use of assistive technologies—and to help clinicians select the best therapy for a particular patient.

"Our staff can use the PDAs to collect data on a patient right in the clinic, then automatically download it into the computer," says DeRuyter. "And we're pilot-testing a standardized system that can automatically produce a profile of that particular patient and compare it to normative data to indicate whether or not this person is a potentially good candidate for a technology.

"So, for example, a clinician who's considering prescribing a hearing aid can input the profile of a particular patient and learn whether there's a reasonable chance that the patient will actually use the device."

The center is currently beta-testing the system with one of its sites in Canada and is conducting discussions with industry regarding commercialization.

BETTER INTERPRETERS

Even with the range of assistive technologies available today, the task of self-expression is wrought with frustration for many people with communication disorders. Since 1998, DeRuyter has served as principal investigator for a collaborative Rehabilitation Engineering Research Center (RERC) focused on developing new and improved communication technologies. Funded initially by a $4.5-million grant and renewed with a second $4.75-million grant from the NIDRR, the RERC is directed by Kevin Caves.

Designed for people who are physically unable to speak, this handheld communication aid translates typed words into digitized speech (read more on page 36).

The "virtual center" consortium comprises Duke; Augmentative Communication Inc. of Monterey, California; Pennsylvania State University; State University of New York at Buffalo; Temple University; University of Nebraska at Lincoln; and Children's Hospital Boston—with each member working on specific new technologies.

In one project, the Duke RERC is developing a speech recognition system that deciphers slurred speech and translates it into text or clear synthesized speech. Caves and collaborators are creating "vocabulary models" that represent characteristic speech patterns of people with stroke, Parkinson's disease, or cerebral palsy, for example. These models are similar to those used in commercial speech recognition programs such as Dragon Naturally Speaking. Just as those programs offer special vocabularies for dictation of medical or legal terminology, the RERC envisions a special vocabulary for a user with imperfect speech.

The end result of the project, says Caves, could be a handheld speech recognition device that could adapt as a person's disease progresses. Given that some 2 million people in the U.S. have severe speech difficulties, such a device could have wide application, he says. The Duke researchers are developing the system in partnership with the Naval Air Systems Command Training Systems Division in Orlando, Florida—part of an effort to bring advanced defense technology to bear on assistive communications. (Military applications include creating flight training simulations that respond to voice commands, for example.)

DeRuyter, Caves, and their colleagues are also developing an advanced "eye gaze" system that would enable paralyzed people to create text by visually targeting characters or words on a computer screen. Current commercial eye-gaze systems are unwieldy, they say, because the systems crowd far too many characters, words, or icons on a screen for a user to precisely target. So the Duke researchers are developing a hierarchical "eye-gesture" approach, in which the person need only target one of a limited number of areas on the screen. The computer interprets each gesture and anticipates from the word or phrase in the targeted area a selection of other words or phrases that the user might wish to express. It then displays them in a simplified array from which the user can choose to add to the text. Using such an adaptive system, the user could create text with far fewer and less precise glances, say DeRuyter and Caves.

Such technologies need not be sophisticated to overcome communication barriers, says Caves. For example, he is adapting a simple commercial remote paging device to give a disabled user the ability to register the degree of urgency of a call to a caregiver.

"In long-term care situations, caregivers often must respond to every call as if it were an emergency," he says. "They don't know whether the patient is having an emergency or just needs the TV channel changed. So we've developed a system that enables the user to send different messages to a remote pager worn by the caregiver. It gives the patient more privacy and reduces wear and tear on the caregiver."

THE POWER OF UNDERSTANDING

Besides creating new technologies, the RERC is developing training programs to enable people with communication disorders—the nation's most underemployed group—to function on the job. In one project, a "Writer's Brigade" of people with such disorders has undergone coaching in writing skills and is producing articles on RERC research for publication.

Caves also teaches a hands-on course in Duke's Pratt School of Engineering in which students design and build devices for the disabled.

"This course not only teaches students about rehabilitation engineering," says Caves, "it also gives them an awareness that when they go into their careers, they have to think about people with disabilities in their designs. They come to realize that even small changes, like requiring less grip strength to operate a device, can open up their designs to more people—from the elderly to the disabled."

Such knowledge and understanding, emphasize DeRuyter and Caves, can be just as important as the most advanced machines in connecting people like Denise Carlson with their loved ones, offering a source of vital support as they battle the disease that engulfs their bodies. □

Learn more about Duke's work with assistive technologies at the following Web sites:

www.aac-rerc.com
www.ATOutcomes.com
www.dukespeechandhearing.com

A SCI-FI FUTURE:
Bypassing the disabled body

Even the most advanced computerized communication aids will seem quaint antiques in the next couple of decades, thanks to pioneering advances in "brain-machine interfaces" by Duke neurobiologist Miguel Nicolelis, MD, PhD, and his colleagues.

In 2003, the researchers stunned the scientific world with their report that monkeys could learn to operate a robotic arm using only their brain signals.

Now, says Nicolelis, advances in basic science will rapidly lead to practical devices to give mobility and communication abilities to the disabled. He foresees, for example, wearable, brain-operated robotic "suits" that could give mobility to paraplegics. Brain control could also enable fully functional prosthetic limbs with a dexterity matching natural limbs, he says.

One key to such advances, says Nicolelis, is advanced electrodes—with sensing regions arrayed along the electrode's length. These electrode arrays could record thousands of separate channels of brain signals, recording from brain regions in three dimensions. Computer analysis techniques already exist to decipher signals from such electrode arrays and translate them into robotic movement, says Nicolelis.

He and his colleagues also found that the monkey's brains in robot control experiments adapted so completely that their neuronal circuitry controlled the robotic arm as if it were their own.

Such adaptability, as well as the enormous increase in electrodes, offers a new potential for the systems, says Nicolelis.

"We can now think about not just recording from electrodes, but using them to stimulate the brain to provide fake tactile feedback," he says. "This is the Holy Grail of brain-machine interfaces—closing the loop so that neurons can be both recorded from and stimulated."

To read more on Nicolelis's research, visit dukemedmag.duke.edu/article.php?id=267.

Medical liability reform: Curing a crisis

Our nation should act now to protect the ultimate victims of runaway lawsuits—patients

by Charles Hammond, MD

AN AILING MEDICAL liability system is seriously jeopardizing patient care and is driving physicians in some specialties to move their practices, stop offering certain services, or retire altogether. The condition is especially critical for my fellow obstetricians-gynecologists. In high insurance premium states like Florida, for example, $1 million of liability coverage for ob-gyns can cost up to $250,000 a year (even before their first delivery)—and worse yet, in some areas no coverage is available. Many ob-gyns have dropped obstetrics from their practices, leaving women to ask, "Who will deliver my baby?" Too often the answer is a physician far from home, resulting in a race to the hospital when labor begins and perhaps a birth in an ambulance or the back seat of the car.

Doctors in other areas of medicine, including neurosurgery, orthopedic surgery, and emergency medicine, also face skyrocketing insurance premiums and difficult decisions about the future of their practices. As HMO reimbursement for care is fixed (and declining), many physicians simply can't afford to practice high-risk specialties.

DIAGNOSIS: A SYSTEM IN CRISIS

Why has this crisis developed? A 2003 General Accounting Office report noted that although multiple factors contribute to increased premium rates, losses on medical malpractice claims—which make up the largest part of insurers' cost—appear to be the primary driver of rate increases in the long run. Medical malpractice costs totaled nearly $25 billion in 2002, or $85 per person, compared with $5 per person in 1975. Fighting a lawsuit—even one that never goes to trial (and more than half are dropped or settled without payment)—is a major expense for insurance companies and costs the doctors they insure time, money, and emotional distress.

Surprisingly, only 7 percent of malpractice cases end with a jury verdict, and 80 percent of those result in a favorable verdict for the physician. But the 600 percent rise in mega-verdict awards in the last 15 years, the average of which reached an astonishing $3.5 million in 2000, has helped feed the greed of unscrupulous lawyers and clients.

When a patient is harmed by a physician's negligence, then that person deserves to be compensated in a way that's both fair and reliable. But our liability system is so flawed that there's little or no correlation between getting sued and negligence. It promotes the practice of defensive medicine, with doctors ordering more tests and procedures than would be necessary based solely on professional judgment. Concerns about liability have likely contributed to the climbing rate of Cesarean sections, now hovering around 25 percent. It's important to note here that despite more C-sections the incidence of cerebral palsy in newborns has stayed exactly the same, and studies show that the cause of neonatal seizures, mental retardation, or cerebral palsy in more than 90 percent of affected children is unknown, but is not due to the birth process and usually occurs before labor begins.

TREATMENT: MEANINGFUL REFORM

Ten medical associations representing more than 230,000 specialty physicians have joined forces to form Doctors for Medical Liability Reform (www.ProtectPatientsNow.org). It exists to promote passage of federal medical liability reform legislation that includes a cap on non-economic damages awarded in medical liability cases. Also known as "pain and suffering" awards, non-economic damage awards are easily inflated, impossible to calculate, often manipulated by plaintiffs' attorneys, and are fueling the steep increases in physicians' insurance costs. This legislation will not limit economic compensation awarded for lost income, inability to work, long-term care, or medical expenses.

California's Medical Injury Compensation Reform Act (MICRA), enacted in 1975, has been the model for medical liability reform legislation in this country. It includes a $250,000 cap on non-economic damages; in-

"Medical students are gravitating to lower-risk specialties because of the rising cost of medical liability insurance . . . . A decade ago we'd have 700 applicants for seven residency slots, whereas now we have 150. If this trend continues, who will train the next generation of ob-gyns, neurosurgeons, and emergency surgeons—and who will deliver your grandchildren?"

stallment payments for future damages (in lieu of a lump-sum payment); and mandated limits on attorney fees. California's liability premiums have increased 167 percent since reforms were enacted, compared to 505 percent nationally. But only a handful of states have instituted similar types of reform.

Last year the American College of Obstetricians and Gynecologists identified 23 Red Alert states with an insurance crisis threatening the availability of physicians to deliver babies. Fixing the broken medical liability system with federal legislation is the best way to reverse the flight of ob-gyns and other higher-risk specialty physicians from Red Alert states.

Another adverse side effect of the crisis is that medical students are gravitating to lower-risk specialties because of the rising cost of medical liability insurance. We've seen the trend at Duke: a decade ago we'd have 700 applicants for seven residency slots, whereas now we have 150. If this trend continues, who will train the next generation of ob-gyns, neurosurgeons, and emergency surgeons—and who will deliver your grandchildren?

MEDICAL COURTS: A CURE?

Attorney Philip K. Howard is the founder of Common Good, a legal reform coalition (www.cgood.org). Describing the cap on damages as "a bandage on a mortal wound," Howard proposes such remedies as limiting lawyer fees, raising the bar for gaining approval to go forward with a suit, and creating special medical courts, patterned after courts for taxes, patents, workers' compensation, and vaccine injuries. He feels that neither lay juries nor most judges have the technical knowledge to weigh complex medical evidence.

A medical court, staffed with expert judges and without juries, could screen claims, make rulings, and award reasonable compensation for actual economic losses and pain-and-suffering damages based on a standard schedule. Howard believes that this idea will be opposed at every step by trial lawyers, who often talk about the "right to sue" when something goes wrong medically. "But what about the right of doctors to a system of justice that reliably distinguishes between right and wrong?" Howard queries.

Although physicians are the targets in this battle, the ultimate victims are our patients, who pay more for *and* have less access to health care. Show your support of the federal legislation by encouraging your senators and representative to vote for reform. The scales of justice are out of balance, and until this nation enacts commonsense tort reform, our patients will continue to suffer. □

Charles B. Hammond, MD, is the E.C. Hamblen Professor and chairman emeritus of Obstetrics and Gynecology at Duke. He served as a national advocate for medical liability reform as the 2002-2003 president of the American College of Obstetricians and Gynecologists.

controversies in medicine

Medical liability reform: The case for creativity

There are better solutions than capping awards for non-economic damages

by Clark C. Havighurst, JD

DESPITE THE MEDICAL PROFESSION'S current sense of urgency about the need for malpractice reform, the reform idea *du jour*—capping monetary compensation for "pain and suffering" and other non-economic damages—is not very appealing from a policy perspective. Although it would lower insurance premiums somewhat and keep some non-meritorious claims out of court, its main effect would be to reduce the attractiveness of many meritorious cases to plaintiffs' lawyers, who without the prospect of non-economic damages might find them not worth pursuing. This effect not only would deprive patients of modest means of remedies for serious injuries, but would also diminish doctors' incentives to exercise due care in treating such patients. One can understand why physicians—and Republicans with wealthy constituents—might like this remedy, but it is not very good social policy.

More fundamentally, nearly all the malpractice reforms adopted, or even seriously discussed, in recent decades have focused only on keeping malpractice risks insurable at affordable rates. No one, in other words, has made a serious effort to get the tort system to do effectively the job that society should, in theory, expect it to do—that is, induce the health care system to take measures to reduce patient injuries to the point where additional precautions would not be justified by the number or seriousness of the injuries prevented. Unfortunately, it is probably asking too much of legislators, pressured by physicians from one extreme and by plaintiffs' lawyers from the other, to expect them to redesign the tort system to do this difficult job. Nevertheless, the challenge should not be defined as being simply to keep liability insurance affordable or to ensure fair compensation of negligently injured persons. Instead, the goal should be to get the system to optimally deter patient injuries. Compensating injuries is only a means to this socially important end.

LIABILITY CAN IMPROVE QUALITY

Recent publicity about medical errors has called attention to quality failings in various systems within which individual doctors care for patients. To be sure, liability risks have inspired some significant improvements in hospitals, including major improvements some years ago in anesthesia equipment and practice that lowered previously high injury rates to near negligibility. But getting health systems generally to re-engineer themselves to optimize quality requires powerful incentives, not just commitments to do better. Inevitably, too many people are locked into conventional ways of thinking and doing and will resist or subvert the fundamental system changes that are necessary to minimize errors and improve quality. The quality literature has drawn helpful analogies to the airline industry, which has achieved a remarkable safety record. But the differences observed between health care and airlines underscore how far the health care system is from having a culture that actually achieves safety goals as opposed to merely paying them lip service.

I once heard Harvard's David Blumenthal, MD, compare the quality-improvement challenge facing the medical care system to the challenges faced by American car makers in the 1970s and 1980s, when foreign manufacturers began producing vehicles of far superior quality. Under competitive pressure to improve or die, the American companies eventually concluded that they could not turn things around by making merely incremental changes but instead needed to reinvent their entire production processes. Although Blumenthal said he could see on the horizon no comparable near-death experience to motivate American health care providers to radically improve quality, I commented that America's trial lawyers might provide the needed stimulus. Lest this seem too threatening, let me suggest how the liability system might be made a constructive force for fundamental quality improvement without breaking the back of the medical profession.

"The challenge should not be defined as being simply to keep liability insurance affordable or to ensure fair compensation of negligently injured persons. Instead, the goal should be to get the system to optimally deter patient injuries."

TARGET SYSTEMS, NOT DOCTORS

To begin with, malpractice law accomplishes little by targeting individual doctors. Doctors have liability insurance, usually priced without much regard to their individual experience, and they therefore do not face, even indirectly, the actual dollar cost of the injuries they individually cause or might prevent. Any incentive to improve, therefore, lies in their fear of being sued, meritoriously or not. Perversely, this *in terrorem* effect is felt most acutely by the most conscientious physicians, precisely those who are least likely to need an incentive to maintain quality. Moreover, given the relative rarity of claims and the perception that they strike randomly, like lightning, and not necessarily because of any failing on the doctor's part, it is easy for doctors to persuade themselves that there is nothing they can do to protect themselves besides being nice to patients. Quality improvements are likely to be few in a system that concentrates on singling out individuals for blame.

On the other hand, real quality improvements could reasonably be expected if liability for physician negligence were imposed 'vicariously' on corporate entities in a position to assign tasks, check work, and effect (or insist upon) system changes. Such an entity, whether a hospital or a health plan, would either self-insure or pay premiums reflecting its experience and would thus have an incentive to invest in error control. It would also see a bigger picture than individual physicians see, including opportunities to save liability costs by improving patient outcomes. It could also reasonably demand that its physicians cooperate in quality-improvement endeavors. The failure of managed care was in large measure, it seems to me, a result of health plans' assumption of responsibility for controlling costs while irresponsibly leaving doctors legally on the line for patient injuries. Vicarious liability would do much to align the interests of health plans and hospitals with the values and interests of physicians.

Liability need not be imposed only because some legal standard of care was violated. Manufacturers are regularly held liable for injuries their products cause without proof of anyone's negligence in their production or design, with the result that they work very hard to prevent injuries from occurring. It is possible to imagine a health plan in which patients are automatically compensated through experience-rated insurance for certain bad outcomes—those that physicians agree generally should not occur. Savings on lawyers' and experts' fees in such a non-fault-based system would make it possible to pay many claims for economic loss. Moreover, the opportunity to save even more money by preventing injuries should inspire needed system changes.

There are many other reforms, short of these radical ones, that would represent constructive improvement. For example, health plans could be given more freedom to give their subscribers, by contract, a different set of legal rights than the costly ones the tort system currently provides. Such "private" reforms might include limits on awards, changes in the way the applicable standard of care is established, and the use of low-cost alternative mechanisms to resolve claims. Lower premiums would reward those consumers who opted out of the costly system the legal monopoly has designed for their presumed protection.

These comments are intended mostly to show how the malpractice debate might be opened up to permit more creative and constructive ideas to be introduced. The ubiquity and seriousness of medical errors make it imperative, it seems to me, to put some radical proposals on the table. Trial lawyers would have much more to lose from these proposals than the medical profession, which should value the benefits that would accrue to patients if the liability regime were redesigned to actually promote the quality of care. □

A leading legal scholar on health care law, Clark C. Havighurst, JD, is William Neal Reynolds Professor Emeritus of Law at Duke University and a member of the Institute of Medicine of the National Academy of Sciences. For Web links to several of his recently published articles on the health care industry, visit dukemedmag.duke.edu.

Gifts from individuals and organizations are the largest source of non-government support for Duke's research, education, patient care, and service missions. Here are some recent examples of philanthropic partnerships that will make a difference to human health for generations to come.

Seed money targets cancer and the environment

Fred and Alice Stanback of Salisbury, NC, have given **$100,000** in seed money for a new partnership between the Duke Comprehensive Cancer Center and the Nicholas School of the Environment. Researchers from the two areas will collaborate to advance our understanding of how genes interact with the environment—specifically why some people develop cancer in response to environmental toxins and others don't. The initiative's ultimate goal is to identify genes that elevate risk and develop targeted drug interventions to lower susceptibility.

Better health by numbers

A **$2 million gift** from Leonard and Tobee Kaplan of Greensboro, NC, will establish two funds named in their honor—a distinguished university professorship in computational medicine and a research fund for personalized health planning. Computational medicine employs genetics, biostatistics, and high-speed data analysis to predict individuals' health risks. Personalized health planning makes use of that information to develop strategies to prevent or delay disease—an approach known as "prospective health care."

Atkins professorship seeks obesity solutions

With causes much more complex than just diet and lifestyle, obesity is now linked to chronic health problems from depression to heart disease, diabetes, and arthritis. The diet developed by the late Robert C. Atkins, MD, while controversial, forced the medical community to reexamine long held beliefs about nutrition and metabolism. With $40 million in assets, the Robert C. Atkins Foundation continues to support research into the causes and treatment of obesity. A recent **$2 million gift** to Duke will establish the Robert C. and Veronica Atkins Professorship and fund research, clinical care, and education in nutrition and metabolism at Duke.

Integrative medicine breaks ground

Thanks to a **$10 million gift** from John and Christy Mack of Rye, NY, Duke will break ground in May on a Center for Integrative Medicine on Duke's Center for Living Campus, pending approval by the Duke University Board of Trustees. According to director Tracy Gaudet, MD, the new center will develop and scientifically test a new model of medicine that embraces the whole person—mind, body, spirit, and community—with healing interventions from both traditional and complementary and alternative medicine.

Nursing gets a new home

In March, the Duke School of Nursing broke ground on its new $22.8-million headquarters building on Trent Drive, funded in part by philanthropic contributions. Manning the ceremonial shovels were Victor J. Dzau, MD, chancellor for health affairs and president and CEO of Duke University Health System; Catherine Gilliss, DNSc, dean of the School of Nursing and vice chancellor for nursing affairs; Richard Brodhead, PhD, Duke University president; and Mary Champagne, PhD, former dean of nursing.

To learn more about how you can support medical education, research, and patient care at Duke,

Albert Eye Research Institute dedicated

Philanthropist Ruth Albert celebrated the grand opening of the Albert Eye Research Institute at Duke along with (from left) David Epstein, MD, chairman of ophthalmology at Duke University Eye Center; R. Sanders Williams, MD, dean of the School of Medicine; Richard Brodhead, PhD, president of Duke University; Victor J. Dzau, MD, chancellor for health affairs; and Ralph Snyderman, MD, chancellor emeritus.

The new state-of-the-art Ruth and Herman Albert Eye Research Institute (AERI) was officially dedicated on April 8. Principal benefactor Ruth Albert, as well as other donors, joined Duke administrators, Eye Center staff, and guests for the event, which was held in the facility's garden.

Albert, along with her husband, Herman (deceased), generously gave the $8 million gift that made construction of the facility possible. The Albert family—who has given significant gifts to the Duke Comprehensive Cancer Center, as well, including $3.5 million to support the Herman and Ruth Albert Lung Cancer Genomics Fund—has grown to know Duke well over the past eight years. Herman was a patient of both the Executive Health Center and the Cancer Center, where he was treated for lung cancer by Thomas D'Amico, MD. Ruth was successfully treated by the Eye Center's Alan Carlson, MD, for a potentially blinding condition; their daughter has also received medical care at Duke.

The family's gift to the Eye Center will impact the lives of countless others by strengthening and expanding Duke's already renowned ophthalmology program, Duke leaders said.

The dream for AERI began in the mid-nineties but started moving toward reality in 2001 when Leonard and Rose Herring pledged the first $1 million, followed by a major endowment from the Estate of William Wannamaker to support eye research, and another million-dollar gift from Evelyn Hunter-Longdon in memory of her husband, Stanley Longdon. In 2001, the Alberts made their donation, the largest single gift in the Center's history. Subsequent major gifts by Leonard Herring, James Gills, MD, the Duke Private Diagnostic Clinic, The Duke Endowment, and donations from the many friends of the Eye Center have made AERI possible.

"The Duke Eye Center has an outstanding history of bringing the most advanced treatments to people throughout the Southeast and far beyond," said Dzau at the event.

For instance, Eye Center efforts led to the development of a new surgical technique—macular translocation—that can restore vision in some people who have lost their eyesight due to age-related macular degeneration. A partnership with Ghana, West Africa, will enable researchers to collect and test thousands of blood samples in order to investigate the genetic susceptibility for glaucoma, the leading cause of blindness in African-Americans. And researchers are examining the uses of stem cell therapy in repairing retinal cells damaged by diseases like retinitis pigmentosa.

"This spectacular new facility—with its state-of-the-art research laboratories and clinical areas—will allow Dr. Epstein and his team to achieve the next level of prominence as one of the country's top centers for eye research, education, and treatment," Dzau said.

Eye Center staff started moving into the AERI in February, the pediatrics service saw its first patients in early March, and researchers will move in this summer.

A boost for global health

Durham developer Gary M. Hock has given **$1.5 million** for the Gary M. Hock Distinguished University Professorship in Global Health. Based in Duke's new Hubert-Yeargan Center for Global Health, the professorship will support initiatives on HIV/AIDS and infectious diseases in developing countries. The Hubert-Yeargan Center was established in 2004 and grew out of more than 20 years of research, education, and service partnerships between Duke infectious diseases faculty and medical and government entities in Tanzania, China, Pakistan, Brazil, Kenya, and Thailand.

Back to basics in heart research

Bill and Peggy Britt of Chapel Hill, NC, have given **$1 million** to the Department of Medicine to advance the potential of stem cell research to benefit humans. Duke researchers continue to aggressively study adult and placental stem cells for their potential to replace and repair damaged muscle and tissue to treat diseases of the heart and other vital organs.

APPOINTMENTS

Nobel laureate joins Duke

Peter C. Agre, MD, winner of the 2003 Nobel Prize in Chemistry, will join Duke in July as vice chancellor for science and technology.

In the newly created post, Agre will work closely with Duke leaders and faculty to guide the development of Duke's biomedical research enterprise, enhance its ability to support and attract the world's top scientists and students, and help assess and address global health care needs.

Agre received his medical doctorate from Johns Hopkins University School of Medicine in 1974. He took a residency in internal medicine at Case Western Reserve University and a fellowship in hematology/oncology at the University of North Carolina at Chapel Hill. In 1981 he returned to Hopkins, where he progressed through the ranks of the departments of medicine and cell biology and became a full professor in biological chemistry in 1993. Agre was elected to membership in the National Academy of Sciences in 2000 and to the American Academy of Arts and Sciences in 2003.

In 2003, he shared the Nobel Prize in Chemistry for revealing the molecular basis for the movement of water into and out of cells. His 1992 paper in the journal *Science* with Johns Hopkins physiologist Bill Guggino, PhD, documented the discovery of the first water-channel protein, dubbed an aquaporin.

"Peter is one of the most accomplished physician-scientists of our era," said Victor J. Dzau, MD, chancellor for health affairs, in announcing the appointment. "But he is even further distinguished by his passion to improve the lives of people throughout the world."

Dzau said he sought Agre's expertise as a champion and critic of scientific and medical issues that have important societal implications.

"Too often, academic medical centers and universities have been silent on issues that are important to the future of our society," said Dzau. "As leaders of these institutions, I think we have an obligation to express our views and step into the public debate on important issues. I have asked Peter to use his position at Duke to do precisely that."

Agre's dual role—as an architect who will help to shape Duke's medical research enterprise, and as public figure who will serve as the institution's spokesperson on key scientific issues—will be unique among academic medical centers in the United States, said Dzau.

Read an interview with Agre on page 6.

St. Geme named chair of pediatrics

Joseph St. Geme III, MD, professor of pediatrics and molecular microbiology at Washington University School of Medicine, will become chair of the Department of Pediatrics at Duke July 1.

A nationally recognized expert in basic research and clinical treatment for pediatric infectious diseases, St. Geme is "an outstanding clinician with a strong track record of leadership who will build on the strengths of our pediatrics faculty and research," said medical school dean R. Sanders Williams, MD, in announcing the appointment.

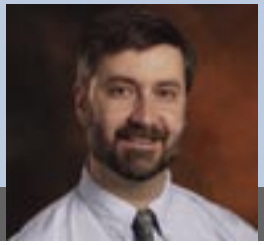
St. Geme's own research focuses on the genetic and molecular basis of virulence by *Haemophilus influenzae*, a bacterium that causes middle ear infections, bronchitis, sinusitis, pneumonia, and meningitis. He has worked to create a pediatric vaccine to prevent these widespread infections, which are often fatal in developing countries.

St. Geme earned his MD from Harvard in 1984. He completed residency training in pediatrics at the Children's Hospital of Philadelphia, serving as chief resident from 1987 to 1988, and was a postdoctoral fellow in infectious diseases and microbiology at Stanford from 1988 to 1992. He has been with Washington University since 1992.

St. Geme is president-elect of the Pediatric Infectious Diseases Society. His numerous awards include the American Heart Association Established Investigator Award, Infectious Diseases Society of America Squibb Award, the Pediatric Infectious Disease Society Young Investigator Award, and the March of Dimes Foundation Basil O'Connor Award.

As chair of pediatrics at Duke, St. Geme will oversee the department's clinical and research activities. Duke is one of the largest health care providers for children in the Southeast.

Read an interview with St. Geme on page 52.



Health System names chief compliance officer

Lori Feezor has been named associate vice president and chief compliance officer for Duke University Health System (DUHS).

An attorney specializing in health care law and risk management, Feezor will lead DUHS compliance efforts and help ensure that its management, employees, and affiliated physicians are knowledgeable about all applicable laws and regulations. In addition, Feezor will oversee the health system's program to safeguard the privacy of patients' health information. She will report to Victor J. Dzau, MD, chancellor for health affairs at Duke and president and CEO of DUHS.

"Lori's appointment demonstrates our strong commitment to providing exceptional leadership in our compliance and privacy programs," said Dzau. "Compliance programs are critically important because they involve every department in the health system and touch every patient we serve."

Prior to joining Duke, Feezor represented health care clients at the law firm Kennedy Covington Lobdell & Hickman, LLP, and was principal attorney for The Feezor Group, PC, in Washington, DC. She previously served as risk manager for the health system of the University of California, Davis, and as assistant general counsel for University Health System of Eastern Carolina in Greenville, North Carolina.

Feezor wrote and edited the *North Carolina Patient and Provider Rights Guide*, has authored numerous journal articles, and is a frequent presenter at state and national conferences. She is a member of the Health Care Compliance Association and serves on the Health Law Executive Council of the North Carolina Bar Association.

Goldstein heads new Center for Population Genomics and Pharmacogenetics

David B. Goldstein, PhD, has joined Duke's Institute for Genome Sciences & Policy (IGSP) as director of the new Center for Population Genomics and Pharmacogenetics.

Population genomics aims at understanding genome variation and evolution both within and across species. Pharmacogenetics is the study of how genetic and genomic variation affects people's responses to medicines. Combined, these areas yield information on genetic diversity and how it contributes to both disease susceptibility and variability in response to drugs.

"Pharmacogenetics represents one of the first and most promising opportunities to bring advances in genomics to the practice of medicine," IGSP Director Huntington Willard, PhD, said of the decision to create the center. "Especially in an era when the safety of several major drugs is being questioned, it is important that we provide new tools to be sure that individual patients are getting the right drug at the right dose at the right time."

Goldstein added that the new center will be a full participant in assessment of the social and ethical implications of genomics research, with a particular interest in creating mechanisms to ensure that the development of genomic medicines is fully inclusive, providing improvements in health care to all people.

Goldstein, who earned his PhD from Stanford, has been the Wolfson Professor of Genetics at the Galton Laboratory in the Department of Biology at University College, London, since 1999. He is the recipient of the Wolfson Research Award, given by the UK's Royal Society, for his work in human genetics and genomics.

New IGSP Center for Evolutionary Genomics to be led by Wray

The Center for Evolutionary Genomics, established in 2002 in Duke's Department of Biology, has officially become part of the Institute for Genome Sciences & Policy (IGSP). **Gregory A. Wray, PhD**, has been appointed director of the new IGSP center.

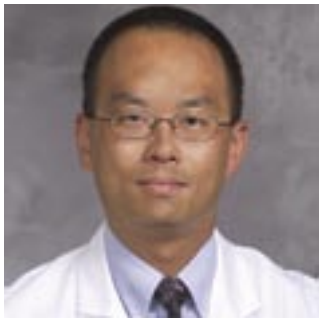
The center's work will focus on understanding how the changes in the content and organization of genomes have contributed to the diversity of life on Earth, as well as the processes that have shaped these changes.

According to IGSP Director Hunt Willard, PhD, the addition of this center broadens the scope of the IGSP's multidisciplinary research. "Consideration of evolutionary principles and the generation and analysis of large comparative datasets is critical to many aspects of genome research. Adding this center is a natural step for us and will greatly enhance the work in many of the other IGSP centers and throughout the campus."

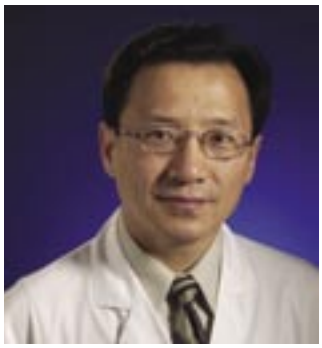
Wray, who received his PhD from Duke in 1987, has spent his career studying the evolutionary histories and population genetics of organisms ranging from fungi to humans. He received a "Young Investigator Award in Molecular Evolution" from the Alfred P. Sloan Foundation in 1995.

The new center joins six others within the IGSP: the Center for Applied Genomics & Technology, the Center for Population Genomics & Pharmacogenetics, the Center for Genome Ethics, Law & Policy, the Center for Genomic Medicine, the Center for Models of Human Disease, and the Center for Bioinformatics & Computational Biology.

Bruce A. Sullenger, PhD



Paul C. Kuo, MD



Fang-Fang Yin, PhD

Sullenger to direct new Center for Translational Research

Bruce A. Sullenger, PhD, the Joseph and Dorothy Beard Professor of Experimental Surgery and newly appointed chief of Experimental Surgery, has been named director of the new Duke Center for Translational Research.

The interdepartmental research initiative will focus on the preclinical development and initial testing in humans of novel therapeutics and medical technologies. The center's overarching goal is to develop an intellectual environment that will facilitate the interchange of ideas between physicians and translational researchers as they come together to conceive, develop, and perform human clinical studies to test innovate concepts to combat human disease.

Coup for Kuo

Paul C. Kuo, MD, professor and chief in the Division of General Surgery, has been appointed vice chair of research for the Department of Surgery.

He will oversee space and research resource allocations as well as focus on the areas of research performance metrics, mentorship, communication, and the development of an integrated strategic plan for departmental research.

Yin to direct RadOnc physics

Fang-Fang Yin, PhD, former head of medical physics at Henry Ford Health System, has been named the director of radiation oncology physics and associate director of the graduate program in medical physics at Duke.

Yin is noted for developing a patented methodology for evaluating digital imaging systems and expert systems for computer-aided diagnosis of masses in digital mammograms and chest radiographs. He said he hopes to help Duke develop a leading radiosurgery program in cranial and extracranial disease sites, develop a leading intensity-modulated and image-guided radiation therapy program, and continue to enhance education programs in medical physics.

Michael Ehlers became the newest HHMI investigator at Duke this spring.

Michael Ehlers, MD, PhD, an associate professor of neurobiology, has been named a Howard Hughes Medical Institute (HHMI) investigator by HHMI. He was one of 43 scientists selected in a national competition for the prestigious honor.

Ehlers' research concentrates on the intricate molecular machinery by which neurons in the brain signal one another, and how they adjust their connections in the process of laying down new memories. His basic research contributes to understanding of how such processes can be compromised with aging and neurodegenerative diseases.

He received his MD and PhD degrees from Johns Hopkins and his BS in chemistry from the California Institute of Technology. His honors include the 2003 Eppendorf and Science Prize in Neurobiology, for the most outstanding neurobiological research by a young scientist performed during the past three years, and the Wakeman Scholar Award in Neurobiology.

Ehlers joins eight other Duke University scientists who are now HHMI investigators, with their research supported by the institute.

Janice Massey was elected to leadership posts in two national associations.

Neuroscientist **Miguel Nicolelis** got the royal treatment while lecturing in Sweden.

Justine Strand became the first physician assistant to be elected president of a state medical society foundation.

Janice Massey, MD, has been elected a director of the American Board of Psychiatry and Neurology as well as president-elect of the American Association of Neuromuscular and Electrodiagnostic Medicine. A national leader in the fields of neuromuscular and electrodiagnostic medicine, Massey is a professor of medicine at Duke, director of the Duke Electromyography (EMG) Laboratory, and co-director of the Myasthenia Gravis Clinic. She also directs Duke's fellowship program in EMG and Neuromuscular Disease.

William J. Steinbach, MD, received the 2005 Dade Behring MicroScan Young Investigator Award from the American Society for Microbiology (ASM), the Committee on Awards, and the American Academy of Microbiology. Steinbach is an assistant professor of pediatrics and member of the Center for Microbial Pathogenesis.

J. Victor Nadler, PhD, received the 2005 American Society for Pharmacology and Experimental Therapeutics (ASPET) Epilepsy Award in recognition of outstanding research leading to better clinical control of epileptic seizures. Nadler is a professor of pharmacology and cancer biology and of neurobiology.

Rochelle Schwartz-Bloom, PhD, professor of pharmacology and cancer biology, received the $5000 Science Educator Award from the Society for Neuroscience. The award recognizes an outstanding neuroscientist who has made significant contributions to educating the public, including K-12 teachers and students, about neuroscience.

Miguel Nicolelis, MD, PhD, was named one of the 2004 *Scientific American* 50 for his work enabling monkeys to control a robot arm via brain waves (see page 39). That honor, announced in the magazine's December 2004 issue, was closely followed by another; Nicolelis was invited to deliver the 2005 Segerfalk Foundation Lecture in Lund, Sweden. This lecture award is presented to scientists who have made outstanding contributions to research of special relevance to neuroscience. The May lecture was followed by a dinner in Nicolelis's honor at Trolleholm Castle (pictured above).

Redford B. Williams, MD, has been named president of the International Society of Behavioral Medicine (ISBM). Williams is a professor of psychiatry and behavioral sciences, medicine, and psychology, and director of the Behavioral Medicine Research Center at Duke. His research has focused on identifying psychosocial factors that increase the risk of medical disorders, the biobehavioral mechanisms whereby such factors contribute to pathogenesis, and the development of behavioral interventions aimed at ameliorating the health-damaging effects of psychosocial risk factors.

Dan Blazer, MD, MPH, the J.P. Gibbons Professor of Psychiatry and Behavioral Sciences at Duke, is serving as president of the American Association of Geriatric Psychiatry for 2005-2006. AAGP works to enhance the knowledge base and standard of practice in geriatric psychiatry through education and research and to advocate for meeting the mental health needs of older Americans.

Gerard Blobe, MD, PhD, professor of medicine and of pharmacology and cancer biology, has received the American Association for Cancer Research (AACR) Gertrude B. Elion Cancer Research Award for 2005. The $50,000 award fosters meritorious basic, translational or clinical cancer research by a tenure-track scientist at the level of assistant professor at an academic institution anywhere in the world.

H. Kim Lyerly, MD, director of the Duke Comprehensive Cancer Center, has been selected chair-elect of the United States Army Medical Research and Materiel Command, Department of Defense Breast Cancer Research Program (BCRP) Integration Panel. The panel advises the BCRP, deciding on the distribution of research funds. Since the BCRP's inception in 1992, more than $1.5 billion has been spent on peer-reviewed research targeted toward the program's vision to eradicate breast cancer. Lyerly will serve on the panel's executive committee in 2005 and become chair in 2006.

Justine Strand, chief of the Physician Assistant (PA) Division in the Department of Community and Family Medicine and a graduate of the Duke University PA program, has been elected president of the North Carolina Medical Society (NCMS) Foundation. The Foundation, the philanthropic arm of the Society, provides access to quality health care for patients in underserved communities, and is also responsible for the NCMS Leadership College, which recruits and trains young physicians and physician assistants to serve as leaders in their communities and at the state and national level.

ANESTHESIOLOGY

Nina E. Charnoff
919-681-4877
Particular Clinical Interests and Skills: Pediatric anesthesia
Faculty Rank: Assistant Professor
Division: Anesthesiology
MD Degree: State University of New York Downstate, 1981
Residency: Anesthesiology, New York Hospital, 1981-1983
Anesthesiology, Boston University Hospital, Massachusetts, 1983-1984
Fellowship: Pediatric Anesthesia, Children's Hospital Boston, Massachusetts, 1984-1985

MEDICINE

Dahlia A. Blake
919-934-8399
Particular Clinical Interests and Skills: Pulmonary critical care medicine, special training in sleep medicine, special interest in COPD, asthma, sleep apnea and sleep disordered breathing
Faculty Rank: Associate Professor
Division: Pulmonary, Allergy and Critical Care
MD Degree: UMDNJ - Robert Wood Johnson Medical School, New Jersey, 1996
Residency: Surgery, Staten Island University Hospital, New York, 1997
Internal Medicine, UMDNJ - University Hospital, New Jersey, 1999
Fellowship: Pulmonary Critical Medicine, UMDNJ - University Hospital, New Jersey, 2003

Gwendolen T. Buhr
919-660-7567
Particular Clinical Interests and Skills: Long-term care, Alzheimer's disease, development of educational curricula in long-term care, quality improvement in LTC
Faculty Rank: Associate
Division: Geriatrics
MD Degree: The University of Texas Health Science Center at San Antonio, 1998
Residency: Internal Medicine, Moses H. Cone Memorial Hospital, North Carolina, 1998-2001
Fellowship: Geriatric Medicine, Duke University Medical Center, North Carolina, 2001-2004

John W. Hollingsworth
919-684-4588
Particular Clinical Interests and Skills: Pulmonary fibrosis, asthma, COPD, sarcoidosis
Faculty Rank: Associate
Division: Pulmonary, Allergy and Critical Care
MD Degree: University of Texas Medical Branch, 1996
Residency: Internal Medicine, University of Texas Medical Branch, 1999
Fellowship: Pulmonary and Critical Care Medicine, Duke University Medical Center, North Carolina, 2004

Sunil V. Rao
919-668-8700
Particular Clinical Interests and Skills: Interventional cardiology
Faculty Rank: Assistant Professor
Division: Cardiology
MD Degree: The Ohio State University College of Medicine, 1996
Residency: Internal Medicine, Duke University Medical Center, North Carolina, 1996-1999
Fellowship: Cardiology, Duke University Medical Center, North Carolina, 1999-2003
Interventional Cardiology, Duke University Medical Center, North Carolina, 2003-2004

Jonathan A. Stiber
919-681-5816
Particular Clinical Interests and Skills: Consultative cardiology, congestive heart failure, arrhythmias, ischemic heart disease, calcium signaling and muscle biopsy
Faculty Rank: Associate
Division: Cardiology
MD Degree: New York University, 1997
Residency: Internal Medicine, Duke University Medical Center, North Carolina, 1997-2000
Fellowship: Cardiology, Duke University Medical Center, North Carolina, 2000-2004

PEDIATRICS

Piers C. A. Barker
919-681-5166
Particular Clinical Interests and Skills: Use of echo and non-invasive imaging for the diagnosis and management of congenital heart disease in the fetus through to the adult, with particular focus in using echo to guide catheter-based interventions
Faculty Rank: Assistant Professor
Division: Cardiology
MD Degree: Cornell University Medical College, New York, 1995
Residency: Pediatrics, Johns Hopkins Hospital, Maryland, 1998
Fellowship: Pediatric Cardiology, University of Michigan, 2001

Michael G. Camitta
919-681-2916
Particular Clinical Interests and Skills: Pediatric cardiology; echocardiography including fetal, transthoracic, and transesophageal imaging; pediatric adult and congenital heart disease; cardiac MRI; clinical research studies
Faculty Rank: Clinical Associate
Division: Cardiology
MD Degree: University of Texas Health Science Center at San Antonio, 1996
Residency: Pediatrics, Duke University Medical Center, North Carolina, 1996-1999
Fellowship: Pediatric Cardiology, Duke University Medical Center, North Carolina, 1999-2002

ON THE SPOT

Q. Drug-eluting stents have been FDA-approved for a year now. How are they changing patient care?

A. "The proportion of patients treated with drug-eluting stents versus traditional stents has risen dramatically, from 20 percent to nearly 80 percent in the last year. The data show that academic medical centers and high-volume hospitals are the most likely to use the new stents, and we've seen a definite improvement in patient outcomes, with fewer patients returning for procedures and a 20 to 25 percent drop in bypass surgeries.

"However, drug-eluting stents have also opened a whole new can of worms. The stents are more expensive and they require an extended and costly post-procedure medication regime to prevent the formation of blood clots. This medication is an expense some patients can't afford, and may explain the socioeconomic disparities that exist between patients who receive the new stents and patients who receive more traditional bare-metal stents that don't require prolonged, expensive post-procedure medications."

—Sunil V. Rao, MD

SURGERY

Idriss F. Salim
919-681-2916
Particular Clinical Interests and Skills: Evaluation and treatment of congenital and acquired heart disease in infants, children, and adolescents; cardiac arrhythmias, syncope, and sudden death; cardiac pacing and defibrillation; electrophysiologic studies and ablation of cardiac arrhythmias
Faculty Rank: Assistant Professor
Division: Cardiology
Degrees: MD, Duke University Medical Center, North Carolina, 1996; PhD, Duke University Medical Center, North Carolina, 1995
Residency: Pediatrics, Rainbow Babies and Children's Hospital, Case Western Reserve University, Ohio, 1996-1999
Fellowship: Pediatric Cardiology, Duke University Medical Center, North Carolina, 1999-2003

Joanne J. Lager
919-668-1100
Particular Clinical Interests and Skills: Bone marrow transplantation, umbilical cord blood transplantation, hematologic malignancies, adjustment to illness
Faculty Rank: Clinical Associate
Division: Blood and Marrow Transplantation
MD Degree: Duke University School of Medicine, North Carolina, 1998
Residency: Pediatrics, UNC Hospitals, North Carolina, 2001
Fellowship: Pediatric Hematology/Oncology, Duke University Medical Center, North Carolina, 2004

Jeffrey C. Hoehner
919-681-5077
Particular Clinical Interests and Skills: Neonatal surgery, treatment of infants and children with tumors
Faculty Rank: Assistant Professor
Division: Pediatric Surgery
MD Degree: Duke University School of Medicine, North Carolina, 1988
Residency: University of Iowa Hospitals and Clinics, 1993
PhD, Pathology, University of Uppsala, Sweden, 1996
Fellowship: Pediatric Surgery Fellowship, University of Toronto Hospital for Sick Children, Canada, 1998

Robert E. Isaacs
919-668-5241
Particular Clinical Interests and Skills: Comprehensive approach to spine care, minimally invasive and endoscopic spine surgery to complex spine surgery including spinal oncology
Faculty Rank: Assistant Clinical Professor
Division: Neurosurgery
MD Degree: Baylor College of Medicine, Texas, 1995
Residency: Neurosurgery, Vanderbilt University, Tennessee, 1996-2001
Fellowship: Endoscopic and Complex Spine Surgery, Rush University, Chicago Institute of Neurosurgery & Neuroresearch, 2001-2002

Kelly E. Maloney
919-660-2237
Particular Clinical Interests and Skills: Bladder carcinoma, benign prostatic hypertrophy, general urology
Faculty Rank: Assistant Professor
Division: Urology
MD Degree: Dalhousie University, Canada, 1989
Residency: General Surgery, Dalhousie University, Canada, 1989-1991
General Surgery/Urology, Duke University Medical Center, North Carolina, 1991-1996

James Stephenson "Steve" Wilson
919-660-2324
Particular Clinical Interests and Skills: General surgery with special interest in breast, biliary, colorectal and endocrine surgery
Faculty Rank: Assistant Professor
Division: General Surgery
MD Degree: University of North Carolina School of Medicine, 1975
Residency: Medical College of Virginia, 1975-1980

ON THE SPOT

Q. How do you help children and families cope with a devastating diagnosis like cancer?

A. "It's always struck me that, for as many families as there are, there are as many ways to cope. And since there's no one right way, it's my job to guide each family in their search for what works for them. Thankfully we can now cure 75 percent of kids with cancer. This good news is the result of years of research and study made possible by families who have chosen to cope in part by helping others.

"To participate in research studies, the federal government requires researchers to obtain assent from children age seven and older. I'm working on a study with Dr. David Wendler at the NIH and Dr. Philip Rosoff at Duke to assess how children and families make decisions about participation in medical research so that we can make sure we are obtaining assent in a developmentally appropriate manner. I hope that working on this project will help me aid families in the coping process as well as the decision-making process."

—Joanne J. Lager, MD

Three questions

A chat with Joseph St. Geme III, MD, the incoming chair of Duke Pediatrics

You've built a career as a leader in the care of children and the laboratory investigation of pediatric infectious diseases. Why were you interested in joining Duke as an administrative leader?

A great number of reasons—the institution's overall excellence, the quality of the medical school and hospital, the current strength of the Department of Pediatrics, and the terrific leadership. From the beginning, I've thought: What a great team to be a part of. I'm excited about joining the academic community at such a dynamic institution, with its strong sense of purpose and impressive spirit of creativity.

I do plan to participate in patient care and clinical teaching in a tangible way at Duke, although I will need to modify how much time I can spend on the wards and in clinic. My research is very important to me as well. I'm bringing four members of my lab from Washington University with me, and we look forward to continuing our work here at Duke.

What are your goals for the Department of Pediatrics?

Duke Pediatrics is already in a very strong position regionally and nationally, and we have wonderful opportunities to become even stronger.

In our inpatient setting within Duke University Hospital, I'd like to continue creating a true children's hospital environment, with pediatric-trained providers at every stage of care. On the outpatient side, a new pediatric emergency medicine center will be constructed soon, and I look forward to helping make that facility a vital regional source of pediatric care and an important venue for pediatric education and clinical research. We'll also be looking at ways to leverage our manpower resources to expand the reach of Duke Children's to other sites around the Triangle.

I'd also like to capitalize on Duke's strengths in the basic sciences and the interactive environment on campus to increase the scope and impact of laboratory investigation in pediatrics.

What are some of the main challenges facing pediatrics as a field, and how do you think Duke can help address them?

The growing trend of enrolling youngsters in clinical trials of medications offers enormous opportunities to improve pediatric care, while at the same time posing legitimate concerns. With Duke's strong commitment to patient safety and impressive resources such as the Duke Clinical Research Institute, we are poised to become a premier center for collaborative clinical research in pediatrics.

Another of my priorities is to encourage more Duke medical students to pursue careers in pediatrics, especially academic pediatrics—the numbers of people choosing to go into the field are relatively low both here and nationally. I hope to work with other faculty to make students aware of the unique rewards associated with caring for children and the exciting opportunities for research relevant to child health.

Read more about St. Geme's appointment on page 46.

CONTINUING MEDICAL EDUCATION AT DUKE
For more information on the courses listed below, please contact the Duke Office of Continuing Medical Education at 919-684-6485 or visit docme.mc.duke.edu.

DUKE CME CALENDAR

ON-SITE COURSES

COURSE	DATE	LOCATION	CREDIT	REGISTRATION
RADIOLOGY Concepts of MR & CT Imaging	June 20-24, 2005	Kiawah Island, SC	21 credits	919-684-7758 or www.civm.duhs.duke.edu/kiawah2005.pdf
PSYCHIATRY Visiting Fellowship in ECT	July 2004-June 2005	Durham, NC	40 credits	919-681-8742 or pmusser@duke.edu
ANESTHESIOLOGY 8th Annual Duke Cardiothoracic and Regional Update	June 25-28, 2005	Hilton Head Island, SC	21.5 credits	919-681-6753 or layton003@mc.duke.edu
RADIOLOGY 2005 Duke Radiology Summer Postgraduate Course	July 25-29, 2005	Myrtle Beach, SC	21.5 credits	919-684-7228 or sykes010@mc.duke.edu
RADIOLOGY Musculoskeletal MRI @ the Workstation	August 20-21, 2005; or October 22-23, 2005	Washington, DC; or Chicago, IL	11.25 credits	919-684-7228 or sykes010@mc.duke.edu
MULTISPECIALTY Emerging Issues in Thoracic, Breast, Prostate and GI Oncology	September 30-October 2, 2005	White Sulphur Springs, WV	7 credits	Attn: Monica Roberson 3100 Tower Blvd. 6th Flr. Durham, NC 27707
RADIOLOGY Musculoskeletal MRI & Neuroimaging: An Update	October 15-18, 2005	Asheville, NC	18 credits	919-684-7228 or sykes010@mc.duke.edu
RADIOLOGY A Practical Approach to Musculoskeletal MRI	October 29-November 2, 2005	Las Vegas, NV	16 credits	919-684-7228 or sykes010@mc.duke.edu
RADIOLOGY PET/CT & Abdominal Imaging: An Update	November 5-8, 2005	Walt Disney World Resort, FL	18 credits	919-684-7228 or sykes010@mc.duke.edu
MULTISPECIALTY 32nd Annual Postgraduate Course—The Alexander Spock Symposium	November 5-6, 2005	Durham, NC	9.75 credits	Attn: Thomas Murphy, MD DUMC, Box 2994 Durham, NC 27710
RADIOLOGY Abdominal Imaging & Musculoskeletal MRI Update	January 14-17, 2006	Nassau, Bahamas	18 credits	919-684-7228 or sykes010@mc.duke.edu
RADIOLOGY A Practical Approach to Musculoskeletal MRI	February 18-21, 2006	Walt Disney World Resort, FL	16 credits	919-684-7228 or sykes010@mc.duke.edu

ONLINE COURSES

RESEARCH ETHICS

"Social Sciences Research in Medical Settings"

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"Protecting the Confidentiality and Privacy of Patients"

"Protecting Research Subjects"

"What Counts as Research with Human Subjects?"

"Children Involved as Subjects in Research"

"Ethical and Regulatory Considerations When Bringing a Medication to Market"

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These activities have been approved for AMA PRA credit.

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DUKE MEDICINE 75 EST. 1930

Nobel man

In a recruitment universally hailed as a coup, Peter C. Agre, MD, winner of the 2003 Nobel Prize in Chemistry, will join Duke as vice chancellor for science and technology on July 1. "After many years as a bench scientist, I've become increasingly interested in contributing to science in a broader way," says Agre. "The work I'm about to begin at Duke will help shape the next generation of scientists, who will determine whether our nation will continue to lead the world in science and medicine."

Read more on page 6.

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