Duke Medicine review 2008

A year of advances in research and patient care

Driven to make a difference

Wilburt C. Davison, MD, founding dean of Duke University School of Medicine, described the culture of this institution as one of dissatisfaction with the status quo, no matter how advanced that status may be. From its earliest days, Duke has pushed to do better because we know we can and we believe we must.

More than 75 years after our founding, we are today among the top medical institutions in the country. And yet, we are still dissatisfied. We know we can do more to further our research, improve our patient care, enhance our health-care training and continuing education, and better the health of our local and global communities. We intend to learn more, act faster, think harder, reach farther.

This new publication is one way we hope to extend our reach. Through *Duke Medicine Review*, we want to broaden our conversations with our patients and colleagues, including physicians and researchers beyond the borders of Duke Medicine.

In the words of former North Carolina governor and U.S. senator Terry Sanford, president of Duke University from 1970 to 1985, we at Duke have an "outrageous ambition." Our mission is nothing less than to transform medicine and health, through innovative scientific research, rapid translation of breakthrough discoveries, education of future clinical and scientific leaders, and advocacy and practice of evidence-based medicine to improve health and eliminate health inequalities. To achieve these goals, we have to be bold; we must set high standards and we must perform to and beyond those standards.

Examples of how the people of Duke Medicine put these principles into practice are highlighted in this issue of *Duke Medicine Review*, from our work to develop the latest genomic tests for cancer and heart disease to our quest to find effective therapies for intractable diseases such as hepatitis and diabetes. We hope that among these innovations you will find something that may serve you in your own practice, as you join us in the quest to achieve the best possible health of communities everywhere.

Victor J. Dzau, MD
President and CEO,
Duke University Health System
Chancellor for Health Affairs,
Duke University
James B. Duke Professor of Medicine

Duke Medicine review 2008

Duke Medicine Review includes content from the Duke Medicine News Office and *DukeMed Magazine*, a biannual publication of Duke Medicine's Office of Marketing and Creative Services. To subscribe to *DukeMed Magazine,* please call 919-419-3289 or e-mail dukemedmag@mc.duke.edu.

Duke Medicine Review
DUMC 3687
Durham, NC 27710

Web: dukemedicine.org/review

Editor:
Kathleen Yount

Designers:
Jennifer Sweeting
David Pickel

Creative Director:
Kevin Kearns

Production Manager:
Margaret Epps

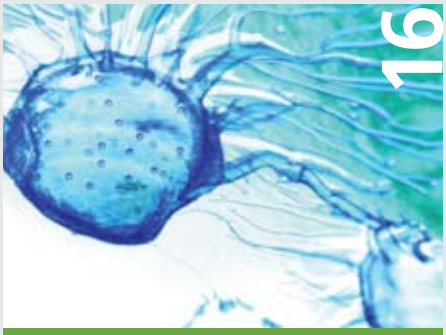
Contributing Writers:
Jeni Baker
Bridget Booher
Sarah Chun
Michelle Gailiun
Debbe Geiger
Carol Harbers
Lauren Schaftel Williams
Kathleen Yount

Contributing Photographers:
Scott Dingman
Chris Hildreth/
Duke Photography

IN THIS ISSUE

GENOMICS RESEARCH
A major new study aims to unlock the secrets of heart and liver disease, osteoarthritis, and obesity.

HEART ATTACKS
A bold collaboration changes treatment of heart attacks across North Carolina.

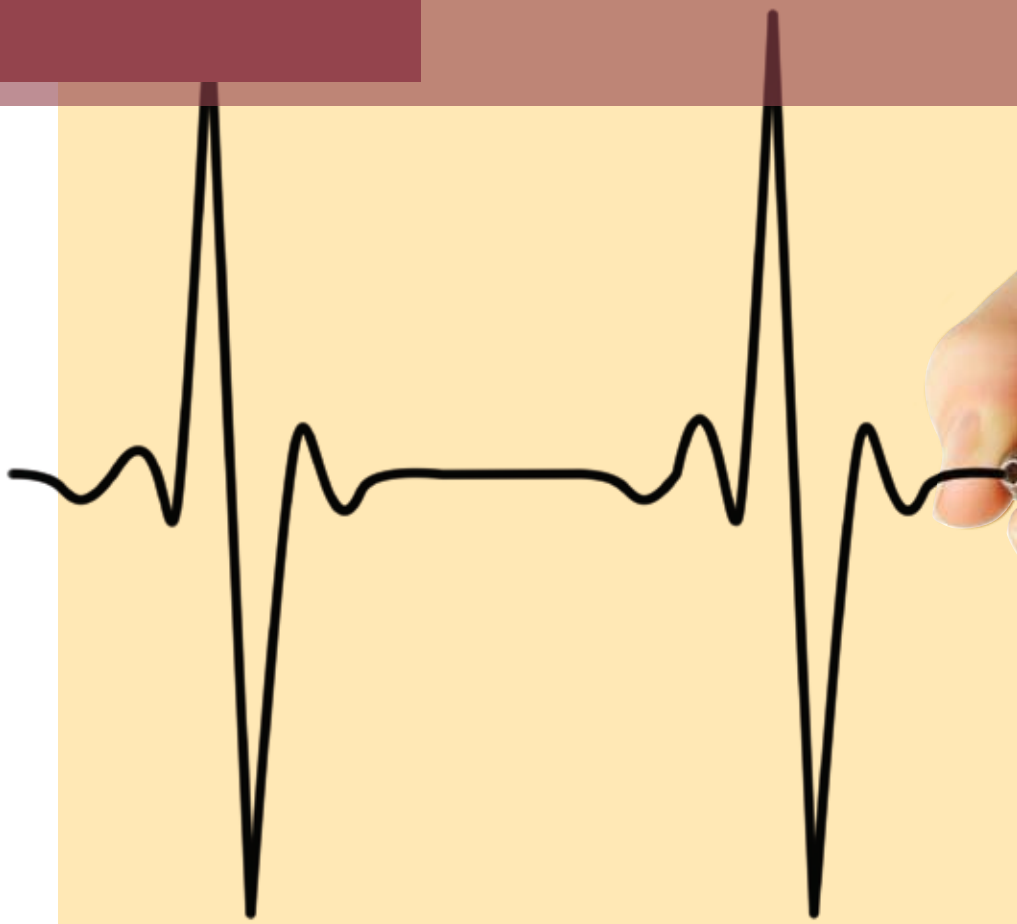


CHEMOTHERAPY
Genetic tumor profiling is making selection of chemotherapy more specific and successful.

HEPATITIS C
Clinical trials lead to two new ways to battle the disease.

TYPE 2 DIABETES
Can educating patients about their genetic risk factors affect their behavior?

BRAIN TUMORS
A promising vaccine is helping some glioblastoma multiforme patients extend their survival by years.



Improving prediction of sudden death after a heart attack

ACCORDING TO THE 2005 VALIANT (Valsartan in Acute Myocardial Infarction Trial) results, risk of sudden cardiac death is greatest in the first 30 days after a heart attack. But researchers at the Duke Clinical Research Institute say the factors that predict such deaths change over time.

The investigators reviewed the records of 14,703 patients enrolled in VALIANT. "Patients who die in the first few weeks after a heart attack can experience abnormal heart rhythms that can lead to sudden death," says Jonathan Piccini, MD, a cardiology fellow at Duke. "However, multiple studies show that implantable defibrillators don't really seem to alter death rates during that period. So it occurred to us that there may be other important risk factors for sudden death, and that these risk factors may change with time."

Piccini and colleagues found that by 30 months, 7.3 percent of the patients had died of sudden cardiac death. Those who died tended to be older, were more likely to have diabetes, had not been prescribed a beta-blocker, and had experienced a heart attack before enrolling in VALIANT. "We also found that while low blood pressure and a high resting heart rate are strong initial predictors of sudden cardiac death, over time heart failure and an earlier heart attack were even more robust predictors," says Piccini.

One risk factor that was consistently predictive over time was impaired kidney function. Piccini says the reasons why are not clear, but poor kidney function appears to be associated with higher likelihood of arrhythmia in general, and particularly in patients who have suffered a heart attack. Piccini presented the findings at the annual meeting of the American College of Cardiology.

PCI: Safer through the arm, more common through the leg

WHEN IT COMES TO STENTING, physicians are continuing to choose to gain entry to the circulatory system through an opening in the leg instead of the arm, even though the latter option appears to be safer, say researchers at Duke Clinical Research Institute.

"Bleeding complications are reduced by 70 percent when interventional cardiologists go in through a radial artery in the wrist," says Duke cardiologist Sunil Rao, MD, lead author of the study, which appears in the August issue of *Journal of the American College of Cardiology: Cardiovascular Interventions*. "But our research shows that only a tiny fraction of stenting procedures are done this way. The study suggests that maybe it's time to change the way we practice."

Researchers reviewed data from 593,094 cases of percutaneous coronary intervention (PCI) in 606 hospitals from 2004 to 2007. They found that the arm approach had gained favor during the four-year period, but still comprised only 1.3 percent of the total number of procedures. They also found that 40 percent of radial PCI were performed in only seven centers, and that academic medical centers were most likely to be sites of radial PCI use.

"The findings are somewhat surprising, given that numerous studies have shown that radial PCI is similarly successful to femoral PCI, and that radial PCI can significantly lower the risk of bleeding, especially among women, patients younger than 75, and people undergoing PCI for acute coronary syndrome," says Rao. He says previous studies have also shown that radial PCI also may cost less because it can mean shorter time in the hospital for some patients.

A new blood test for heart disease?

DUKE SCIENTISTS HAVE IDENTIFIED 11 genes in circulating blood that can identify both the presence and severity of coronary artery disease (CAD), which affects some 15 million Americans. The results of their study were reported at March's annual meeting of the American College of Cardiology.

"We believe this set of genes is exquisitely sensitive to many inflammatory changes that occur when plaque is building up in arterial walls," says Duke cardiologist and senior author William Kraus, MD. "Our study shows that the activity of these genes is proportional to the extent of the disease—meaning that a simple blood test based on these genes could tell us not only if someone has CAD, but also how bad the problem is."

Such a diagnostic test could help both patients and physicians avoid what can be a complex and costly series of electrocardiograms, echocardiograms, stress tests, and angiography—and enable patients with positive blood tests to be fast-tracked into the cath lab for treatment of their blockages.

William Kraus

Stem cell therapy to repair damaged hearts

THIS FALL, DUKE CARDIOLOGISTS will be enrolling 50 patients with severe heart damage in a new clinical trial that will use autologous stem cell infusions to strengthen damaged heart muscle.

Study leader Christopher Granger, MD, says laboratory and animal studies have shown that several types of cells found in bone marrow—when infused directly into the heart—can promote growth and block cell death, leading to stronger, better-functioning heart muscle.

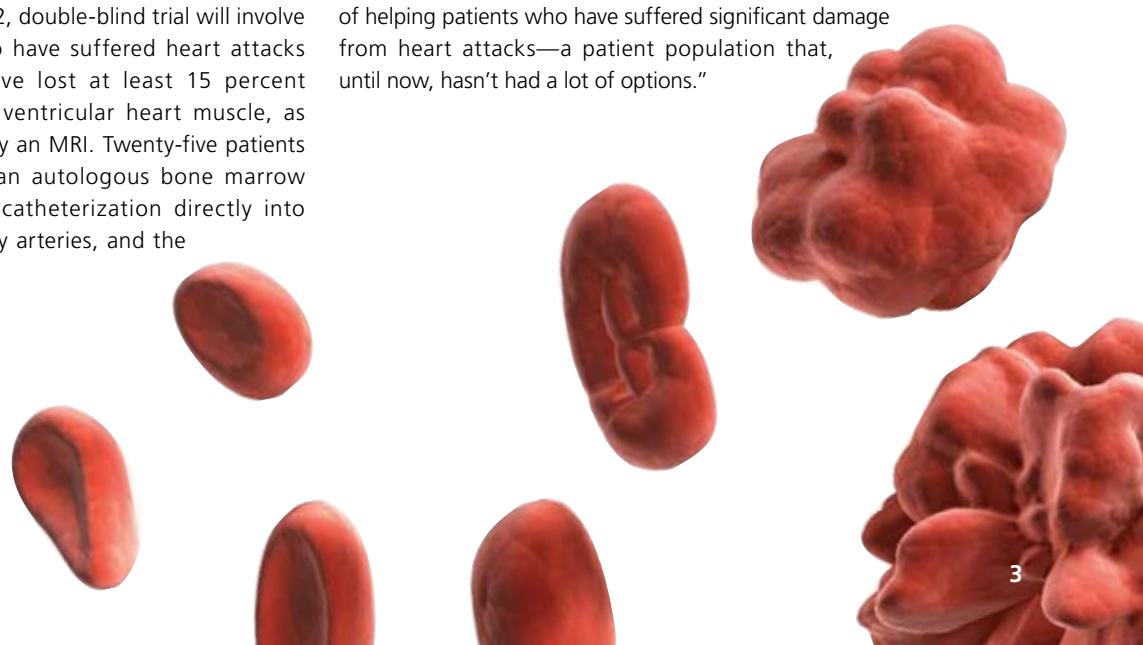
Granger says that while initial studies (mostly conducted in Europe) have been promising, it's not entirely clear which transplanted cells are most beneficial in restoring cardiac function, nor how they go about accomplishing that goal. "There are only about 400 people in the world who have ever undergone autologous bone marrow infusions, and the results have been mixed," he says. "We need to know so much more about how this promising new approach can work."

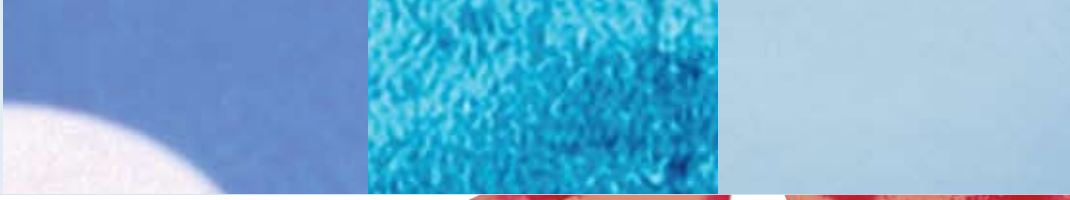
Christopher Granger

The phase 2, double-blind trial will involve patients who have suffered heart attacks and who have lost at least 15 percent of their left ventricular heart muscle, as determined by an MRI. Twenty-five patients will receive an autologous bone marrow infusion via catheterization directly into their coronary arteries, and the other 25 will be infused with a placebo. To be included in the study, participants will have to have undergone PCI and successful stenting. The protocol calls for researchers to measure heart function over the following year, with a special focus on arrhythmias and any change in left ventricular function.

"Previous studies involving patients have shown this to be a safe procedure, with few side effects," says Granger. "Patients will be getting their own cells—a mixture of generative cells their bodies would normally be using to keep them healthy—so we are not concerned with any of the ethical or moral issues surrounding the use of embryonic stem cells.

"Autologous bone marrow therapy is full of promise," says Granger. "We don't know if it will work, of course, but the evidence suggests that it may well be helpful, and if it is, it will offer us a whole new way of helping patients who have suffered significant damage from heart attacks—a patient population that, until now, hasn't had a lot of options."





Cardiology at the crossroads
Multi-vessel heart disease

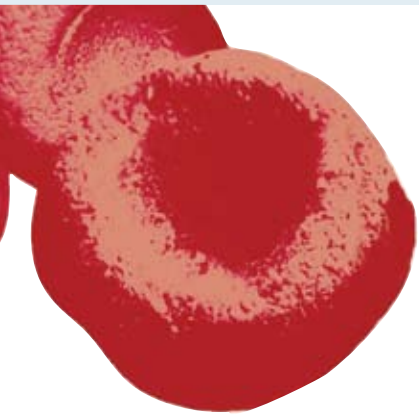
The "best" treatment may not be what you think. Three Duke heart experts debate the merits of three key interventions.

BY JENI BAKER

Coronary artery disease (CAD) is still the leading cause of death among both women and men, comprising more than 70 percent of all heart disease mortality. In general, the more arteries involved, the sicker the patient. People with multi-vessel disease are often scared, confused, and overwhelmed. Nearly all say that they just want to get it "fixed."

That's where things can get tricky.

This article is condensed from the original "Controversies in Medicine" feature that appeared in the summer 2008 issue of *DukeMed Magazine*. You can find the original version online at **dukemedmag.duke.edu**.



Robert M. Califf *is the Donald F. Fortin, MD, Professor of Cardiology, vice chancellor for clinical research, and director of the Duke Translational Medicine Institute.*

E. Magnus Ohman *is a professor of medicine and director of Duke Heart Center's Program for Advanced Coronary Disease.*

Peter K. Smith *is a professor of surgery and chief of cardiovascular and thoracic surgery at Duke.*

So tricky, in fact, that the first annual Thomas Ryan, MD, Duke Heart Center Lecture, held at Duke in late 2007, was dedicated to debating this important issue.

Entitled "Multi-Vessel Coronary Disease: PCI, Surgery, or Maybe Both Are Wrong?," the event began with the presentation of a case study by moderator Mark F. Newman, MD, chair of anesthesiology. Newman reported the particulars of patient "Mr. G," as well as his angiogram results, which revealed coronary disease in three arteries.

The case was then discussed by Peter K. Smith, MD, chief of the Division of Cardiovascular and Thoracic Surgery, and Robert M. Califf, MD, and E. Magnus Ohman, MD, both of the Division of Cardiovascular Medicine.

Each spoke primarily in favor of a different intervention for patients who, like Mr. G, suffer from multi-vessel disease, their positions reflecting the larger ongoing debate within the medical community.

Those interventions fall under three main categories:

- Percutaneous coronary intervention (PCI), which includes angioplasty and stenting (commonly performed together)
- "Surgery," which typically refers to the coronary artery bypass graft (CABG or "cabbage")
- Medical management, including drug therapy and patient behavior modification

DukeMed Magazine asked Smith, Califf, and Ohman to recap their remarks on this controversial topic.

PCI: Minimally invasive, widely performed

The immediate risks of complications and infection associated with PCI are significantly lower than those of open surgery. There's less post-procedure pain, recovery is quicker, and the risk of cognitive decline sometimes associated with CABG surgery is eliminated. The preferred intervention for people in the midst of heart attacks, PCI gets blood flowing to the heart within 90 minutes, as opposed to the approximately three hours it takes with surgery.

PCI—in particular, stenting (also known as percutaneous transluminal coronary angioplasty, or PTCA)—has also been widely criticized. Plagued by safety and efficacy concerns, stenting has been the topic of an ongoing debate comparing bare-metal stents (BMS) to drug-eluting stents (DES).[1,2,3]

"PCI has evolved a lot and continues to evolve—from standard balloon angioplasty to BMS to DES and now to newer forms of DES," says Ohman, who specializes in performing PCI and leads the Duke Heart Center's Program for Advanced Coronary Disease. "It provides a new way forward for patients—especially older patients and those with more complex disease—by lowering the risk of recurrence and offering a tremendous reprieve from their symptoms."

PCI isn't for everyone, but for many patients, it's "a great option that's associated with fewer symptoms and a higher quality of life," Ohman says. "When a patient is a candidate for both PCI and bypass surgery, I think it makes sense to offer the less invasive PCI as the first line of defense."

Smith, the surgeon, agrees that because PCI isn't as physically traumatic for patients as bypass surgery, it's sometimes the better option for patients who may not be well enough to survive surgery—such as those with advanced age or prior cardiac surgery, and even some with three-vessel disease.

But, Smith believes, "It's not fair to recommend PCI for a patient and say, 'You can always have surgery later if this doesn't work.' The public gets the idea

"Cardiologists had to give up some of the control we were used to having. It was a hard habit to break. But once we saw the results, we knew we could trust the process." — JAMES JOLLIS

Attacking heart attacks—fast

A TEAM OF NORTH CAROLINA doctors, nurses, hospitals, and emergency medical service workers has come up with a way to provide faster, more effective treatment for heart attack patients. Working as partners, rather than as rivals, caregivers at 65 hospitals and associated emergency medical teams were able to dramatically slash the time from diagnosis to treatment with potentially lifesaving therapies. In fact, the project was recognized by the American Heart Association as one of the top 10 research advances of 2007.

Design of the RACE (Reperfusion of Acute Myocardial Infarction in North Carolina Emergency departments) project was based on a trauma treatment system. Everyone focused on a single goal—to provide the fastest, most beneficial care to the greatest number of heart attack patients eligible for reperfusion, or artery-opening therapy.

To do so, all caregivers worked to "move care forward"—that is, enabling first responders to do as much of the work as possible, including diagnosing a heart attack. Paramedics were trained to do the work of ER physicians, and ER physicians were trained to do the work of cardiologists. A single phone call from the field was enough to bring an angioplasty team to the cath lab; hospitals had to admit heart attack patients, even if they didn't have any beds.

"Cardiologists had to give up some of the control we were used to having," says James Jollis, MD, a Duke cardiologist and senior author of the study. "It was a hard habit to break. But once we saw the results, we knew we could trust the process."

Over two years, physicians collected information on 2,000 patients, measuring pre- and post-intervention times between key processes, such as arrival at the hospital door to angioplasty or clot-busting therapy, and transfer times between hospitals. Times improved between 17 and 41 percent in all areas.

"This strategy is the first to demonstrate substantial, system-wide improvement on a statewide scale," says Duke's Christopher Granger, MD, a lead investigator of the project, which was presented at the 2007 annual meeting of the American Heart Association. "We are pleased that the RACE experience has created a model for change throughout the rest of the country."

that surgery and PCI are equivalent—which isn't true for patients with three-vessel disease, for whom surgery is life-prolonging compared to PCI," he says. "Proponents of PCI are basically saying, 'We never said it would save anybody's life; we just wanted to improve their symptoms.' And they should acknowledge that this is the case when they discuss options with patients who have life-threatening coronary disease."

Ohman points to the fine line between "improving symptoms" and "saving a life," citing the randomized ARTS II trial,[4] the largest follow-up study of its kind to compare surgical and PCI patients. ARTS II looked at 607 patients one year out and showed that "the drug-eluting stent is every bit as good as bypass surgery for treating multi-vessel disease," Ohman says.

Despite the ongoing controversy, PCI continues to be the most commonly used intervention for coronary artery disease. The American Heart Association (AHA) reports that more than 1.2 million PCIs were performed in the United States in 2005—approximately two-thirds in men and one-third in women. (Duke cardiologists perform more than 1,300 PCIs every year.)

But while data show that stents have gotten safer, the overall use of angioplasty appears to be waning, according to a recent analysis conducted by the National Cardiovascular Data Registry.

"The rise of angioplasty procedures has leveled off and appears to be on the decline," Duke cardiologist Eric Peterson, MD, told *USA Today* after reviewing the data. This could be because some believe that PCI in general is an overused strategy for treating multi-vessel disease that would be more effectively treated with CABG surgery and/or medical management.

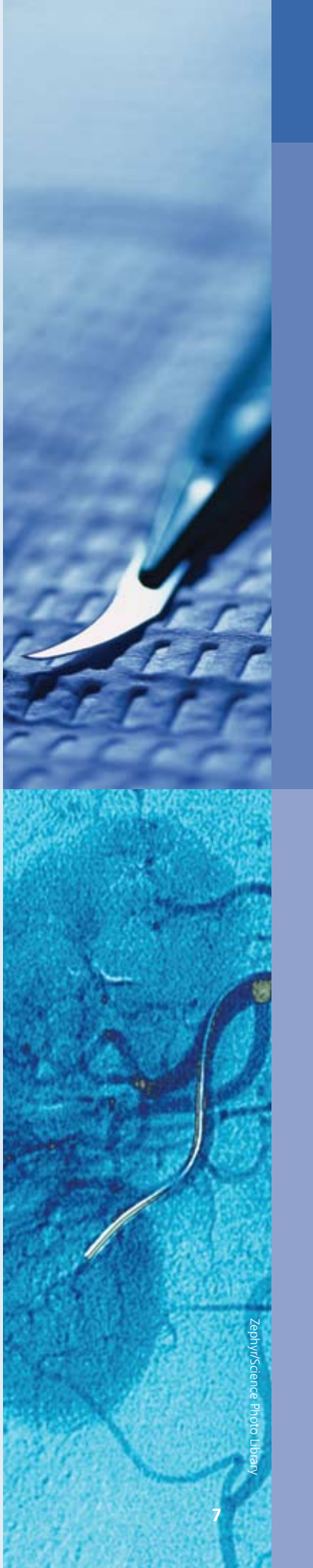
> "When a patient is a candidate for both PCI and bypass surgery…it makes sense to offer the less invasive PCI as the first line of defense."
>
> —E. MAGNUS OHMAN

Bypass surgery: Tried and true

CABG is major surgery. Patients face months of recovery time, a large external scar, and increased risk of stroke. "The risk of stroke associated with CABG is about 10 times that associated with PCI, and strokes occur very rarely as a result of PCI," Ohman says, adding that most patients fear that CABG will result in neurological complications, as well.

Although many patients opt for PCI to avoid these risks, the AHA reports that approximately 470,000 CABG surgeries were performed in the United States in 2005—some 325,000 in men and 145,000 in women. Duke Heart Center surgeons alone performed over 600 bypass surgeries annually between 2003 and 2007.

Smith says that's because the procedure is tried and true, with proven benefits and very low mortality and complication rates. "The advantage of surgery is that it's definitive, it's durable, and evidence shows that in almost all cases, it is effective," says Smith, who specializes in performing the procedure. "CABG completely bypasses the disease, and in many cases, it simply doesn't come back"—particularly with artery grafting, he adds, although the disease can return with vein grafts.



Zephyr/Science Photo Library

> "We need to give patients [medical treatments] first, and if those fail, then try the expensive and risky treatments."
>
> —ROBERT M. CALIFF

A 2006 Duke analysis[5] of outcomes from more than 18,000 heart patients found that patients who received bypass surgery lived an average of 5.3 months longer than those treated by angioplasty—and that both bypass surgery and angioplasty provided more benefit for patients than medicine alone.

Because bypass surgery has shown the greatest longevity benefit in treating three-vessel disease—"potentially the most lethal form of heart disease," says Smith—"it's the clear winner for many of those patients."

Ohman concurs. "CABG certainly offers the best long-term solution for some people. The more severe the disease and the more vessels are involved, the more appropriate surgery becomes."

Medical management: A solid foundation

Because it is recommended as both a singular strategy and for use in conjunction with PCI and surgery, medical management actually transcends and supplements all other multi-vessel disease interventions. Drug therapies and lifestyle modifications can help prevent further deterioration of the heart muscle in patients with existing damage.

"Medical management is the bedrock of treating coronary disease," says Califf. "Regardless of anything else patients have done, medical treatment should be the standard of good medical therapy and the first option we offer our patients.

"The Duke data[6] show that patients who are on multiple effective treatments—which can be a first-rate aspirin, beta-blocker, and statin, available for four bucks a month from Wal-Mart—have about a twofold reduction in their risk of death compared to patients who do not adhere to their medication regimens.

"The issue is that the real benefit is in medical therapy," Califf continues. "PCI doesn't prolong survival in most patients, so you're not losing anything there by going with medical management, and CABG obviously has a higher risk than medical treatment."

"If we cardiologists could just do our jobs in our own treatment environment and give patients simple four-dollar-a-month plans, we would save literally thousands of lives," he says. "We need to give patients the important treatments first, and if those fail, then try the expensive and risky treatments."

Smith agrees that medical management plays an important role for surgical patients, and its use as an alternative to both PCI and CABG may be underutilized. "Advances in medical therapy have led to more promising results than anticipated in treating patients with one- and two-vessel disease, whom the COURAGE trial[7] showed aren't being helped as much with PCI."

The key to the best outcome? Honest dialogue

Since each multi-vessel disease intervention has its pros and cons, how does one decide which is likely to have the best outcome for a given patient? By having a truthful and thorough doctor-patient conversation, these experts say.

"Many doctors tell their patients, 'You've got bad blockages, and we need to bypass

or dilate those blockages, because if we don't, you're going to have a heart attack or die,'" Califf says. "And that's simply not validated by the randomized trials; it's not true. But it's something we frequently tell our patients because it avoids a much longer discussion about what's really going on in terms of the risks versus the benefits of these various interventions."

Many people assume, for instance, that minimally invasive procedures are inherently safer—and therefore always "better"—than open surgeries. Take the surgery-versus-PCI issue, for example.

"Surgery has risks like pain, infection, and recovery time that people understand up front," Smith says. "But multi-vessel coronary disease patients should understand that PCI's ongoing cumulative risk of restenosis is less obvious, with studies showing that surgery compares more favorably to PCI the longer patients are followed."

Patients may have different perceptions of risk when considering medical management, as well. Some may perceive this strategy as having the lowest risk because it doesn't involve any type of surgery. Others may see it as being more risky than the other options because they don't believe medication and lifestyle changes can successfully treat their heart disease.

"It's only natural for patients to think that if they have a stent placed or undergo a bypass that their disease is 'fixed'—and doctors can easily get away with saying, 'It's lucky we found this blockage; now we can fix it,'" Califf says. "A doctor who offers patients a potentially risky procedure must be able to show that it's likely to help them."

Another issue, Califf says, is that many patients have difficulty translating probability into risks that are meaningful to them. For example, when comparing a treatment said to have a 10 percent risk of death with one said to have a 90 percent survival rate, people are more likely to choose the second option, even though the actual degrees of risk are equal.

Heart attack patients OD—on aspirin

WHEN IT COMES TO ASPIRIN, Duke researchers say less is more in the early treatment of heart attack.

A study in the January 15, 2008 *Circulation* shows that a low dose of aspirin appears to be just as effective as a higher dose of the drug in initial treatment of ST-elevation myocardial infarction (STEMI), one of the most common types of heart attack. A lower dose also is safer because it is associated with less major or moderate bleeding.

Aspirin is one of the most widely prescribed drugs in the world, and Duke cardiologist Jeffrey Berger, MD, says people—physicians included—may underestimate its power. The very same mechanism that can break up life-threatening clots can increase the chance of serious bleeding, which could necessitate a transfusion or lead to stroke or even death. "So we need to be very careful in how much aspirin we prescribe," Berger says.


Jeffrey Berger

Berger led a team of researchers in reviewing the effects of a low versus a high dose of aspirin in nearly 50,000 patients suffering from STEMI in two international trials. Three-quarters of the patients got a low dose of aspirin (162 mg or less), and the rest got a higher dose (325 mg). Investigators tracked death rates and episodes of serious bleeding in both groups for up to 30 days following therapy.

The only difference between the two groups in terms of short-term outcomes was a difference in bleeding: those patients who took the higher dose of aspirin had significantly more bleeding than those who took the lower dose.

The study does not provide the definitive answer regarding dosing because it was observational in nature, and the participants in the trials were not randomized to preset dosing levels or compared with controls. Still, Berger feels it offers enough evidence to suggest that clinicians take another look at their practice. "If a lower dose of aspirin is just as good—and more may be harmful—why risk it?"

Assessing risk and benefit

Patient factors

Patient factors that figure into the risk-versus-benefit equation commonly include:

- **Age and health status—**A patient may be too elderly or ill to withstand surgery, for example—or to wait for the effects of medical intervention. Medical management alone or in conjunction with PCI may be the most appropriate choice for someone with minimal disease.
- **Goals, values, and concerns—**A big issue is quality versus quantity of life. Some people prefer better years to more years; some, the opposite. Patients might think about what they hope to achieve through treatment. The stamina to keep running marathons? The ability to perform daily activities and play with the grandchildren? Relief from debilitating symptoms? Other factors can include patients' affinities for (and aversions to) particular treatments, insurance or financial concerns, and so on.
- **Lifestyle and compliance—**Some patients follow their doctor's instructions to a tee; others don't. Some aren't likely to quit smoking, take up regular exercise, or improve their diets; others view their condition as a call for meaningful lifestyle change. Some are very self-motivated; others might benefit from working with a health coach.

Additional factors

Other factors also can come into play when choosing a treatment for multi-vessel disease.

"The patient made me do it" phenomenon: While patients are encouraged to educate themselves and take a proactive role in their own health, they are increasingly arriving at their initial cardiologist visits with Internet printouts in hand and a treatment in mind—without having discussed their individual risks and benefits with their doctors, and frequently armed with data that are murky at best.

Unclear and/or biased data: Unfortunately, the large body of existing research data about treating multi-vessel CAD can lead to confusion, not clarity. The length and type of the study, as well as the number of participants, obviously influence the quality and meaning of the data.

And different uses and interpretations of the word "multi-vessel"—which can mean two, three, or four vessels—mean that data from studies of patients with different degrees of disease may be combined, accounted for multiple times, and/or simply unclear.

"Most 'multi-vessel' CAD studies have in fact looked only at patients with two-vessel disease—not three- or four-vessel disease—and the distinctions are critical in terms of both compromised patient health and the interpretation of the data," Smith says. "People can take these results to mean what they want them to mean when making a case for or against a particular therapy."

> "It's one thing to advocate for the procedure you do, but it can be an entirely different thing to advocate for the patient."
>
> —PETER K. SMITH

Physician expertise and bias: A physician or hospital's experience with and/or bias toward particular treatments plays a role in which strategies are recommended to people with heart disease.

"It's one thing for doctors to advocate for the procedures they do, but it can be an entirely different thing for them to advocate for their patients," Smith says. "We should help our patients develop a perspective beyond what happens today, present them with information honestly, and never present a procedure as an option when another one would be more appropriate."

Califf agrees. "Let's have the courage to tell our patients the truth about what we know about each of these treatment strategies, and take the time to explain all of the risks and benefits."

While the morbidity and mortality associated with coronary artery disease is devastating, both doctors and patients can thank ongoing advances in medicine for the variety of life-saving treatment options available today. Selecting the right one to treat a patient's multi-vessel disease means working together to make a carefully informed, patient-centered decision. □

[1, 3] N Engl J Med. 2007 Mar 8;356(10):1009–19. Epub 2007 Feb 12.

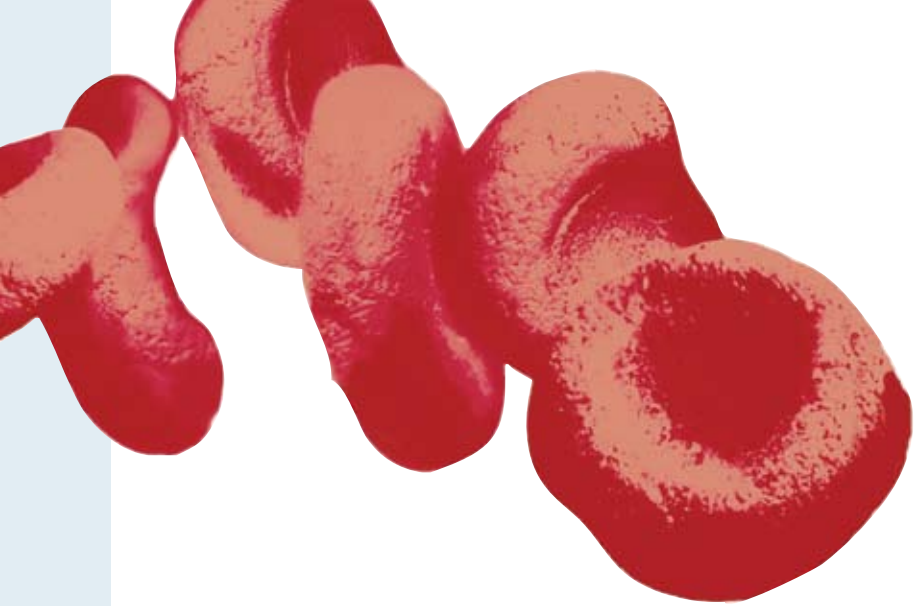
[2] J Am Coll Cardiol. 2007 Nov 20;50(21):2029–36.

[4] Heart. 2004 Sept;90(9):995–8.

[5] Ann Thorac Surg. 2006 Oct;82(4):1420–8; discussion 1428–9.

[6] Circulation. 2006 Jan 17;113(2):203–12. Epub 2006 Jan 9.

[7] N Engl J Med. 2007 Apr 12;356(15):1503–16. Epub 2007 Mar 26.



A new heart-attack drug on the horizon

KAI-9803 may prevent reperfusion injury

A NEW DRUG BEING TESTED AT DUKE may soon change the fates of people who suffer heart attacks. The drug has passed initial safety tests in human trials, the results of which were published in the February 19 *Circulation*, and it will next be tested for efficacy in a larger study.

The heart suffers damage from two major insults during a heart attack: first, when a blockage in a coronary artery prevents blood and oxygen from getting to the heart muscle, and then again when the patient undergoes percutaneous coronary intervention, or PCI (such as balloon angioplasty and stent placement), to open the blocked coronary artery. Although PCI can be lifesaving, restoring blood flow to the heart (called reperfusion) after a period of no blood flow can itself contribute to muscle damage.

The new drug, known as KAI-9803, blocks the activity of an enzyme called delta protein kinase C that is involved in heart muscle cell death after PCI. Researchers randomized 154 patients who had suffered heart attacks and were eligible for PCI into either one of four dosing levels of KAI-9803 or a placebo. Physicians injected the drug directly into patients' coronary blood vessels during the PCI procedure.

"The goal of the treatment is to flood the heart with the drug immediately before blood flow is restored, and then again immediately afterwards," says Duke cardiologist and lead investigator Matthew Roe, MD. "Bathing the area affected by the heart attack with this novel compound may block the damaging cascade of events that are triggered specifically by delta protein kinase C."

Although the trial (known as DELTA-MI) was not designed to demonstrate the efficacy of KAI-9803, researchers say early data—such as lessened damage to the heart muscle and improvement in electrical conductivity in the heart that corresponded to restoration of blood flow—suggest it is a promising compound. "We may not be able to intervene in the first stage of a heart attack," says Roe, "but we think there may be ways to limit damage caused by reperfusion injury."

Matthew Roe

Cardiac surgery drug proves dangerous

THE LARGEST STUDY TO DATE of the controversial cardiac surgery drug aprotinin (trade name Trasylol) shows that it increases death rates and damages kidney function. Aprotinin was commonly used to limit bleeding during surgery until it was temporarily suspended from marketing in the United States in November 2007 when a small Canadian study showed similar findings.

"We're not surprised by the results," says Duke anesthesiologist Andrew Shaw, MD, lead author of the paper published in the February 21 *New England Journal of Medicine*. However, the Duke study is significant because "it is more than twice the size of the next largest study of aprotinin," says Shaw.

Andrew Shaw

The data were collected on patients who underwent surgery between 1996 and 2005, when aprotinin was thought to be safe. The Duke team started analyzing its database of patients after a 2006 study reported that aprotinin may increase the risk of heart attack, stroke, and serious kidney injury. Of the 10,275 patients studied, 13.2 percent received aprotinin, 66.8 percent received aminocaproic acid (another drug used to limit bleeding), and 20 percent received no therapy. All patients underwent coronary artery bypass surgery, and 1,181 of them also underwent valve surgery. Patients who received either aminocaproic acid or no therapy did not have the high rates of death or poor kidney function seen in the aprotinin group.

Shaw says the new study does not rule out the possibility that the increased death rate was due to high-risk, sicker patients receiving the drug. "The question to answer next is whether the increased death rate is due to differences between the patient groups that we were unable to detect, or to exposure to the drug."

Coaching—in person or online—helps prevent weight regain

Laura Svetkey

IN THE LARGEST AND LONGEST STUDY of weight-loss maintenance, researchers from Duke and three other centers discovered that both personal contact and computer-based support can help people keep weight off more effectively than going it alone.

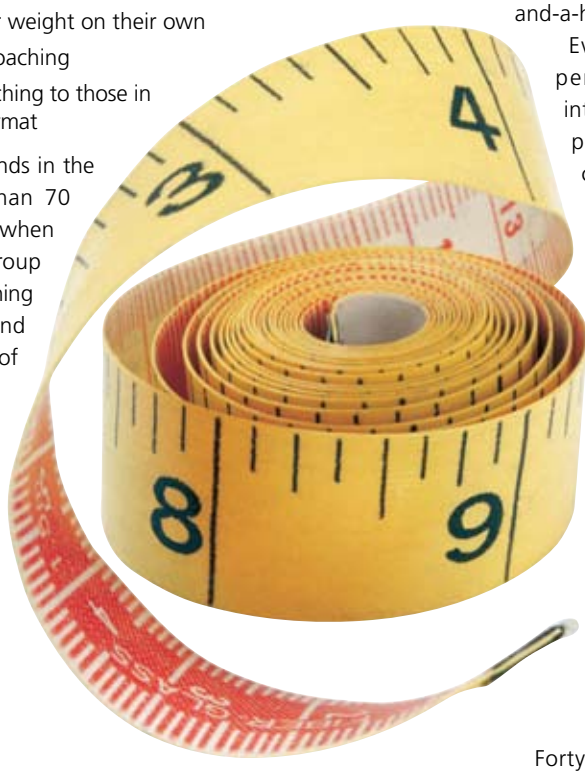
After a six-month intensive weight loss program, the 30-month study randomly assigned 1,032 people who had lost at least nine pounds to three groups:

- Self-directed (control)—Patients managed their weight on their own
- Personal contact—Patients received monthly coaching
- Computer-based—Patients received similar coaching to those in the personal contact group, but in an online format

Participants lost an average of nearly 20 pounds in the intensive weight loss program—and more than 70 percent weighed less at the study's end than when they started. Those in the personal contact group experienced a 77 percent success rate in maintaining some weight loss, and the computer-based and self-directed groups saw 69 and 67 percent rates of success, respectively.

For the first 24 months, members of both the personal contact and computer-based groups regained less weight than the control group, but at 30 months, only the personal contact group weighed significantly less than the control group.

"These results send a strong signal to those who believe that obesity is such an intractable problem that nothing can be done about it," says lead author Laura Svetkey, MD, of the Duke Hypertension Center and the Sarah W. Stedman Nutrition and Metabolism Center. "Our research shows that this is not true, with the majority of participants losing and keeping weight off for two-and-a-half years."



Even though the effects of the personal contact and Internet interventions were modest, "every pound lost improves health and can lower the risk of hypertension and diabetes," Svetkey says. "Our patients have shown that under the right conditions, long-term weight control is an achievable goal worth pursuing."

Study results appeared in the March 12, 2008 *Journal of the American Medical Association*.

Weight loss surgery for type 2 diabetes

Effective, but no magic bullet

EARLIER THIS YEAR weight loss surgery was heralded as a potential cure for diabetes, after studies reported dramatic cases of post-surgical remission, particularly after gastric bypass surgery. The phenomenon is thought to be due to changes in the way hormones are secreted from the gut and the pancreas following gastric bypass, which re-routes how food is sent from the stomach to the small intestine.

A new Duke study shows that the surgery itself is not a magic bullet—that weight loss is still a major reason why severely obese people with type 2 diabetes experience disease improvement or remission following surgery. "Yes, there are physiologic changes related to the restructuring of the gastrointestinal tract that appear to influence the rapid improvement in diabetes following gastric bypass," says Eric DeMaria, MD, director of bariatric surgery at Duke. "But our study shows the patients who were able to get off medications completely and go into remission were the ones who lost the most weight." The study, presented in June at the American Society for Metabolic and Bariatric Surgery, shows that the more weight patients lost, the higher their chances of disease improvement.

The Duke study followed 314 patients with diabetes who underwent gastric bypass surgery from January 2000 to October 2006. Of the 314 patients, 71 required insulin therapy to control the disease. After 12 months, all the patients were able to reduce the dose or number of their diabetes-related medications. Forty-eight percent of the 71 insulin-dependent patients had achieved remission.

However, DeMaria stresses that losing weight during the first three weeks to six months following surgery is critical for patients who ultimately put their diabetes into remission. "We're a culture of quick-fix people," he says. "Everybody loves the idea that diabetes is gone the day after surgery. But we know that an important mechanism is in place if the operation fails over the long term: poor behavior. Eating high-fat junk food and sweets, grazing or constant eating between meals, lack of exercise—those are major contributors to failure of weight loss surgery, and failure causes recurrent diabetes."

Diabetes prevention

Will genomic information affect behavior?

BEHAVIOR MODIFICATION is the most effective way to prevent and treat type 2 diabetes—and it is also the hardest strategy for patients to use successfully. A new clinical trial beginning this winter will explore whether genetic counseling affects the behavior of people at risk for type 2 diabetes—and, ultimately, if it affects health outcomes.

Duke researchers Alex Cho, MD, Scott Joy, MD, and Geoffrey Ginsburg, MD, PhD, are launching a three-year, 1,000-patient trial in which participants will be screened for four genetic markers that are associated with type 2 diabetes. All the patients will receive conventional counseling about type 2 diabetes (risk behaviors and lifestyle management). People whose genetic analysis shows one or more markers for diabetes will be randomly assigned to either conventional counseling alone or conventional counseling paired with genetic counseling about their personal risk for developing the disease.

Cho describes the study as a test of genetic counseling as a "virtual teachable moment"—whether patients who know that they have genetic predisposition to type 2 diabetes will be able to integrate lifestyle modifications before they actually progress to a disease state. "We're looking to see whether people will change their behaviors, and whether health outcomes such as heart disease will be affected by genetic assessment and counseling."

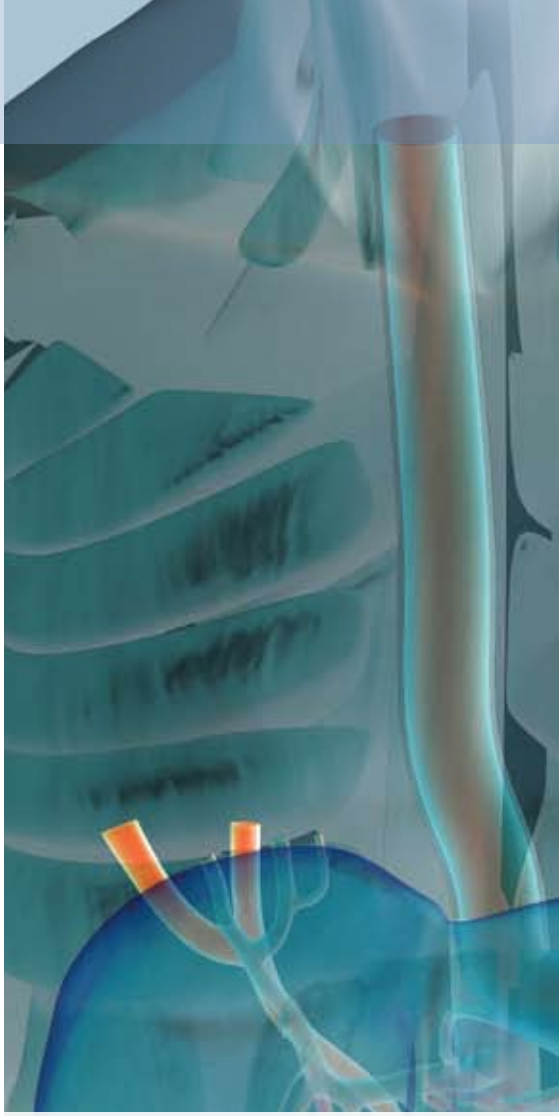
Osteoporosis drug reduces fatal post-fracture frailty

A HIP FRACTURE IS OFTEN a harbinger of more ills to come. A broken hip significantly increase a person's risk of permanent walking impairment, the need to spend time in a long-term care facility, and further fractures in both hips; more important, approximately 15 to 25 percent of patients will die within a year of their fracture.

A new Duke-led study has shown that the osteoporosis drug zoledronic acid, given intravenously once a year, significantly reduces not only the occurrence of new fractures but also the incidence of death in patients who have had a hip fracture. A study of 2,127 patients found that those who received zoledronic acid (U.S. trade name Reclast) within 90 days of surgery for a hip fracture showed a 28 percent reduction in death and 35 percent lower chance of suffering another fracture.

"Very few patients [currently] get treatment for osteoporosis after fracturing a hip," says study leader Kenneth W. Lyles, MD, a Duke geriatrician and endocrinologist, so "we believe that using a drug like zoledronic acid can be instrumental in reducing the frailty so common in the elderly."

Though the link between this treatment and the reduction in mortality warrants further study, he says, "These data show that we can go beyond cutting the risks of future fractures to reducing the death rate after these disabling fractures." The results of the international clinical trial appeared in the November 1, 2007 *New England Journal of Medicine*.

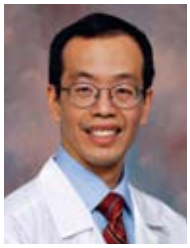


How gastric reflux may trigger asthma

ANYWHERE FROM 50 TO 90 PERCENT of patients with asthma experience some aspect of GERD, or gastroesophageal reflux disease. But can GERD cause asthma, or is it the other way around? Duke researchers appear to have solved at least a piece of a puzzle that has mystified physicians since the relationship was first noted in the 1970s.

In the lab of Duke immunologist Shu Lin, MD, PhD, researcher Andrew Barbas and his colleagues inserted minuscule amounts of gastric fluid into the lungs of mice (mimicking the human process of micro-aspiration, or breathing in tiny amounts) over a period of eight weeks, then compared the immune response of these mice to that of mice who were exposed to allergens but not the gastric fluid. Mice with the gastric fluid in their lungs developed a T-helper type 2 response—a type of immune system reaction characteristic of asthma. The immune systems of the other mice responded in a more balanced manner.

"This is the first experimental evidence in a controlled, laboratory setting linking these two very common conditions in humans," says Lin of the study, which was published in July in the *European Journal of Clinical Investigation*. "These data suggest that chronic micro-aspiration of gastric fluid can drive the immune system toward an asthmatic response."



Shu S. Lin

William Parker

"This does not mean that everyone with GERD is going to develop asthma, by any means," says William Parker, PhD, a co-author of the study. "But it may mean that people with GERD may be more likely to develop asthma. If there is an upside to this, it is that developing GERD is something we can often treat and control."

Drug boosts platelets in hepatitis C patients

IT'S NOT A CURE, BUT this may be some of the best news patients infected with the hepatitis C virus (HCV) have heard in a long time: A new drug, eltrombopag, appears to be effective in boosting low platelet counts, one of the major reasons why patients can't initiate or endure antiviral therapy.

Other drugs that can restore normal platelet levels are infusions of platelets or injections; eltrombopag is a pill taken just once a day.

Researchers at Duke and other centers worldwide studied eltrombopag (U.S. trade name Promacta) in 74 patients with low platelet counts and cirrhosis of the liver due to HCV infection. They found that it boosted platelet counts in a majority of patients at each of three dosage levels, enabling most of them to continue or start conventional antiviral treatment.

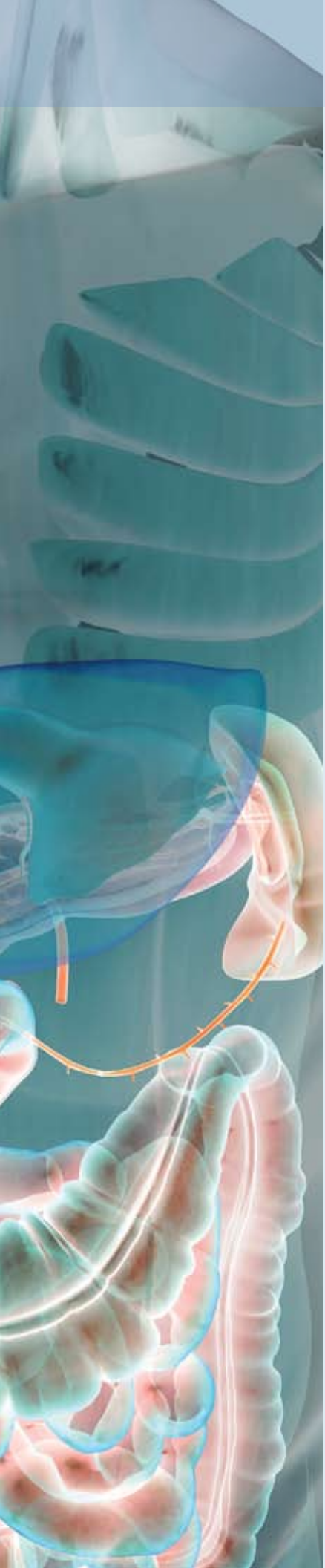
"We feel this is an important development for many people infected with the hepatitis C virus worldwide," says John McHutchison, MD, professor of medicine and associate director of the Duke Clinical Research Institute. "A significant number of patients with HCV infection will at some point develop platelet problems that will compromise their being able to receive or complete the best treatments we have. Anything we can do to prevent that from happening would improve their care."

The findings appeared in the November 29, 2007 *New England Journal of Medicine*.

John McHutchison

Advances in hep C

JOHN MCHUTCHISON IS the co-author of the most recent guidelines for treatment of hepatitis C. He's also one of the lead investigators of the MURDOCK study (page 26), which is analyzing biological samples from hepatitis C patients to look for genomic patterns that correlate with treatment outcomes. He says that Duke researchers are leading the investigations of the two largest and leading therapeutic options for hepatitis C therapy, including the first phase 3 trial of a potential protease-inhibitor treatment strategy. This trial is being conducted in cooperation with Vertex, who is manufacturing the drug.



The great diverticulitis debate

IT SENDS MORE THAN 130,000 Americans to the hospital each year. The symptoms—pain, gassiness, nausea, fever—can be so severe the sufferer may think it's an attack of appendicitis. But despite its prevalence and the toll it takes on victims, the best way to treat diverticulitis still a matter of debate, says Danny Jacobs, MD, chair of Duke's Department of Surgery, who authored an article on the topic in the November 15, 2007 *New England Journal of Medicine*.

An inflammation of the diverticula (sacs in the colon wall), diverticulitis comes in two basic varieties—complicated diverticulitis, when an abscess is present, or uncomplicated diverticulitis, when there's not. Both are painful enough to make sufferers seek relief, but the best ways to provide it aren't always clear.

"It's an area of controversy—how many attacks of uncomplicated diverticulitis must occur before you recommend surgery?" says Jacobs.

According to Jacobs, surgery has commonly been recommended after two attacks of uncomplicated diverticulitis to minimize the chances of a future attack, "but now the thinking is that surgery is not always required—especially for the many folks who have milder attacks," he says. Instead, he recommends that they continue to receive conservative medical treatment, including antibiotics and perhaps eating more fiber (interestingly, the condition is almost nonexistent in undeveloped countries where people eat very high-fiber diets).

Surgery may be indicated in certain uncomplicated cases, however, such as when patients develop fistulas: abnormal connections between the colon and other organs like the bladder, vagina, small bowel, or even the skin. In these cases, surgery is uniformly recommended.

The age of a patient also matters. Duke surgeon Christopher Mantyh, MD, notes that diverticulitis is becoming less of an older person's disease—in part because the medical community is diagnosing it better—and that there is some controversy as to what to do with younger patients. "If a patient is younger than 40, they could have a more aggressive form and perhaps should be treated with surgery."

Danny Jacobs

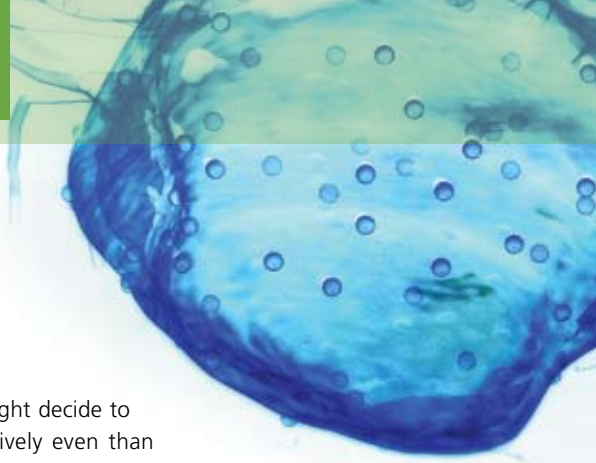
Christopher Mantyh

On the flip side, complicated diverticulitis—for which surgeons typically recommend removing part of the bowel—does not necessarily mean an immediate trip to the operating room. "Complicated diverticulitis usually requires hospitalization, but, especially at Duke, we can drain these abscesses percutaneously," Mantyh says. "This, along with antibiotics, will resolve the abscesses and convert an emergent operation to an elective procedure that does not require a temporary colostomy."

Fortunately, surgical treatment of diverticulitis can be easier on patients than it has been in the past, thanks to modern advances. "We can and should offer laparoscopic surgery," says Jacobs. "That doesn't mean this approach is right for every patient, but there is far less discomfort and fewer complications."

Although laparoscopy is becoming more common, not every surgeon uses the minimally invasive technique. "Colorectal procedures are on the high end of the learning spectrum for laparoscopic surgery," says Mantyh, who does perform laparoscopy for diverticulitis. "It requires advanced skills in laparoscopy, and can be difficult if the colon is very diseased."

Jacobs notes that Duke's residency training program exposes residents to as much laparoscopic surgery as possible. "In the past, we also have offered continuing education courses in which other surgeons work with our surgeons and take those skills back into their communities," he says. "We hope to do more of that in the future."



Matching chemotherapy to a tumor's genes

DUKE MEDICINE IS NOW using genomic analyses to develop tumor-specific treatment plans for patients enrolled in clinical trials for advanced non-small cell lung cancer, early stage breast cancer, and prostate cancer.

This first-of-its-kind series of studies is based upon the research of Joseph Nevins, PhD, and Anil Potti, MD, both of Duke's Institute for Genome Sciences & Policy (IGSP). The studies used genomic analysis to create unique tumor profiles, which they combined with that patient's clinical characteristics to predict his or her individual response to conventional chemotherapy drugs. The ongoing clinical trials will use this technique to guide the choice between a traditional chemotherapy regimen and an alternate drug.

In the breast cancer studies, for example, researchers looked at almost 1,000 breast tumor samples and corresponding patient data. By using the clinical and genomic tools together and cross-comparing data, the researchers were able not only to say that a particular patient has a "high" risk of recurrence, but also to be specific—for instance, they could predict that a particular patient was 90 percent likely to see her cancer recur. These findings appeared in the April 2 issue of the *Journal of the American Medical Association*.

"With this information, we might decide to treat this person more aggressively even than someone else who is considered 'high risk' but who may have only a 60 percent likelihood of recurrence," Potti says. "Moreover, we can identify specific options for chemotherapy in such patients as well, by correlating gene expression in a tumor with its response, or non-response, to certain chemotherapies.

"Our goal is to treat patients on a more individualized basis, matching the right drugs with the right patients," says Potti. "The combination of these two assessments may allow us to do that with unprecedented accuracy."

"At Duke," says Nevins, "we have devoted a great deal of time and resources so that we can use genomics *now* to determine which of the current available treatments is most likely to be most effective for each patient."

For information about these trials, call Traci Foster at 919-681-8659 or visit genomestohealth.org.

Anil Potti

Joseph Nevins

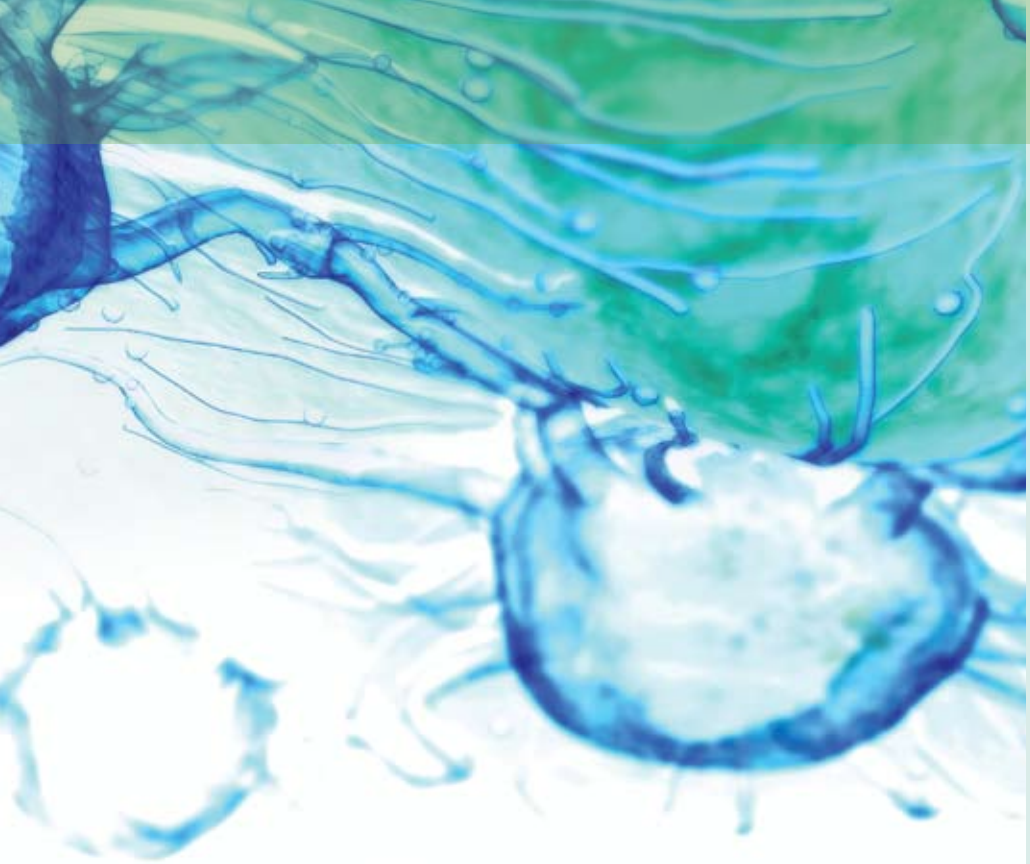
"Young" breast cancers have more aggressive genes

RESEARCHERS AT the Duke Comprehensive Cancer Center and the Duke Institute for Genome Sciences & Policy may have discovered part of the reason why young women's breast cancers tend to be more aggressive and less responsive to treatment than the cancers that arise in older women—and it's all in the genes.

Duke researchers looked at samples of nearly 800 breast tumors from women in five countries on three continents and divided them into age-specific cohorts. The investigators found more than 350 sets of genes that were active only in the tumors of women under age 45. Conversely, tumors arising in women over age 65 did not share these activated gene sets. The results appear in the July 10 *Journal of Clinical Oncology*.

"The breast tumors that arose in younger women shared a common biology, and this discovery was truly remarkable," says Kimberly Blackwell, MD, a breast oncologist at Duke and senior investigator on the study. "The genes that regulate things like immune function, oxygen supply, and mutations that we know are related to breast cancer, such as BRCA1, were preferentially expressed in the tumors taken from younger women, but when we compared younger women's tumors to older women's tumors, we found those same gene sets were not expressed in the 'older' tumors."

Researchers have already developed compounds that target some of the activated gene expression pathways that the Duke team discovered, and many of these compounds have promise for combating young women's tumors, Blackwell says. "Many of the gene sets we saw in 'younger' tumors distinguished these cancers from 'older' tumors, but the reverse was not true—there was nothing we saw in the older women's tumors that set them apart genomically. Identifying these distinguishing characteristics may be the first step in developing more effective treatments for these younger patients."



Obesity blurs PSA interpretation

STUDIES LED BY DUKE Prostate Center researchers warn that doctors may be missing early prostate cancers in obese men. "Obese men have more blood circulating throughout their bodies than normal-weight men," says Duke urologist Stephen Freedland, MD. "As a result, the concentration of prostate-specific antigen, or PSA, in the blood—the gold standard for detecting prostate cancer—can become diluted."

Stephen Freedland

In a study published in the November 21, 2007 *JAMA*, researchers compared the medical records of almost 14,000 patients who had undergone radical prostatectomy surgery for the treatment of prostate cancer between 1988 and 2006 at Johns Hopkins, Duke, or one of five Veterans Affairs hospitals making up the Shared Equal Access Regional Cancer Hospital (SEARCH) cohort. They analyzed the relationship between body mass index and PSA concentration levels, finding that a higher body mass index directly correlated with higher blood volume and lower PSA concentrations. Lead author Lionel Bañez, MD, says that men in the most obese group had PSA concentrations that were 11 to 21 percent lower than those of normal-weight men.

Freedland led a subsequent study, published this August in the journal *BJU International*, which showed that obese men whose prostate cancers were detected by PSA testing had more than twice the risk of cancer recurrence after surgery than their normal-weight counterparts. This compared to essentially no increased risk among obese men who were diagnosed early in the "PSA era"—when PSA was not used as frequently—or among men whose diagnosis followed abnormal rectal examinations. Freedland hypothesized that the lower PSA values among obese men led to delay in diagnosis, resulting in more aggressive disease at diagnosis. Researchers hope that these data will be a catalyst to encourage alternate screening methods—or a lower threshold for worrisome PSA levels—in obese men.

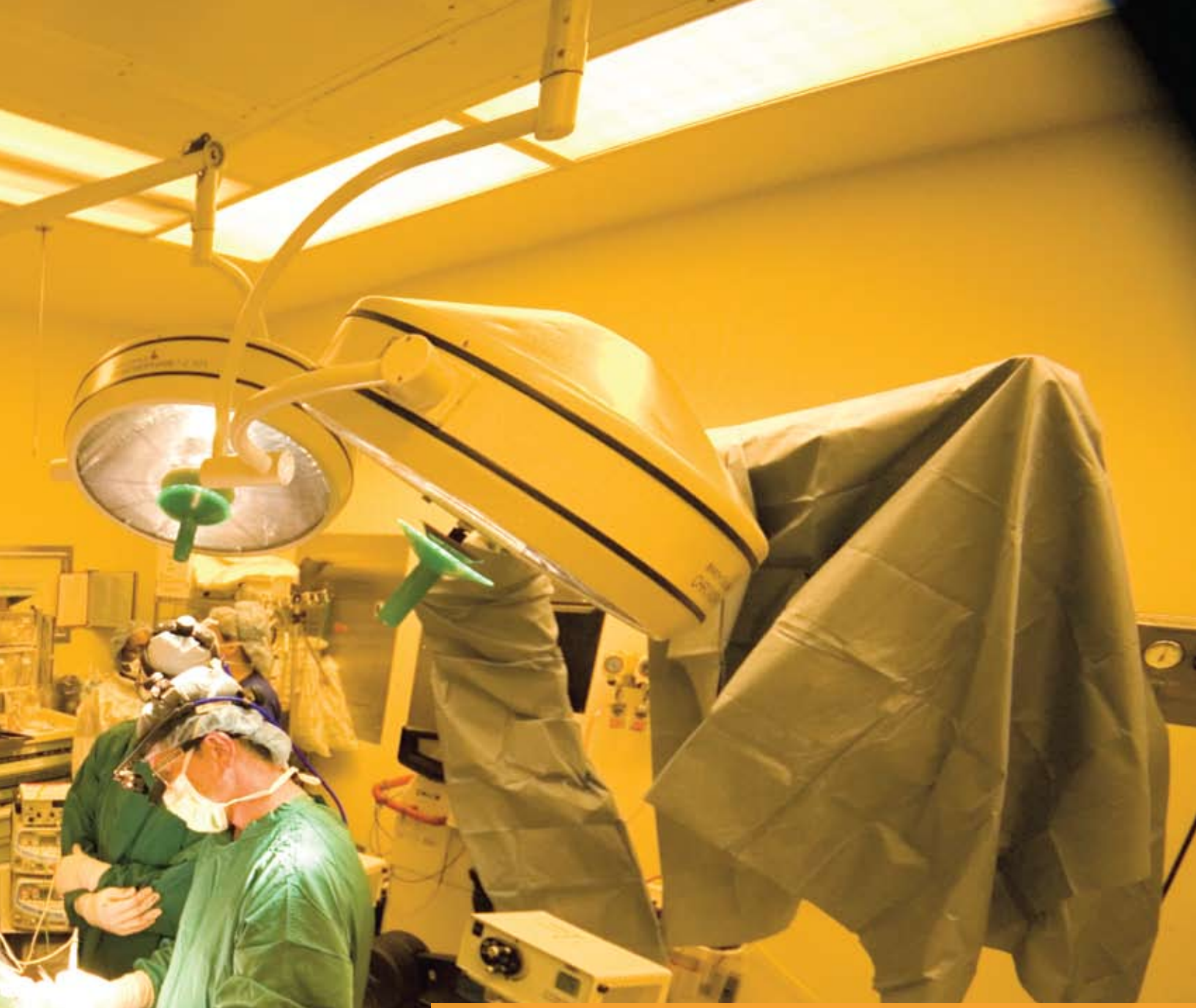
Potential blood test for lung cancer

A TEST FOR FOUR BLOOD PROTEINS may provide a less-invasive follow-up for patients who have suspicious lesions on chest radiographs or computerized tomography (CT) scans, according to a Duke study published in the December 10, 2007 *Journal of Clinical Oncology*.

"CT scans have a very high false positive rate when trying to discover lung cancer," says lead investigator Edward Patz Jr., MD, a Duke radiologist, so patients often must undergo invasive procedures like biopsy to confirm the results. "This study is the first step in developing a test that would allow us to sample a patient's blood and determine whether more invasive testing and treatment are necessary."

Using the four blood protein markers, known as CEA, RBP, SCC, and AAT, researchers were able to distinguish which patients had cancer with over 80 percent accuracy, Patz says. They will next perform a larger study, with the ultimate goal of developing a screening system by which patients could have the blood test before imaging. Those found to be at high risk would have a CT scan for further evaluation.


Mind
Over Matter



Neurosurgeon John Sampson is among the pioneers working on a vaccine that harnesses the body's immune system to fight deadly brain tumors, offering hope where there was none.

by Bridget Booher
photography by Chris Hildreth

Adapted from an article that first appeared in the July-August 2008 issue of *Duke Magazine*, which can be found online at **dukemagazine.duke.edu**. Reprinted with permission.

<< Going In: Sampson performs a craniotomy on a patient who's awake, to avoid damaging nerve and speech centers.

On the third floor of Duke North in Operating Room 4, neurosurgeon John Sampson is using what looks like a blunt, two-pronged fork to probe sections of a patient's exposed brain. Weeks earlier, an MRI had revealed a shadow near the front of the man's skull, an ominous intruder whose appearance on the black-and-white scan resembled a satellite view of an advancing hurricane. Sampson suspects a high-grade tumor, possibly a glioblastoma multiforme—the most common and deadliest form of brain cancer.

The tumor had been growing stealthily in the patient's head until, one day in April, the sixty-eight-year-old man sat down, exhausted, and could not get up. A flurry of medical tests and phone calls later, he is now at Duke Medical Center, in the hands of one of the top brain tumor surgeons in the world.

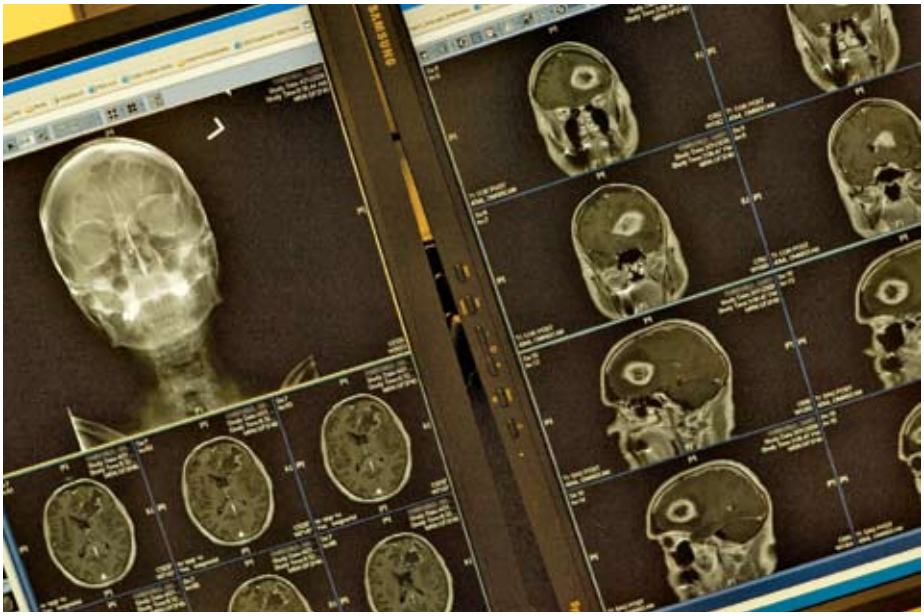
Because the growth is pushing against the left frontal lobe in an area that controls speech and facial expressions, Sampson is performing a craniotomy while the patient is awake, slowly and methodically cutting his way deeper and deeper into the brain. Throughout the three-hour operation, Sampson will rely on the patient's responses to cues to help guide catheters, aspirators, and three-dimensional imaging tools to target the spot where the burrowing tumor resides.

Under the layers and layers of surgical drapes that cover the patient, nurse practitioner Denise Lally-Goss huddles close to the man's face, talking gently. To the rest of the OR team, the voices are muffled, barely discernible. She holds up flash cards and prompts the man to identify what images are pictured.

"This is a…" says Lally-Goss.

"Frog," the man says.

"This is a…"



Malignant intruder: MRI reveals a stealthily growing tumor.

"Comb."

Through a hole in the patient's skull roughly the size of a computer mouse, Sampson and his surgical assistant are mapping out safe entry points through the brain's dura mater to get to the interior of the delicate frontal lobe. It's as if Sampson is in a house he knows like the back of his hand, but it's night, and all the electricity has gone off. The man's responses are like a dime-store flashlight, pointing Sampson toward safe passage, or warning him away from danger.

Then the patient starts missing cards.

"Two out of five," Lally-Goss calls out to Sampson.

And then, "Okay, he missed all five."

"Get him to count to ten," says Sampson.

No response.

Like a thunderclap, Sampson bellows the patient's name, commanding all the energy and attention in the beeping, humming operating room. **"We need you to be loud. Tell me what's on the cards. This is a…"**

"Chair!" exclaims the man, correctly.

"This is a…"

"Rabbit!"

"This is a…"

"Fork!"

Back on track. Sampson gently chides Lally-Goss. "Denise, this is no time to be using your indoor voice. I need you to really get in his face and keep him focused."

Two hours into the operation, Sampson has isolated the tumor, a white spongy contrast to the vibrant deep pink of its host. After the meticulous precision used to cut around the cancerous area, its removal is surprisingly quick. A section of the golf-ball-sized growth is whisked to the lab for analysis. Sampson and his colleagues use an ultrasound wand to scan the brain for residual tumor, then begin the process of closing up the groggy patient's head.

The initial lab analysis indicates what later tests confirm: a grade IV glioblastoma multiforme, a highly malignant, fast-growing cancer for which there is no cure. Most recur within six months. The vast majority of patients are dead within eighteen months.

Every year, between 10,000 and 20,000 people in the United States are diagnosed with glioblastoma multiforme (GBM) tumors. No one knows what causes them. They are primary tumors, meaning that they begin in the brain rather than metastasizing from somewhere else in

the body. GBMs are insidious. They send tentacles into the brain, becoming inextricably wrapped around healthy tissue; even though neurosurgeons can remove what appears to be the bulk of the tumor, virulent cancer cells are invariably left behind. The usual course of treatment is removal (when possible), followed by radiation and chemotherapy. This standard of care has not changed significantly in nearly fifty years.

A native of Canada, John Sampson was recruited straight out of medical school at the University of Manitoba to join Duke Medical Center's neurosurgery residency program in 1990, and he's been here ever since. He sometimes tells people that he briefly considered becoming a general practitioner because he liked the idea of forging lifelong relationships with patients. But it's hard to imagine Sampson, or any of his colleagues at the Preston Robert Tisch Brain Tumor Center, for that matter, content with performing routine physicals and annual check-ups. Brain surgeons tend to be mavericks, tireless and intensely driven, offering patients the promise of hope when other doctors have exhausted all options.

Early in his residency, Sampson knew that mastering complex surgical challenges wouldn't satisfy him over the long haul. Performing delicate brain surgery was one thing, but understanding the pathology of brain tumors—and perhaps unlocking the mystery of what causes them in order to better treat them—was quite another. He took three years out of his residency to work alongside Darell Bigner M.D. '65, Ph.D. '72, an internationally known expert on brain tumors, earning a Ph.D. in tumor immunology and learning how to design and conduct clinical trials.

Since then, Sampson and his colleagues at the brain tumor clinic have helped pioneer the use of immunotherapy—he calls it "the holy grail of therapy"—which uses the body's immune system to fight cancers like GBM. "Chemotherapy and radiation are systemic rather than specific," Sampson says, "so they kill the good cells along with the bad cells. But immunotherapy is very specific. It targets only the tumor cell, and leaves healthy cells untouched."

Through painstaking trial and error, Sampson and fellow researchers developed a vaccine that slowed the reappearance of GBM-specific tumor cells in mice. By 2001, he had received National Institutes of Health funding and approvals to conduct clinical trials in humans. There were no guarantees that it would work; patients who agreed to enter the trials knew that it was risky, unproven. It could be ineffective. It could make the tumor come back even stronger. Or maybe, just maybe, it could buy them more time.

Two days after the craniotomy in Operating Room 4, Cam and Peggy Mitchell fly in to Raleigh-Durham International Airport for their monthly trip to Duke Medical Center. The two have known each other since childhood; her sister sat behind Cam in first grade. Cam was diagnosed in 2004 with a grade IV GBM. His doctor in Grand Rapids, Michigan, gave Mitchell a pamphlet about GBM and told him, "Sorry, there's nothing we can do."

Mitchell's oncologist, though, knew about the research being conducted at Duke. He made a few calls. On a Saturday morning, about a week after his

Tools for survival

Duke neuro-oncologist Henry Friedman, MD, says clinical innovation is the reason why survival time for Duke brain tumor patients is steadily growing. "Sixty-six percent of our adult patients and 75 percent of our pediatric patients are enrolled in clinical trials where they can try the newest therapies," he says. "Nationally, fewer than 5 percent of adult brain tumor patients are enrolled in trials."

In addition, Friedman says, the Preston Robert Tisch Brain Tumor Center does what few other centers do: prescribe drugs that have been approved by the FDA for other cancers. For example, 35 patients whose tumors had returned after initial standard treatment were part of a pilot project that administered irinotecan, a standard chemotherapeutic agent, in combination with bevacizumab (U.S. trade name Avastin). Almost half saw no tumor progression after six months, and almost 80 percent were still alive six months after diagnosis—a significant increase from the typical 50 percent six-month survival after GBM recurs.

"We speculate that bevacizumab and irinotecan each attack a particular characteristic of the tumor independently or they work together, with the bevacizumab suppressing the growth of blood vessels, which makes the tumor more susceptible to the chemotherapy," says Duke neuro-oncologist James Vredenburgh, MD, who led the study. "Further studies will tease out the exact mechanism of the therapy's success and we also hope to study the effectiveness of this treatment in patients with newly diagnosed GBM."

—DUKE MEDICINE NEWS

Henry Friedman

James Vredenburgh

The future of the CDX-110 vaccine

From initial success in the lab to promising results in patients, new medicines and therapies have to clear many hurdles before they can be disseminated to the general public. CDX-110, the brain tumor vaccine developed by Duke neurosurgeon John Sampson and manufactured by AVANT Immunotherapeutics, is well on its way to becoming part of the new treatment regimen available to oncologists.

This year, Pfizer, in conjunction with AVANT, is launching a multisite Phase II/III study to determine whether CDX-110 should become the new standard of care for patients diagnosed with glioblastoma multiforme (GBM) tumors. More than twenty brain tumor centers across the country are participating in the randomized study.

GBM has long been considered an "orphan disease," a designation for conditions that affect fewer than 200,000 people. People diagnosed with orphan diseases often find that therapies to treat their conditions are scarce, owing to the huge financial commitments that underlie research and development. But because CDX-110 targets a mutant protein found in a host of other cancers, the pharmaceutical industry has taken an interest in its development.

"To go to a Phase III trial takes hundreds of millions of dollars these days," says Sampson. "Typically that requires having a huge venture capitalist or big pharma getting involved. In this case, big pharma is getting involved." If the CDX-110 trials go well, he says, Pfizer Inc., one of the world's largest pharmaceutical companies, will conduct the final round of testing before applying for FDA approval to market the drug. In mid-April, Pfizer paid AVANT $40 million and promised a $10 million equity stake for the worldwide rights to the vaccine.

Since the vaccine is only effective in treating tumors with a particular mutation, it won't ever be a cure-all for people diagnosed with GBM. Still, it's more promising than anything else on the market. (Temozolomide, the most recent chemotherapy drug used to target brain tumors, only extends survival rates a couple of months, on average.) Given the slow pace of getting drugs tested and approved for use in the general population, though, the vast majority of people currently diagnosed with GBM will be dead before CDX-110 receives final market approval.

—BRIDGET BOOHER

To learn more about this and other clinical trials at the Preston Robert Tisch Brain Tumor Center, call 919-684-5301.

diagnosis, Mitchell's phone rang. It was John Sampson, calling from his home. Mitchell could hear Sampson's two young sons playing in the background. Sampson explained that he was starting to enroll human subjects in an experimental clinical trial.

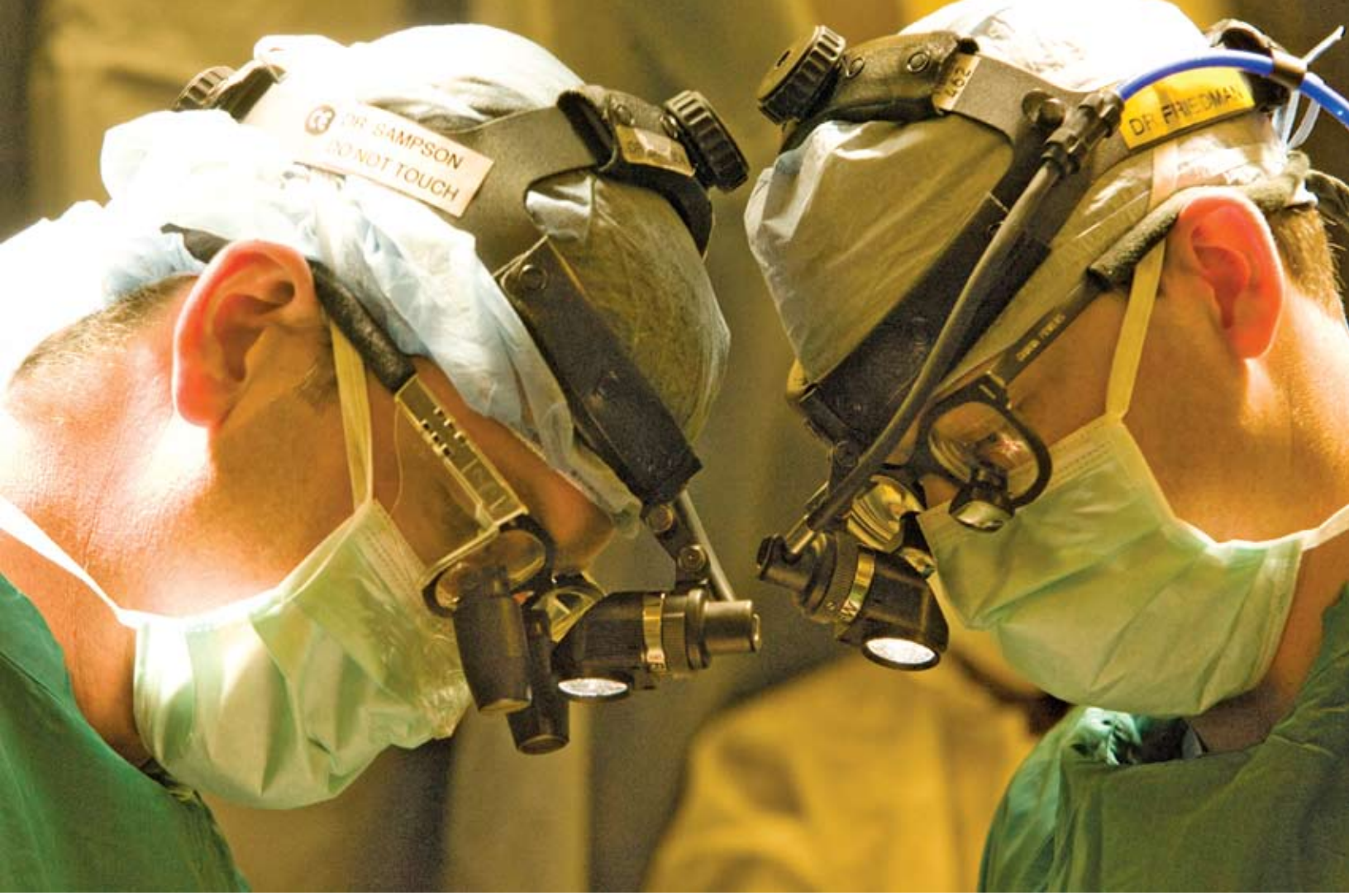
Was Mitchell interested?

"When you're first given the news that you have a stage-four brain tumor, you really don't expect to survive," says Mitchell. Faced with the prospect of certain rapid decline or the slim hope that he might live a few months longer to see his beloved brood of nieces and nephews pass the next birthday or kindergarten graduation, Mitchell didn't hesitate. "People have told me that they would never want to be a guinea pig, but I don't see it that way. I thought, Hey, I've got to be willing to try something leading-edge. Someone has to be willing, and I'm going to be that person."

Sampson and his colleagues at the brain tumor clinic have helped pioneer the use of immunotherapy—he calls it "the holy grail of therapy"—which uses the body's immune system to fight cancers like GBM.

In June of 2004, the Mitchells and nearly twenty members of their extended family traveled to Duke to support Cam as he underwent a series of tests to determine whether he qualified for the trial. Trial parameters included, among other factors, how recently the tumor was diagnosed and removed, its size, and whether it contained a specific protein, found on fewer than half of GBMs, that the vaccine was designed to target. When the tests came back confirming that he was a good candidate, "I felt as though I'd been given a lifeline," he says.

Four years later, the Mitchells have come to consider Duke a second home. They've negotiated medical discounts with airlines and hotels, can tell you which food station in the hospital cafeteria makes the healthiest



John Sampson operates alongside neurosurgeon Alan Friedman. Surgeons and oncologists at the brain tumor center are treating more than 2,000 patients from around the world, including the much-publicized surgery on Senator Edward Kennedy.

turkey sandwiches, and know that the local Nordstrom can hem a pair of pants in one business day. And they are on a first-name basis with the dozens of physicians, nurses, and support staff members who oversee Cam's health.

On this particular spring trip, Mitchell receives his forty-eighth dose of vaccine. He's brought a CD containing scans of his latest MRI, conducted bimonthly in Grand Rapids, for Sampson to examine for signs that the tumor has started to grow again. Waiting for the results is agonizing. "My mind starts to begin this circle of thought," says Mitchell. "What if I have a recurrence? What if the test is inconclusive? What if the radiologist misses something? Everything related to my treatment is so new that there are no 'norms' to rely on."

Later that afternoon, Mitchell gets the good news that the tumor has not returned. Not this month. Not today. It's a small, temporary reprieve between the exhilaration and dread that have become, in Peggy's words, "the new normal."

Cancer occurs when cells mutate. In some, but not all, GBMs, these mutations take place on the epidermal growth factor receptor (EGFR) of the tumor's surface cells. The mutation, known as EGFRvIII, was discovered by Duke's Darell Bigner and his cancer-research colleagues at the Johns Hopkins University who conduct GBM research. EGFRvIII has also been implicated in a range of other cancers, including breast, ovarian, metastatic prostate, colorectal, and head and neck cancers.

The brain tumor vaccine, which consists of a slightly modified portion of EGFRvIII, triggers the immune system into attacking just those cancer cells. Called CDX-110 and manufactured by AVANT Immunotherapeutics, the vaccine was developed by Sampson and Amy Heimberger, who completed her internship and residency at Duke. She is now an associate professor at the University of Texas' M.D. Anderson Cancer Center and the lead investigator for a concurrent brain tumor vaccine

"The vaccine works with exquisite specificity," says Sampson (above). "It's like a silver bullet."

trial at Texas. "The vaccine works with exquisite specificity," says Sampson. "It's like a silver bullet."

Before enrolling in the clinical trial, and on subsequent visits to Duke, patients must undergo a series of tests to make sure the tumor hasn't started growing back. For the first two months, the vaccine is administered every two weeks, and then monthly as long as there are no signs of recurrence. The only side effects are slight swelling or redness near the injection site.

Because of the virulent nature of GBMs, physicians are accustomed to seeing them recur within months. In the clinical trials, Sampson says, the average recurrence is pushed out to nearly two years. Even more remarkable, "We now have patients who are three and four years out with no recurrence," he says.

When the trials started in 2004, patients received the vaccine alone. More recently, Sampson wanted to know what might happen if the vaccine was used in conjunction with temozolomide, the standard chemotherapy drug given to brain tumor patients. "The problem with temozolomide is that, like any chemotherapy, it kills off cells indiscriminately," says Sampson. "Our hypothesis was that using the temozolomide would kill so many white blood cells that it would essentially cancel out the benefit of the vaccine." As it turned out, using temozolomide enhanced the immune system tremendously, and in fact, the higher the dose, the better the body's overall immune response.

"We're now seeing patients who not only achieve very high immune responses over time, but whose immune responses just get stronger and stronger and stronger—to the point where we're seeing [immune] levels not typically seen with any vaccine," says Sampson. "It's unusual in nature that an immune response gets stronger and stronger. But that has been the case with this therapy."

So far, over 70 percent of patients who have enrolled in the vaccine trials at Duke are alive after two years, and over 50 percent are alive after four years.

Ryan DeGrand is among the fortunate 50 percent. A self-described Type-A personality, he ran 5K races in and around his hometown of St. Louis and routinely worked fifteen-hour days as the vice president of ProAm Golf, a golf equipment company founded by his father in 1975.

In 2004, at the age of thirty-two, he developed crushing headaches that didn't respond to over-the-counter medicine. Finally, unable to stand the pain, DeGrand went to a local emergency room, where a CT scan revealed a baseball-sized tumor—a GBM. With a four-year-old son and a newborn daughter at home, he and his wife, Kathryn, were suddenly faced with the unthinkable.

"I played sports all my life. I never smoked. I eat well and work out at least twice a week, so there was no way in my mind that I could get cancer," says DeGrand. With the same drive he brought to other areas of his life, DeGrand refused to believe the doctors who told him there was nothing that could be done. "I remember walking to my car that day and thinking, those are the most negative guys I've never met, and I'm not going to listen to them." DeGrand researched his options, and quickly honed in on the trials at Anderson Cancer Center and Duke. He flew to Durham to meet with Sampson and see whether he qualified for the clinical trials. He did, and in August of 2004, he began getting the vaccine.

"What I like about the vaccine is that it's making my body stronger," says DeGrand. "It's boosting my immune system and making it healthier, as opposed to chemo, which weakens your whole system. It's also why I like Duke; instead of being on the defensive and waiting to treat the next bad thing that happens, they are always looking at ways to improve the treatment and make it even better."

DeGrand, like Mitchell, is often asked how much longer he plans to come back to Duke. "Why would I stop?" he says. "As long as my immune system keeps getting stronger and the tumor doesn't come

back, I'll keep getting the vaccine. I hope I'm still coming back here in twenty-five or thirty years."

Still, DeGrand acknowledges that he and his wife can't allow themselves to imagine what their lives will be like a year from now, much less a couple of decades hence. "I really try to take one day at a time," he says. "If I start to forecast things that might happen six or eight months from now, I can fool myself into thinking that I'm beating the deal. We talk hypothetically about taking a trip with the kids at Christmas. But realistically, we can't start making those plans until September or October."

In late April, ABC News' *World News Tonight* aired a short segment on DeGrand and his treatment at Duke. In the days that followed, Sampson's office was deluged with hundreds of e-mail messages and phone calls from people all over the world who had seen or heard about the vaccine. Could they, or a loved one, get in?

Nurse practitioner Lally-Goss and a clinical trials coordinator triaged the calls, responding to every single one within forty-eight hours. Most patients did not qualify for the vaccine. For Sampson and others on the front line of treating people with GBMs, fielding desperate queries from people who have no other hope further galvanizes them in their quest to stop this deadly disease.

"This is not a cure," says Sampson. "But it's one really good step in that direction." □

A few weeks after the craniotomy described in the lead of this article, the patient's tumor recurred, making him ineligible for clinical trials. He will continue to receive the standard treatment of radiation and chemotherapy.

Bridget Booher is a senior writer for *Duke Magazine*.

Other cancer research highlights

MORE GBM IMMUNOTHERAPY: Duke researcher Duane Mitchell, MD, PhD, is leading an investigation of human cytomegalovirus (CMV) as a target for immunotherapy in GBM patients. More than 80 percent of patients newly diagnosed with GBM exhibit detectable CMV in their blood, as well as in their tumors. Preliminary results from a 13-person trial show that a vaccine that targets the virus appears to have delayed the re-growth of tumors from a typical six to seven months after surgery to more than 12 months.

GASTROINTESTINAL CANCERS: In a study of 15 patients undergoing vaccine treatment for gastrointestinal cancers, Duke oncologist Michael Morse, MD, and colleagues have shown that chemotherapy given in conjunction with the vaccine may boost the immune system's response, allowing it to effectively fight the malignant cancer cells.

MELANOMA: Disabling a protein frequently found on the surface of melanoma cells may make the cancer more vulnerable to chemotherapy, according to a pilot study led by Duke surgeon Douglas Tyler, MD. The findings were presented in June at the American Society of Clinical Oncology annual meeting.

PREVENTING BLOOD CLOTS: An international panel of researchers led by Duke oncologist Gary H. Lyman, MD, has developed evidence-based guidelines for the prevention and treatment of venous thromboembolism (VTE) in cancer patients. VTE affects 4 to 20 percent of cancer patients, and it is one of the leading causes of death in this population. The guidelines were published in the December 1, 2007 *Journal of Clinical Oncology*.

RADIOSURGERY: This spring Duke became the first medical center to use the Novalis Tx system, which destroys tissue by focusing high-energy, precisely shaped beams of radiation from multiple directions. The system allows the physician to target a tumor precisely and minimize damage to healthy surrounding tissue. Treatment takes approximately one hour—as opposed to six hours for preparation and treatment with prior radiosurgery processes. Patients are fitted with a custom mask, which reduces the anxiety of the halo brace that was previously used. John Kirkpatrick, MD, PhD, who is clinical director of radiation oncology at Duke, says that "with this system we can safely, accurately, and efficiently deliver high-dose radiation, while minimizing the side effects of radiation therapy for our patients."

—DUKE MEDICINE NEWS


Michael Morse


Douglas Tyler


Gary Lyman


John Kirkpatrick

Rewriting the textbooks

MURDOCK study will reclassify health and disease—genomically.

DUKE RESEARCHERS ARE NOW PURSUING the first phase of what they call a "Framingham study for the molecular age"—an ambitious study of thousands of patients and their families over time, linking genetic data to disease risk and treatment outcomes. The study will establish an understanding of how disease occurs at the molecular level, and how it varies from one person to the next.

The MURDOCK study (Measurement to Understand the Reclassification of Disease of Cabarrus and Kannapolis) has been made possible by a $35-million gift, and is now under way at the North Carolina Research Campus (NCRC) in Kannapolis, North Carolina, 30 miles northeast of Charlotte. Much like the Framingham, Massachusetts, heart study—which has contributed much of what we know about heart disease today through its tracking of entire families since 1948—MURDOCK will enroll study volunteers from the local community for long-term collection of blood samples and other clinical data. It will also make use of Duke's collection of clinical databases and biospecimen repositories, among the largest such collections in the world. According to its objectives, the study will generate "exquisitely detailed data on individual patients that will engage the best minds in biomedical informatics and biostatistics to detect subtleties in disease that may have profound implications for prevention and management."

"We aspire to be able to give advice to individuals about how to stay healthy and optimally treat illness when it occurs. By combining this information across entire counties using electronic health records, we believe we can provide much better prevention programs for the diseases that are causing death and disability in our society and beyond."

The study's first phase began by aggregating existing clinical data and generating associated molecular data using biological samples from subjects with cardiovascular disease, liver disease, osteoarthritis, and obesity. Genomic linkages and differences found within and across these samples will initiate disease reclassification by identifying patterns and characteristics that may predict risk or response to therapy. Community volunteers will participate in prospective studies that will help validate these findings, which are also expected to reveal underlying mechanisms that may open potential for new treatment strategies.

"We aspire to be able to give advice to individuals about how to stay healthy and optimally treat illness when it occurs," says Robert Califf, MD, director of the Duke Translational Medicine Institute and lead investigator in the MURDOCK study. "By combining this information across entire counties using electronic health records, we believe we can provide much better prevention programs for the diseases that are causing death and disability in our society and beyond."

Home, sweet medical home

Duke is helping to mold a new model of care that's gaining traction nationwide.

A PROJECTED LONGER LIFESPAN is great news for the 79 million baby boomers—the oldest of whom turn 62 this year. But the country already is struggling to care for our graying population, prone to multiple chronic illnesses, and there's no end in sight to the shortage of generalist physicians and geriatric specialists. Total health care spending in the United States is projected to hit $4.2 trillion annually by 2016.

Duke and the Association of American Medical Colleges (AAMC) believe they've found a treatment and are advocating a new model of care called the "medical home," which shifts care from today's traditional medical practice-centered model to team-based coordinated care. Much of that care is delivered in-home to the elderly and frail by mid-level providers in an effort to preempt the likelihood of costly emergency room visits and hospital stays.

In March, the AAMC published a white paper on medical homes and began encouraging its more than 300 member academic medical centers and 250,000 member teaching physicians, medical students, and physician trainees to embrace the medical home model. The AAMC will promote the medical home concept to policymakers, insurance companies, and other health organizations as opportunities arise.

Lloyd Michener, MD, chair of Duke's Department of Community and Family Medicine, who contributed to the AAMC white paper and gave a plenary speech on the topic at the AAMC Physician Workforce Conference, says a fundamental flaw in the current health care system is that it requires everyone—and especially the most ill and immobile—to travel to the doctor's office for even the simplest of visits. As a result, many people do not regularly see their doctors and health problems escalate.

"The medical home concept recognizes the critical role of physicians in health care, but also that we are not always the best or only answer to our patients' problems," Michener says.

"We can't ask doctors to do everything," adds Susan Yaggy, chief of the Division of Community Health at Duke. "We can help by building a team around the patient rather than the physician's practice."

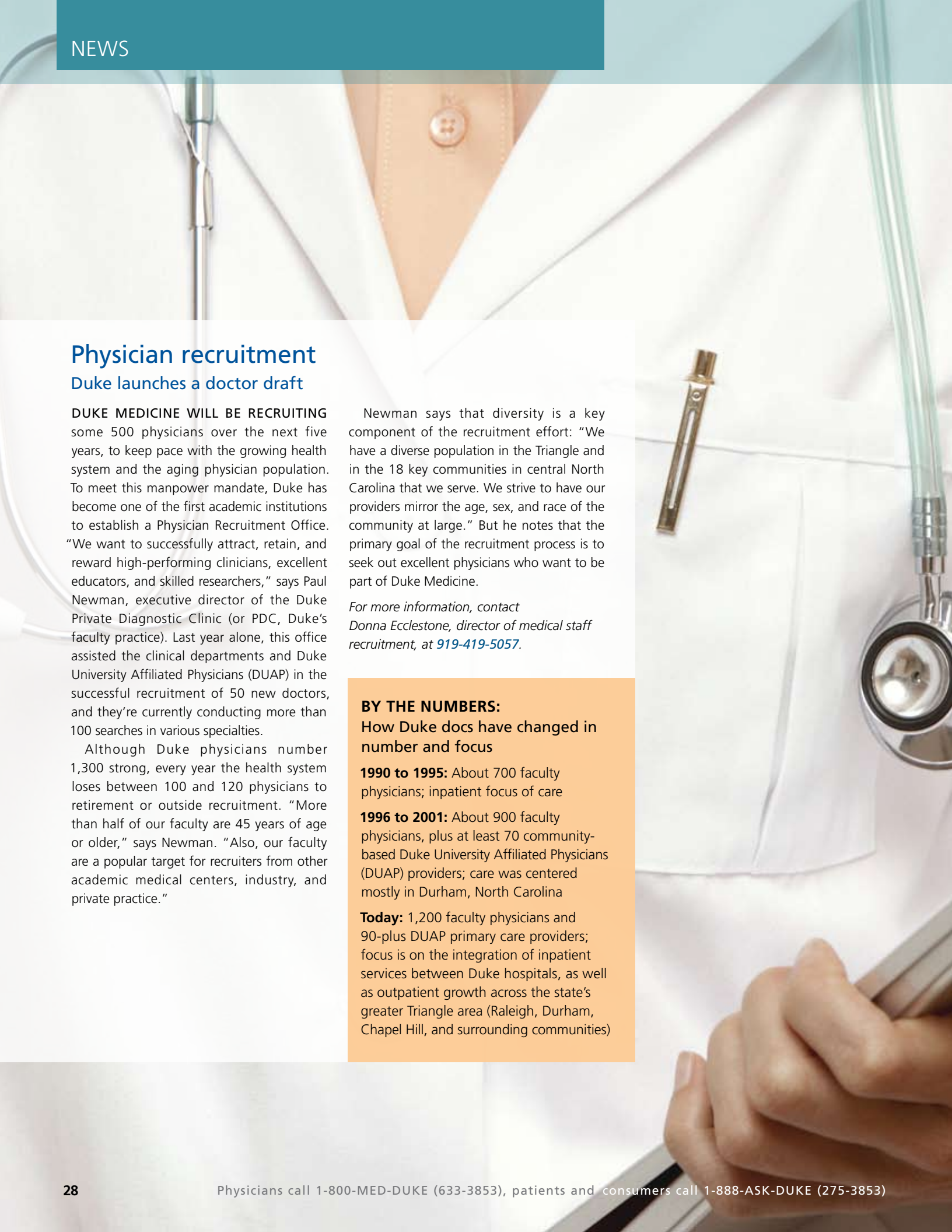
Duke has championed the medical home concept for more than a decade, through its nearly two dozen community health and education outreach programs and the recent retooling of its Family Medicine Residency Program to stress the role of family physician as team leader. Duke also has provided valuable research and outcome results to the study of this new model of care.

For example, in "Just for Us," a medical home program at Duke which serves 300 Medicaid-enrolled, home-bound elderly residents of Durham, North Carolina, there was a 68 percent decrease in hospitalizations, a 49 percent drop in ambulance transport, and a 41 percent drop in emergency room visits for patients enrolled in the program for two years. Other Duke programs are seeing similar results.

Lloyd Michener

Susan Yaggy

Duke is helping to train practicing physicians and other health professionals in the medical home model through the Duke Health Leadership Program (healthleadership.duhs.duke.edu), and a new online training program for certified nursing assistants is also available. To learn more about medical homes, visit medicalhomes.duhs.duke.edu.



Physician recruitment

Duke launches a doctor draft

DUKE MEDICINE WILL BE RECRUITING some 500 physicians over the next five years, to keep pace with the growing health system and the aging physician population. To meet this manpower mandate, Duke has become one of the first academic institutions to establish a Physician Recruitment Office. "We want to successfully attract, retain, and reward high-performing clinicians, excellent educators, and skilled researchers," says Paul Newman, executive director of the Duke Private Diagnostic Clinic (or PDC, Duke's faculty practice). Last year alone, this office assisted the clinical departments and Duke University Affiliated Physicians (DUAP) in the successful recruitment of 50 new doctors, and they're currently conducting more than 100 searches in various specialties.

Although Duke physicians number 1,300 strong, every year the health system loses between 100 and 120 physicians to retirement or outside recruitment. "More than half of our faculty are 45 years of age or older," says Newman. "Also, our faculty are a popular target for recruiters from other academic medical centers, industry, and private practice."

Newman says that diversity is a key component of the recruitment effort: "We have a diverse population in the Triangle and in the 18 key communities in central North Carolina that we serve. We strive to have our providers mirror the age, sex, and race of the community at large." But he notes that the primary goal of the recruitment process is to seek out excellent physicians who want to be part of Duke Medicine.

For more information, contact Donna Ecclestone, director of medical staff recruitment, at 919-419-5057.

BY THE NUMBERS:
How Duke docs have changed in number and focus

1990 to 1995: About 700 faculty physicians; inpatient focus of care

1996 to 2001: About 900 faculty physicians, plus at least 70 community-based Duke University Affiliated Physicians (DUAP) providers; care was centered mostly in Durham, North Carolina

Today: 1,200 faculty physicians and 90-plus DUAP primary care providers; focus is on the integration of inpatient services between Duke hospitals, as well as outpatient growth across the state's greater Triangle area (Raleigh, Durham, Chapel Hill, and surrounding communities)

CONTINUING MEDICAL EDUCATION AT DUKE

For more information or to register for the courses listed below, please contact the Duke Office of Continuing Medical Education at **919-401-1200** or visit **cme.mc.duke.edu**.

ON SITE

COURSE	DATE	LOCATION	CREDIT
ANESTHESIOLOGY			
Anesthesia Camp V	October 2–4, 2008	Montage Resort & Spa, Laguna Beach, CA	17 credits
Preceptorship in Intraoperative Transesophageal Echocardiography	2008: October 13–15, November 3–5, December 1–3 2009: January 26–28, February 23–25, March 16–18, April 6–8, May 4–6, June 22–24	Duke University Medical Center Durham, NC	27 credits
5th Annual Ultrasound for Every Anesthesiologist	October 17, 2008	Rosen Shingle Creek, Orlando, FL	8 credits
Anesthesia Camp 2008	October 29–November 1, 2008	Four Seasons Resort Lana'i, Lana'i, HI	22 credits
Anesthesia Camp II	January 28–31, 2009	Ritz Carlton, St. Thomas St. Thomas, US Virgin Islands	22 credits
ONCOLOGY			
9th Annual Hampton Roads Oncology Education Conference Addressing Novel Therapies in Oncology and Hematology	October 25, 2008	Hilton Virginia Beach Oceanfront Virginia Beach, VA	6 credits
Perspectives in Lung Cancer	January 30–31, 2009	Charleston, SC	8.75 credits
INTERDISCIPLINARY			
3rd Annual Pain Symposium for Non-Pain Specialists	November 1, 2008	Durham, NC	6.5 credits
4th Annual Patient Safety and Quality Conference	December 12, 2008	Marriott Durham at the Civic Center Durham, NC	6 credits
PEDIATRICS			
8th Annual Optimizing Mechanical Ventilation for Infants and Children	October 21–23, 2008	Washington Duke Inn & Golf Club Durham, NC	16.75 credits
35th Annual Postgraduate Course: The Alexander Spock Symposium, Urgent Issues in Outpatient Pediatrics	November 1–2, 2008	Searle Conference Center Durham, NC	10.5 credits
RADIOLOGY			
Musculoskeletal MRI & Neuroimaging Update	October 18–21, 2008	Grove Park Inn Resort & Spa Asheville, NC	20 credits
9th Annual Abdominal Imaging Fellows Symposium	October 18–19, 2008	Duke University Medical Center Durham, NC	8.75 credits
Update on Cardiopulmonary & Abdominal Imaging	November 8–11, 2008	Disney Yacht & Beach Club Resorts Orlando, FL	20 credits
Musculoskeletal MRI & Abdominal Imaging Update	January 17–20, 2009	Atlantis, Paradise Island, Bahamas	18 credits
A Practical Approach to Musculoskeletal MRI	February 14–17, 2009	Disney Grand Floridian Resort & Spa Orlando, FL	19 credits
Breast Imaging and Interventions 2009	March 20–22, 2009	Westin Buckhead Atlanta, Atlanta, GA	18.5 credits
A Practical Approach to Musculoskeletal MRI	April 25–28, 2009	Washington, DC	19 credits
Breast Imaging and Interventions 2009	June 15–18, 2009	Kiawah Island, SC	18.5 credits
SURGERY			
What's New in Venous Disease 2008	December 12–13, 2008	Washington Duke Inn & Golf Club Durham, NC	14 credits
UROLOGY			
Duke Tuesday in Urology	November 4, 2008	Searle Conference Center, Durham, NC	5 credits

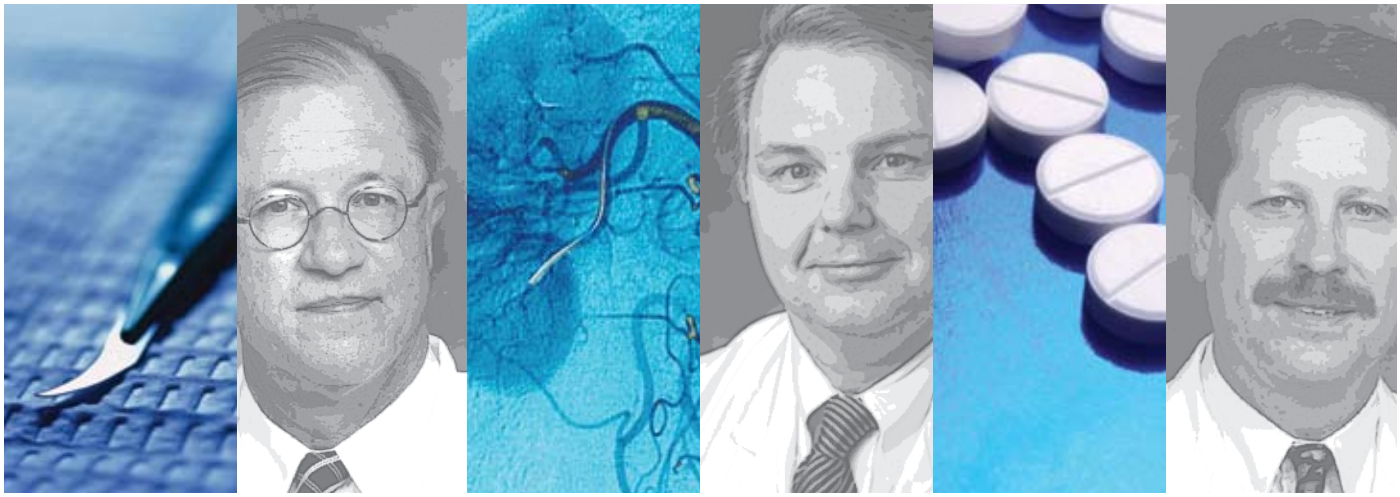
ONLINE

COURSE	DATE	CREDIT
Managing Adolescent Depression in Primary Care: Assessing the Benefits and Risks	Through September 23, 2008	1 credit
Advances in the Treatment of Metastatic Breast Cancer: Emerging Role of Novel Taxanes	Through December 6, 2008	1 credit
The Silent Epidemic: Optimizing CHF Treatment for the African American Patient	Through December 30, 2008	1.5 credits
Insertion of Central Venous Catheters (CVC) Online Module	Through December 31, 2008	2.25 credits
New Insights into Curbing the MRSA Epidemic: Focus on Bacteremia and Endocarditis	Through December 31, 2008	1.5 credits
Skeletal and Hematological Pathology of Type I Gaucher Disease	Through December 31, 2008	1.5 credits
HIV Clinical Directions: Clinical Information for Physicians Treating HIV/AIDS, Issue III	Through February 28, 2009	1.5 credits
13th Annual Duke ACS Symposium Webcast: Evidence-Based Antithrombotic Therapy in ACS	Through March 27, 2009	1.75 credits
Silence Is Suicide: Frontline HIV/AIDS Treatment for African Americans	Through April 29, 2009	1.5 credits
Advances in Treating Renal Cell Carcinoma, Issue I	Through April 29, 2009	1.5 credits
Signposts and Pathways: Multidimensional Care for Patients with Type II Diabetes	Through July 30, 2009	3 credits

The Duke University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

These activities have been approved for *AMA PRA Category 1 Credits*.

DukeMedicine review 2008



"Let's have the courage to tell our patients the truth about what we know about each of these treatment strategies." —ROBERT CALIFF

Last fall Duke cardiothoracic surgeon **Peter Smith, MD**, interventional cardiologist **E. Magnus Ohman, MD**, and cardiologist **Robert Califf, MD**, went three rounds on the question of how best to manage multi-vessel coronary artery disease. Read on page 4 how these specialists debated the often-tricky choices between percutaneous interventions, bypass surgery, and medical management.

Mixed Sources
Product group from well-managed forests, controlled sources and recycled wood or fiber
www.fsc.org Cert no. BV-COC-080214
© 1996 Forest Stewardship Council
FSC 30%

This report is printed on Utopia Two XG, 80-lb text.
Environmental savings realized by using this paper are summarized below:
Lbs of paper used **46,000** | Trees saved **136** | Water saved in gallons **49,540** | Landfill waste reduced in lbs **8,197**
Greenhouse gas reduced in lbs of CO2 **49,557** | Energy consumption reduced in million BTUs **94**

Duke Medicine Review
DUMC 3687
Durham, NC 27710

201013001

Non-profit Org.
U.S. Postage
PAID
Durham, NC
Permit #60