

Becker, right, had an idea that ran counter to conventional psychiatric wisdom, and Drake, left, proved it works.

Strategy began small, is now a national model

Thirty years ago, psychiatrists advised their patients who had severe mental illnesses—like schizophrenia, major depression, or bipolar disorder—not to work.

“We were all taught in training that work is stressful, and we should try to help people decrease stress in their lives so that they can manage their illnesses,” says DMS psychiatrist Robert Drake, M.D., Ph.D. He’s singing a different tune these days. “It turns out that there are now numerous studies to show that not working is more stressful than working,” he says. “People do much better when we help them get into a job, particularly if it’s the right kind of a job.”

Drake coauthored a study, recently published in the *American Journal of Psychiatry*, that followed 1,273 people with severe mental illness at sites in Maine, Connecticut, Massachusetts, Maryland, South Carolina, Texas, and Arizona. The researchers found that those who received integrated psychiatric and vocational support, a model known as supported employment, were more than twice as likely to be competitively employed and almost one and a half times as likely to work at least 40 hours a month. Over a dozen

other studies, including ones that have followed patients for as long as 12 years, confirm that supported employment works.

Jobs: The story of how the mental-health system stumbled upon this successful strategy began in Lebanon, N.H., in the late 1980s. Drake credits Deborah Becker, M.Ed., who was then a vocational counselor at West Central Services, with the innovation. She managed to place people with mental illness in mainstream jobs when no one else could. In those days, people with mental illness, if they did work, did so under the supervision of mental-health professionals in sheltered settings with other mentally ill people, doing administrative, janitorial, or food service jobs. But few developed the confidence to make the transition to real-world jobs, even if they got vocational counseling. Unless the counselor was Deborah Becker.

Becker led her clients through an individualized process of matching their skills, interests, and experiences to suitable jobs. Then she coached them in job-hunting techniques; helped them review employment ads; talked to employers to find opportunities that might not be advertised; accompanied them

to interviews; even talked to employers on her clients’ behalf if they wanted her to.

She believed that her clients could thrive in standard workplaces, as long as vocational and psychiatric services were integrated, so clients could get appropriate counseling and support—sometimes even modification of their medication dosages.

Officials at New Hampshire’s Division of Mental Health became impressed with Becker’s results and “asked us to help them get more people into jobs,” says Drake, who has been director of the New Hampshire-Dartmouth Psychiatric Research Center since 1987. Drake’s research confirmed, he says, that Becker’s “approach . . . was better than any of the other approaches.”

Drake’s team may have merely recognized a good thing rather than actually originating it, but his group was the first to formalize and study supported employment. “Most people credit it with starting here,” says Drake. “To me, it’s just amazing that what started out as a little program in Lebanon is now used all over the world.”

Drake, DMS’s Andrew Thompson Professor of Psychiatry, and Becker, now a research assistant professor of community and family medicine, have been refining and testing the model ever since, as well as teaching others how to use it. They currently have funding from Johnson & Johnson for a demonstration project to help 10 other states develop supported-employment programs.

Real: In most areas without such programs, fewer than 10% of people with mental illness are employed. But with supported employment, “we’ve been able to get the rate up to more like 40% or so,” Drake explains. “When you put people in real job settings, they’re much more successful than any of us believed that they would be.

“They flower once they’re in a setting where they’re around everyday people who don’t have disabilities,” he says. That one thing “helps people change their self-image and move out of the dependent mental patient role.” **Laura Stephenson Carter**



Joseph Cravero, M.D., studied 10,552 pediatric sedation cases and found a near zero rate of severe injury; rates of minor problems were lower for anesthesiologists than for other specialists.

Race affects care at the hospital level

The conventional wisdom as to why black Americans have worse health outcomes on average than whites goes like this: blacks get treated differently by doctors and nurses because of their race.

“That may be true,” says Dartmouth health economist Jonathan Skinner, Ph.D., who led a recent study on the subject, “but we identify a different source of disparity, and that is that blacks go to different hospitals. . . . Most of the disparity—the overall disparity—is caused by what hospital you go to,” he explains, “and what happens within that hospital,” rather than how patients are treated on account of their race. Hospitals that treat mostly blacks have worse outcomes for heart-attack patients—whatever their race—than hospitals that treat mostly whites, Skinner and his colleagues reported in the October 25 issue of *Circulation*.

To reveal this relationship, Skinner, who is also a professor of community and family medicine at DMS, looked at 30- and 90-day risk-adjusted mortality rates in about a million Medicare patients who were hospitalized for a heart attack between 1997 and 2001. The roughly 4,000 hospitals included in the study were divided into groups according to the racial composition of their patients. Both races

received relatively poor care in hospitals that treated predominantly black patients and relatively good care in hospitals that treated predominantly white patients. For example, 90 days after a heart attack, 23.7% of patients in the “blackest” hospitals died, compared with 20.1% of patients in the “whitest” hospitals. That difference may seem small, but Skinner estimates that 1,000 fewer blacks would have died between 1997 and 2001 if they’d been treated in the whitest hospitals.

Although this study looked only at heart-attack patients, one published in the December *American Journal of Public Health* found similar results among premature babies. Both black and white very-low-birth-weight infants were more likely to die in hospitals where over 35% of babies were black versus hospitals where fewer than 15% were black. That paper and Skinner’s (both coauthored by economist Douglas Staiger, Ph.D., an adjunct professor at DMS), lead to the question of why blacks end up at worse hospitals.

Status: The answer, they found, is not socioeconomic status per se. “It’s about where you live,” says Skinner. But, “you shouldn’t be thinking inner-city hospitals necessarily” provide poor care, he cautions. After all, most of the country’s academic medical centers, which usually provide high-quality care, are in inner cities. Skinner suspects that hospitals in the rural, impoverished South are driving the disparities. But that is just a theory at this point and warrants more research.

Skinner is also careful to point out that his study “doesn’t deny” that discrimination exists within hospitals. But it reveals a new target for reducing racial disparities in care. “Targeting quality improvements at hospitals that disproportionately serve blacks,” wrote the researchers, “could dramatically reduce the black-white disparities in care.”

JENNIFER DURGIN



JON GILBERT FOR

Health economist Jonathan Skinner identified a new factor involved in racial health disparities.

Shock resistance

The bodies of most teenage women are well protected against toxic shock syndrome (TSS)—an infection associated with the use of tampons. And African-Americans of any age are slightly more susceptible than whites and Hispanics. Those are key findings of a new DMS study. Infectious disease specialist Jeffrey Parsonnet, M.D., and colleagues looked at ratios between the bacterium that causes TSS and the antibodies that fight it in 3,012 menstruating North American women aged 13 to 40. Since 70% of women in the United States, Canada, and much of Western Europe use tampons, the team noted, TSS—although rare—remains of interest.



Birthright

Low birth weight is closely tied to where a baby is born, found a recent DMS study. Even after adjusting for socioeconomic status, race, and the mother’s health, threefold variations persisted in this key risk factor for infant mortality. The researchers plan to “look more closely at the types of available care and the services received by women in these regions,” says DMS pediatrician David Goodman, M.D. “The areas with better-than-expected rates of low birth weight may be regions with better reproductive and perinatal services.”



Looking at the doctors-dollars link

Do physicians play a role in driving up health-care costs? DMS researcher Brenda Sirovich, M.D., is confronting that loaded question head-on with two studies—one just out and one that's due to be published in 2006. Both reveal a correlation between regional patterns of health-care spending and primary-care physicians' tendency to order tests, procedures, and referrals.

Doctors in areas that spend more per capita on health care, Sirovich has found, are more likely to pursue such interventions than their counterparts in low-spending parts of the country. That link may seem self-evident, but it "has not been made clear before," says Sirovich, who is an internist at the Dartmouth-affiliated VA Medical Center in White River Junction, Vt.

Patterns: Sirovich's research builds on two major findings that researchers at the DMS Center for the Evaluative Clinical Sciences have consistently shown: First, that health-care spending varies widely throughout the United States. And second, that in areas where spending is higher, patients have no better—and often worse—health-care outcomes. Sirovich and her research team want to know what's behind these patterns.

"A lot of the work to date on health-care variations," she says, "has implicitly assumed that physicians are not only behind the variations but that they are responsible for it, based on the decisions they make." Yet that assumption "has not been well studied," she points out.

In her first study, Sirovich analyzed data from the 1998-1999 Community Tracking Study Physician Survey, a nationwide telephone survey of 5,490 primary-care doctors. The surveyed doctors were read six patient vignettes and then asked how often they would take a certain action.

For example, one vignette read as follows: "Consider a 35-year-old man who developed low back pain after shoveling snow three weeks ago. He presents to the office for an

evaluation. On examination there is a new left foot drop." Survey participants were then asked: "For what percentage of such patients would you recommend an MRI?" The results: physicians in the highest-spending regions said they would recommend an MRI to about 83% of such patients, versus 70% for physicians in the lowest-spending regions.

Based on all the vignette responses, Sirovich calculated that doctors in high-spending areas order further evaluation or treatment for approximately 10 more patients per 100 than doctors in low-spending areas. "This finding," she wrote in the *Archives of Internal Medicine*, "held true for every clinical situation save one." That one vignette concerned a 50-year-old man with chest pain and abnormal results on an exercise tolerance test; physicians from all areas responded overwhelmingly in favor of referring him to a cardiologist—suggesting that the best course of action in this case was less subjective than in the other examples.

But "a lot of medical decisions," explains Sirovich, are "not black and white."

Survey: Sirovich's second study also employs a survey—this time one that she and her colleagues in the White River Junction VA Outcomes Group designed. Their survey includes a broader range of questions—including some on screening and follow-up—and richer content, she says.

This survey is also calculated to assess physicians' decisions in clinical situations for which there *are* clear guidelines. In high-spending areas where physicians tend to intervene more frequently, Sirovich wonders,



JON GILBERT FOX

A new study by Brenda Sirovich confirmed a relationship—between physicians' tendency to order tests and other interventions, and regional spending patterns—that had been assumed but never proved.

"are they doing a lot of the right stuff? Are they intervening when evidence says intervene and also intervening in cases where there is no evidence at all?"

Ultimately, Sirovich hopes her research will inform policies aimed at changing patient and physician behavior and controlling health-care costs. Any such policies are "doomed," she says, "unless you understand why physicians and patients, or both, want different things or do different things depending on where [they] live."

She does not presume that her research will answer those questions entirely but rather that it will provide a foundation for further inquiry. JENNIFER DURGIN



An analysis of myths about irritable bowel syndrome by Brian Lacy, M.D., Ph.D., showed that 43% of 261 patients think it's caused by food allergies and 68% by depression.

Once-obscure enzyme is now a hot property

Ten years ago, Lee Witters, Ph.D., was one of only a handful of people studying an obscure enzyme called AMP-activated protein kinase (AMPK). But in the past few years, he says, “a lot of people got really interested.” AMPK is now a hot research topic, having emerged as an important player in cancer, appetite control, and Type II diabetes. Even though the field is much more crowded now, Witters, a DMS biochemist, is still at its forefront, having recently identified an enzyme that regulates AMPK.

Gauge: The cells that make up our bodies need a constant supply of energy to function. AMPK is key in regulating cellular energy. It acts as a gas gauge by sensing how much energy a cell has. “It’s both sensing energy and doing something with that information,” explains Witters, who is the Eugene W. Leonard 1921 Professor of Medicine and of Biochemistry. When the cell has plenty of energy, or a full gas tank, AMPK remains inactive and the cell carries out its normal processes. If the cell

has an energy deficit, or an empty tank, AMPK is activated by another enzyme and tells the cell to conserve energy or to create new energy.

Scientists already knew that the enzyme LBK1 turns on AMPK in response to low energy stores in the cell. Witters and graduate student Rebecca Hurley, along with collaborators in Australia and at Duke University, suspected that other enzymes regulate AMPK, too, and set out to find them. And they did. According to a study recently published in the *Journal of Biological Chemistry*, another enzyme, CaMKK, can also turn on AMPK.

When a normal cell has low energy levels, it won’t divide. But a cancer cell will, according to Witters. In some cases, he believes this may be due to a malfunction in the molecules that regulate AMPK. In fact, scientists had identified LBK1 as a tumor suppressor even before they realized it regulates AMPK. LBK1 normally restrains cell growth but, if it’s missing or inactivated by a mutation, cell growth is uncontrolled. Although more experiments need to be done to prove the theory, Witters suspects that CaMKK may also act as a tumor suppressor.

Tank: “If you could deprive [a cancer cell] of the ability to run when the gas tank is a quarter full, you would thwart the ability of the cell to grow,” explains Witters. He believes that the AMPK pathway may someday be targeted to combat the uncontrolled growth of cancer.

AMPK may also have applications in appetite control and diabetes treatment, too, but Witters believes that in order to successfully target AMPK “you need to know who all the players are.” As the enzyme continues to gain favor among scientists, Witters will keep trying to understand the basic biochemistry behind this important pathway—just as he has for the past decade. KRISTEN GARNER



MARK WASHBURN

Lee Witters and graduate student Rebecca Hurley identified a key regulator of the enzyme AMPK.

Smoke screen

When movie stars light up, adolescents often follow suit, according to the first national study to look at the connection between smoking in movies and smoking initiation. After adjusting for other influences, DMS researchers found that adolescents with the highest exposure to smoking in movies were 2.6 times more likely to smoke than those with the lowest exposure. Onscreen smoking “is a very strong social influence on kids ages 10 to 14,” says DMS pediatrician James Sargent, M.D. “Its impact on this age group outweighs whether peers or parents smoke or whether the child is involved in other activities, like sports.”



Dirty pool

Cholera—a bacterial disease that’s transmitted through contaminated drinking water—relies on a single gene and protein to colonize the human intestine, DMS researchers reported in *Nature*. “We’ve identified a factor that works both in the environment and in the human body,” stated Ronald Taylor, Ph.D., who led the research. Though a vaccine for cholera exists, it’s effective only 50% of the time. This finding “has a strong potential for vaccine and therapeutic development,” according to Taylor, whose group will continue to look for other ways cholera bacteria infect humans.



Early results on 3D breast imaging

Scarcely a month goes by without some media outlet declaring “new hope” for breast cancer treatment or detection. It’s understandable then why Dartmouth radiologist Stephen Poplack, M.D., expresses only *restrained* enthusiasm for a new mammography method he’s studying. “The diagnostic value” of the new technology, called tomosynthesis, says Poplack, appears to be “very impressive.” But, he cautions, “we’re looking at very early results.”

View: Unlike conventional mammography, which produces two-dimensional images, tomosynthesis uses several low-dose x-rays to create a three-dimensional view of the breast. This helps eliminate many of the usual imaging problems—such as shadows and overlapping tissue—that often make diagnosis difficult.

To evaluate the potential of tomosynthesis, Poplack compared the diagnostic mammograms of 98 women with matching tomosynthesis views. (Women have a diagnostic mammogram when their screening mammogram reveals an abnormality.) In 88% of the cases, tomosynthesis provided views equivalent or superior to conventional mammography, according to Poplack. An image was deemed “superior” if it allowed Poplack, and his fellow researcher Helene Nagy, M.D., to see an abnormality better and to gather more information to make a diagnosis. Because the results are “certainly open to bias by the interpreter,” Poplack readily admits, the study needs to be replicated. It’s also worth noting that Hologic, the manufacturer of the tomosynthesis machine used in the study, funded the research.

Poplack, who serves on Hologic’s scientific advisory board, says he doesn’t “stand to gain” if the technology is accepted or not. In fact, for several years he has been working with Dartmouth engineer Keith Paulsen, Ph.D., on several unrelated breast cancer screening and diagnostic technologies (see page 5 in the Fall ’04 DARTMOUTH MEDICINE). Those technologies still hold promise “in terms of getting really new insights into breast disease,” he says. Since tomosynthesis builds off mammography, a well-established and well-studied technology, comparing it with the newer, alternative modalities is a bit like comparing apples and oranges, he adds.

Size: What tomosynthesis can and can’t do will be clearer after the company finishes a larger, multicenter study that includes DHMC and is aimed at gaining FDA approval. For now, the technology’s diagnostic capabilities appear strong. As for its screening merits, Poplack believes tomosynthesis is likely an effective screening tool as well. For example, if tomosynthesis had been used instead of screening mammography on the 98 women in the study, nearly half would not have needed further imaging. But because of the study’s size and structure, “you can’t really translate our results for screening,” says Poplack.

Yet to the extent that small discoveries fuel larger discoveries, perhaps Poplack’s study offers a nugget of “new hope” for improving the detection of breast cancer.

JENNIFER DURGIN



JON GILBERT FOX

When young research subjects took Barbie and Ken shopping in this “grocery store,” alcohol and tobacco often ended up in their carts, found Madeline Dalton, pictured.

Barbie “buys” booze and butts

“Where’s the beer, beer, beer?” That’s no fraternity chant. It’s what a young child wanted to know while “shopping” for an evening with friends as part of a DMS study. The results, published in the *Archives of Pediatrics & Adolescent Medicine*, suggest that preschoolers have already formed attitudes about smoking and drinking.

The study involved a role-playing scenario in which 120 children, aged two to six years, used Barbie and Ken dolls to purchase items from a toy grocery store in preparation for an evening with friends. The store was stocked with 70 different miniature products, including vegetables, meat, fruit, candy, milk, desserts, medicine, cereal, cigarettes, beer, and wine. About 62% of the children bought beer or wine, and 28% bought cigarettes.

Likely: “I didn’t expect such a high percentage of children to buy alcohol or cigarettes,” says study leader Madeline Dalton, Ph.D., a research associate professor of pediatrics at DMS and director of the Hood Center for Children and Families at Dartmouth. “Overall, I think it shows that very young children perceive alcohol and tobacco as appropriate and normal in social situations.” Children were more likely to buy cigarettes if their parents smoked and more likely to buy alcohol if their parents drank more than once a month.

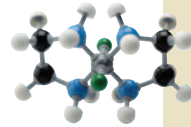
Most studies that examine early attitudes toward smoking and drinking are focused on older children. But this one, which was funded by the Robert Wood Johnson Foundation, suggests that attitudes may form at a much younger age than previously thought.

“It’s difficult to have an impact on middle school-age children with prevention programs if you are getting to them 10 years after they’ve already formed their attitudes,” Dalton points out.

The study certainly suggests that alcohol and tobacco prevention efforts may need to be targeted toward younger children and their parents. But the results need to be confirmed by larger studies.

“I was surprised it received as much media coverage as it did,” observes Dalton, “because it was a pilot study” with a relatively small number of research subjects. “But,” she adds, “I think it opens a lot of doors for future research.”

LAURA STEPHENSON CARTER



Scientists in Dartmouth's Toxic Metals Research Program, with colleagues at SUNY-Stony Brook, got a \$1.4-million grant to study how heavy metals move through the food web in estuaries.

Lost in space: Hearing can suffer on ISS

Who'd have thought that outer space was a noisy place? It is, at least in the International Space Station (ISS). Russian cosmonauts, who have spent the most time aboard the station so far, and a few other astronauts have suffered both temporary and permanent noise-induced hearing loss. And as space flights lengthen, hearing problems could get worse.

The space station is "not noisy at a level that you usually associate with hearing loss," says Dartmouth physician and former astronaut Jay Buckley, M.D. Buckley flew on the Space Shuttle *Columbia* in 1998 as part of the 16-day *NeuroLab STS-90* mission. Noise-induced hearing loss is typically caused by an exposure to sounds of 90 decibels or more. But the space station din is only about as loud as the inside of an airplane in flight—60 to 70 decibels.

"There are probably several factors at play," besides chronic exposure to the noise, Buckley explains. Genetic differences may play a role, with some people being more sensitive to noise than others. The slightly higher carbon dioxide levels in the ISS may also contribute. Even weightlessness, which causes a shifting of

body fluids, including increased intracranial pressure, may be partly to blame.

But before any of the reasons can be determined, there needs to be an effective hearing test that can be administered in a noisy place like the space station. Buckley, with the help of an audiologist and an engineer and funding from NASA, has developed a system that he's sure will work. He teamed up with audiologist Frank Musiek, Ph.D.—a former DMS faculty member who's now director of audiology research at the University of Connecticut-Storrs—and engineer Robert Kline-Schoder, Ph.D.—from Create, Inc., a Hanover, N.H.-based engineering and research development firm.

Probe: Musiek suggested a test that can automatically measure ear function, even in a noisy environment: an otoacoustic emissions test. The test, which is used on earth to screen newborns and some adults for hearing problems, is reliable, accurate, and objective. A small probe placed in the ear generates tones that travel to the inner ear and stimulate the hair cells in the cochlea; the hair cells send back signals that provide clues to how well the person's inner ear is working.

Buckley's team designed the test so it could be self-administered. And Kline-Schoder figured out a way to make the whole thing portable. He built miniaturized electronic components that fit into a laptop computer.

Astronauts will be tested preflight, regularly during a flight, on landing day, and several times postflight. A control group on Earth will take the same tests in a sound booth with real ISS noise (previously recorded in the space station itself) piped in. The only thing that can't be replicated is microgravity.

If all goes as planned, the testing system will fly on the ISS in 2007, says Buckley. LAURA STEPHENSON CARTER



MARK WASHBURN

Jay Buckley has designed a hearing test that can fit in a laptop computer, for use on space flights.

Age-old disparities

Elderly blacks receive fewer life-saving surgeries than whites, researchers from DMS and Harvard reported in the *New England Journal of Medicine*. The team looked at how often certain high-cost operations—such as coronary artery bypasses—were performed on Medicare enrollees from 1992 to 2001. In all 158 hospital-referral regions the

group examined, rates were higher for whites. "We found no evidence," wrote DMS's Elliott Fisher, M.D., M.P.H., and colleagues, "either nationally or locally, that efforts to eliminate racial disparities in the use of high-cost surgical procedures were successful."



Hip-huggers

Elderly patients who have elective hip replacements live longer than their counterparts. But why? Does the surgery itself make a difference? Or are patients who choose surgery healthier to begin with? A

group of DMS biostatisticians found that hip replacement patients do indeed start out healthier, with a 30% lower prevalence of most serious diseases. But even after adjusting for that fact, the life-prolonging effects of the surgery persisted. "Some effect of the procedure itself cannot be ruled out," researcher Jane Barrett, M.Sc., and her team concluded.



Study looks at impact of increasing stent use

Are we doing the right thing? What *are* we doing? Those were the questions guiding a recent study by a group of DHMC cardiologists. Over the past few years, more and more patients with complex heart disease have become candidates for—and are choosing—noninvasive, catheter-based procedures over surgery. But is that a good thing?

Study: Patients “we probably would not have treated” several years ago are now getting such procedures, says cardiologist Craig Thompson, M.D., who led the study. “And frankly,” he adds, “things that even surgeons wouldn’t try to do bypass on, we’re doing fairly routinely these days.”

Catheter-based procedures to treat heart disease involve feeding a flexible tube through an artery in the abdomen or leg, then into the diseased blood vessel on the surface of the heart. The tube, or catheter, functions like a highway, allowing cardiologists to insert tools to clean the vessel and to expand the vessel walls. Then a metal mesh tube, called a stent, is fed through the catheter and placed in the artery to prop it open and help maintain the blood flow. The procedure requires only a small incision, which is why it is considered noninvasive, and it has a much shorter recovery time than open-heart surgery. As stent technology has improved, cardiologists have begun treating patients with ever more severe heart disease.

But “by doing more challenging cases, were we compromising our patient outcomes?” Thompson and his colleagues wondered. The answer, according to their study, seems to be no. DHMC cardiologists have maintained a success rate of about 95%. “Despite increasing complexity,” says Thompson, “we were still holding our own as far as technically being able to do it without causing additional harm.”

Changes: A second aim of the study, explains Thompson, “was to get a sense of what are some of the technical changes in what we’re doing? Are the stents longer? Are they

larger? Do we use more stents per case?”

To attempt to answer these questions, the researchers looked at two groups of patients—of about 1,000 each—who received stents at DHMC. One group got stents between May 2002 and April 2003, and the other between May 2003 and April 2004. The two time periods, though consecutive, differ considerably because of a breakthrough in stent technology. During the first period, DHMC cardiologists were using primarily bare-metal stents. During the second period, they began using drug-eluting stents (DESs), which slowly release medicine that is intended to prevent the formation of abnormal scar tissue and the re-narrowing of the arteries. By the end of the second period, 84% of the procedures were done with DESs. Thompson and his colleagues looked at the data from both periods to see how DESs affected practice patterns and outcomes.

Future: “The DES era has been characterized by longer, more complex procedures involving an increased number of lesions and vessels treated, a longer average stent length, and a [longer] total stent length per patient, despite a similar number of angiographically defined disease vessels,” wrote Thompson and his colleagues in the *American Journal of Cardiology*. These findings are important for the future of stent technology and design.

“There are different device manufacturers, for instance, who would be interested in knowing this” information, says Thompson, whose research was not funded by device manufacturers. His study, which appeared in the journal’s September issue, relied on data from the large catheterization database at DHMC. Since 1993, every patient treated in the catheterization lab—the clinical area where catheter-based procedures are performed—has been entered into a database, which logs demographic information and the medical histories of patients, as well as technical details about the catheterization procedure they received. Roughly 30,000 patients



Craig Thompson doesn't just do stent procedures, he also evaluates how they're done, whether they're done for the right reasons, and what their outcomes are.

have been treated in the DHMC catheterization lab since 1993, making the database “pretty powerful,” says Thompson. “By most standards, we’re one of the highest-volume centers in the country.” The database is primarily used for “internal quality assurance,” he says, but it’s also a great research tool.

Two more studies using the database are due out in early 2006. One looks at DES outcomes in women compared with men. “We’re trying to tease out why women don’t tend to do as well,” says Thompson, “and specifically which women” do not do well. Cardiology studies usually include a “disproportionately low number of women,” he explains, “and occasionally there are gender-specific issues.” The third study focuses on outcomes in patients over 75, who are typically excluded from randomized trials—the studies on which FDA approval of devices is based.

Next, Thompson plans to evaluate the two different brands of DESs now on the market. “What is the relative value of one stent versus the other when it comes to real, live, very complicated patients?” Thompson and his colleagues wonder. “That’s where we’re going with this,” he says. JENNIFER DURGIN



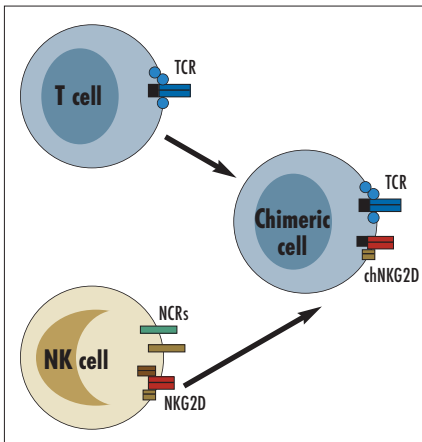
Chimeric cell shows promise against tumors

While the human immune system is often a mighty warrior, fighting off foreign invaders like bacteria and viruses, it's no match for wily cancer cells that can evade the body's defenses and grow into deadly tumors. So scientists keep tinkering with the immune system and working on immunotherapy treatments in the hope of one day defeating cancer.

At DMS, cancer researcher Charles Sentman, Ph.D., and postdoctoral fellow Tong Zhang, Ph.D., created a chimeric, or hybrid, immune cell by combining the best attributes of T cells and natural killer (NK) cells. The chimeric cells have been shown to kill cancer cells in the lab and have eradicated tumors and prevented the formation of new ones in mice.

Surveillance: Normally, immune cells use a process called immune surveillance to identify and eliminate cancer cells, which are detectable as foreign because they express different proteins on their surface than normal cells do. But cancer cells can also evade or suppress the immune system, thus escaping its surveillance and surviving to form tumors.

Scientists want to figure out how to outsmart the cancer cells' evasion tactics.



Combining parts of two different immune-system cells may create a more powerful tumor-killer.

One way might be to develop therapies that strengthen the ability of immune cells to kill cancer cells.

T cells can kill cancer cells directly, but there are often too few tumor-specific T cells to fight a given tumor. T cells survive for a long time, though, and activate other immune cells, enabling the immune system to continue its fight. And T cells that recognize a cancer cell can be given to a patient as immunotherapy.

Receptor: NK cells can also kill cancer cells but are less specific than T cells. NK cells have a receptor called NKG2D that recognizes several proteins expressed on many types of cancer cells but not on most normal tissues. However, NK cells do not live as long as T cells and don't activate other immune cells as strongly.

The DMS researchers discovered that they could modify T cells by adding the NKG2D receptor to them.

"So now we have the recognition benefit of the NK cell [with] the expansion and survival ability of the T cell," explains Sentman, an assistant professor of microbiology and immunology. He believes these new immune cells are attacking the tumor directly and are also "activating the immune system to be much more aggressive against the tumor naturally."

Sentman's chimeric cells could potentially be given to patients to kill cancer cells and reactivate the body's natural immune system against the tumor. He speculates that the chimeric cells could be especially useful in combination with radiation therapy. Cells under stress, such as that caused by radiation, express more of the proteins that NKG2D recognizes. But, he cautions, "there are lots of different parameters that have to be worked out to see if it really is going to be a viable therapy."

Still, he hopes that his chimeric cell will turn out to be a powerful warrior against cancer. **KRISTEN GARNER**

A paper on circadian rhythms by Hildur Colot, M.A., a research associate in genetics, was highlighted for its special significance in the "In-Cytes" section of *Molecular Biology of the Cell*.

Revealing genes

Advanced testicular cancer can often be cured with conventional chemotherapy, and DMS pharmacologists are trying to find out why. In the journal *Oncogene*, they revealed 46 genes that are upregulated by chemotherapy and five that are repressed. Several of the upregulated genes are known to be affected by another gene, called p53. The activation of p53, the researchers now believe, is linked to testicular cancer's hypersensitivity to chemotherapy.

"Many of the gene products" identified in this study "may participate in the unique curability of this disease," they concluded.

Enough is enough

Giving heart-surgery patients anti-inflammatory hormones—a common practice—may have limited benefit, says a study from DMS. The body produces enough of the anti-inflammatory hormone cortisol on its own during and after surgery, researchers found in a study of 60 patients. Patients who received anti-inflammatory medication—glucocorticoids (GCs)—did have more anti-inflammatory agents in their blood, but there were "no identifiable clinical differences between the treatment groups," reported lead author Mark Yeager, M.D., and his coauthors in the journal *Critical Care Medicine*. ■

