



Doctoral student Brooke Jude, left, and microbiologist Ron Taylor study the action of the cholera bacterium.

## One step closer to a vaccine against cholera

The media's coverage of avian flu has made Americans all too familiar with the word pandemic—the worldwide spread of a disease. Yet other pandemics are every bit as troublesome but get much less attention.

In a paper for the December 8 issue of the prestigious journal *Nature*, investigators in DMS's Department of Microbiology and Immunology—Professor Ronald Taylor, Ph.D., and graduate students Thomas Kirn and Brooke Jude—provided vital clues regarding the process by which the bacterium *Vibrio cholerae* is transmitted to humans. *V. cholerae* causes cholera, a severe diarrheal disease that kills thousands of people worldwide every year. A cholera pandemic that began in 1961 continues today; the World Health Organization says the disease is now present in places that hadn't seen a case for 100 years.

**Toxin:** Humans typically get infected with *V. cholerae* by drinking contaminated water or eating food taken from or washed in contaminated water. Once ingested, the bacteria attach to the surface of the small intestine and, after a short incubation period, produce a toxin that triggers massive loss of water and salts into the gut. The resulting diarrhea caus-

es dehydration and electrolyte imbalances that lead to death within three days in 60% of untreated patients. Rehydration with a balanced salt solution can save most patients but is largely unavailable in the rural, developing areas where cholera thrives.

Taylor's lab has been studying how the bacterium colonizes the gut, using a cellular system to test the way different genetic mutants of *V. cholerae* bind to the epithelial cells that line the gut. Bacteria with deficient binding were then analyzed to determine the identity of the disrupted gene. Of particular interest was a mutation in a gene encoding a protein that binds to chitin, a tough carbohydrate which forms, among other things, the exoskeleton of aquatic arthropods.

"Most of the cholera bacteria are bound to zooplankton or phytoplankton in the aquatic environment," says Taylor. "They're not just swimming around. In India, removing plankton by straining water through a sari that has been folded four times is used as an effective way of preventing cholera."

Why should a defect in a gene that determines attachment to chitin also result in deficient binding to gut epithelium? Although

chitin is not found in the gut, Taylor suspected the chitin binding protein was actually linking to a subunit of chitin known as GlcNAc, which is also common in the gut. Thus the same protein could participate in binding to both chitin and gut.

**Gut:** To test this hypothesis, Taylor's team produced a strain of *V. cholerae* lacking the gene that produces GlcNAc binding protein. These mutants bound to both chitin and gut epithelium much less often than wild-type *V. cholerae* did. In a control experiment, binding was partially restored when the gene was reintroduced. And in a mouse model, 10 times fewer mutant bacteria than wild-type bacteria attached to the gut.

Next, antibodies against GlcNAc binding protein were mixed with native *V. cholerae* before it was administered to mice. The addition of the antibody, which inactivated the protein, significantly increased the survival of the infected mice—indicating that bacterial binding to the gut is a major determinant of the progression of infection.

Why does *V. cholerae* colonize the human gut at all? The answer is uncertain, but Taylor has an idea: "*V. cholerae* is an environmental organism. Going into the human gut allows the organism to boost its concentration to manyfold the concentrations that can be achieved in the aquatic environment. This may be essential for its survival."

Two more studies are under way. "First," says Taylor, "we're preparing vaccines against a variety of potential cholera-binding proteins in rabbits and testing their effectiveness in preventing cholera infection in mice. Second, in conjunction with a group at Massachusetts General Hospital, we are testing the possibility of using a skin patch to deliver potential immunogens . . . to humans."

**Effective:** This could be the first step toward developing an effective vaccine for cholera—a goal that has eluded medical science to date. Taylor has no doubt about the importance of the work. "If we want world balance and sanity," he says, "we need to have healthy populations." JOSEPH E. MELTON, PH.D.

ANDY NORDHOFF



In a study of 1,500 patients, DMS gastroenterologist Douglas Robertson, M.D., found that those with diets high in processed meats had a higher risk of developing precancerous colon polyps.

## Diabetes: Progress against complications

Is diabetes a complicated disease? Or a disease of complications? Dartmouth diabetes researcher Paul Beisswenger, M.D., clearly favors the latter view. For unknown reasons, the developed world is in the midst of a diabetes epidemic. Although diabetics who control their blood sugar clearly have better outcomes, years of research and experience have shown that even the most scrupulous regulation of blood glucose does not always prevent progression of the disease.

In 2002, the U.S. spent \$132 billion on diabetes care, yet it remains the leading cause of blindness, amputations, and atherosclerosis. It also causes nearly half of all cases of end-stage renal disease. In all these complications of the disease, there is a very long “silent” phase in which tissue damage smolders at undetectable levels. It has been a source of immense frustration to caregivers that there have been no good ways to evaluate disease progression or to identify the patients most likely to suffer complications so they can be targeted for more aggressive treatment.

Beisswenger’s team has been exploring the chemical causes of this tissue damage. The researchers have focused on the most prevalent theory—that glycation, a non-enzymatic reaction of highly reactive sug-

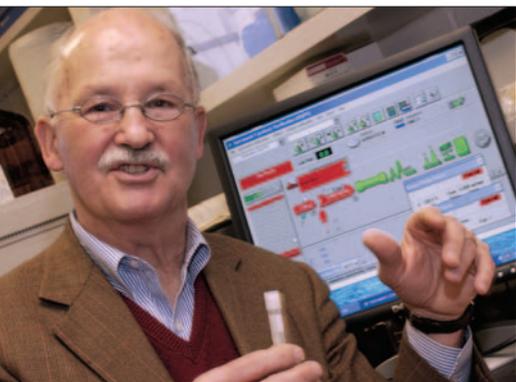
ars, results in the formation of adducts, or compounds, that interfere with normal structure or function. For many years, doctors have evaluated diabetics by measuring a glycated adduct called hemoglobin A1c; it does not itself cause complications but offers a way, along with blood sugar levels, to track the disease’s progression.

**Sugars:** Fifteen years ago, Beisswenger’s team became interested in sugars called dicarbonyls. Glycation of dicarbonyls can result in a process called oxidative stress. The most common dicarbonyl, methylglyoxal (MG), is thousands of times more reactive than glucose. MG is elevated in diabetics, and its concentration seems to correlate with the severity of complications. Beisswenger has shown that people produce varying amounts of MG, perhaps accounting for why only some diabetics progress to serious complications.

He’s also found that diabetics have less of a peptide called glutathione (GSH). The body has protective mechanisms to inactivate MG that may be affected by GSH. But do diabetics who progress make more dicarbonyls such as MG, or lack mechanisms to inactivate them?

Beisswenger recently published, in the journal *Diabetes*, results of studies on three groups of patients: 1) a pilot population at DHMC, 2) a larger group at the University of Minnesota, and 3) a group of Pima Indians in Arizona. The researchers measured their levels of GSH, MG and a related dicarbonyl, and other indicators of oxidative stress.

When those whose disease progressed were compared to nonprogressors, the results clearly indicated that progressors had higher levels of both dicarbonyls and oxidative stress. These findings, if confirmed by a larger study Beisswenger is running, will provide superior tools for identifying progressors as well as targets for new treatments. **ROGER P. SMITH, PH.D.**



ION GILBERT FOX

A team of researchers led by Paul Beisswenger is teasing out subtle differences among diabetics.

### A no-brainer

Heart bypass surgery, in rare cases, can lead to brain injury, but a recent study from DMS and Maine Medical Center suggests a way to reduce the risk. In a small study, the researchers found that papaverine—a drug commonly used during bypass surgery to improve blood flow—was more effective when applied topically to a vessel than when injected into a vessel. Signals indicating reduced blood flow to the brain were observed in seven of 12 patients who were injected with papaverine versus none of 28 who received the drug topically.



### Real-world result

A common treatment for post-traumatic stress disorder (PTSD) doesn’t produce the same result in the real world as it does in randomized controlled trials. DMS researcher Claudia Zayfert, Ph.D., and colleagues observed that only 28% of patients undergoing cognitive behavioral therapy for PTSD finished their treatment, whereas 73% of patients in randomized controlled trials did. The completion rate, they observed in the *Journal of Traumatic Stress*, “although disturbingly low, was better than expected.” And since research definitions of completion differ from clinical definitions, they say, the gap between the studies may not be quite so large.



## Combat affects young vets back home

**W**hen the U.S. invaded Iraq early in 2003, and later that year when the insurgency arose, it wasn't just soldiers in the field who were hurting. Something was happening to young veterans back home—they were hurting not physically, but mentally. That was the finding of a recent study by researchers at the DMS-affiliated VA Medical Center in White River Junction, Vt.

Many more young veterans (age 18 to 44) who use the VA health system reported poor mental health in 2003 than in 2000, the team discovered. Their analysis was based on the results of an annual national survey by the Centers for Disease Control and Prevention (CDC).

**Group:** “Nobody else reported more distress, just this particular group,” says researcher Alan West, Ph.D., who coauthored the study with psychiatrist William Weeks, M.D. West and Weeks found no significant increases in any other group—not in nonveterans, older veterans, nor veterans who receive their care outside the VA system.

In 2000, about 17.5% of veterans aged 18 to 44 who were under VA care reported at least five days of poor mental health in the previous month. In 2003, that number jumped to 29%. When West and Weeks probed deeper, by dividing the calendar year into three periods, the results were even more striking. In the first third of the year (January to April), the percentages for this group were 21% in 2000 and 36% in 2003. The second third of the year showed no significant difference between 2000 and 2003. But the final third of the year showed another spike, from 16% in 2000 to 32% in 2003.

As West and Weeks explain in their paper, published in the journal *Psychiatric Services*, “the first period [of 2003] involved the buildup and launching of Operation Iraqi Freedom, which was televised widely, perhaps inducing considerable anticipatory anxiety among these veterans. With the occupation of Iraq, hostilities subsided during the sum-

mer months. However, during the last third of the year, U.S. casualties increased between the suicide bombing of the Baghdad United Nations headquarters in late August and the capture of Saddam Hussein in December. The reality of a protracted war and its casualties may have first become apparent to the post-Vietnam veterans at this time.”

The authors speculate that the reason older veterans didn't show the same effect is because the current war may be “more emotionally salient to younger veterans,” a third of whom had served in Desert Storm—in the same combat theater. Other studies, West and Weeks note, have shown that “perceived similarity to victims increases a remote observer's distress in response to news of traumatic events.”

To West and Weeks's dismay, 2000 and 2003 were the only years that the CDC survey, known as the Behavioral Risk Factor Surveillance System (BRFSS), asked two questions key to their study: “Are you a veteran?” and “Do you use the VA health system?” Without answers to those questions, West and Weeks cannot expand their analysis to other years—at least not using BRFSS data. They hope the CDC will include those questions in future surveys.

**Novel findings:** In addition to the study's novel findings about veterans' mental health in 2003, the study also demonstrated a new approach for VA research. Veterans' health issues are often studied by comparing various groups or populations of veterans. When veterans are compared to the general population, it is rare that the data for each group is collected in the same way and at the same time, Weeks explains. Comparing veterans to nonveterans “in real time, with the exact same questions done with the same methodology,” says Weeks, “gives you a great op-



JON GILBERT FOX

**Alan West, left, and William Weeks demonstrated a link between young veterans' mental health and the progress of the war in Iraq.**

portunity to contextualize your findings.”

For example, in previous studies, Weeks showed that rural veterans are in poorer health than their urban and suburban counterparts. But “I didn't know if that was a rural veteran issue or a rural issue,” says Weeks, who is an associate professor of psychiatry and of community and family medicine.

**Comparison:** Another study he recently published with West answered that question. VA patients in rural areas have poorer physical and mental health than nonveterans (no matter where they live) and than veterans in urban and suburban areas. “This study is the first direct comparison of veterans in VA medical care to other veterans or nonveterans in a national survey of health problems, health-related functional limitations, and health-care access,” West and Weeks wrote in the *Journal of Rural Health*. That study also suggests that the poor health of rural veterans may be an access problem, such as having to travel long distances to reach the nearest VA medical center.

Using data from surveys of the general population that distinguish between veterans and nonveterans is “a very cost-efficient way” of assessing both veterans' health and VA health care, says Weeks. Such data can provide “a really nice objective view of [VA] performance,” he adds. And, as the *Psychiatric Services* paper demonstrates, lead to compelling findings. JENNIFER DURGIN



A randomized, controlled trial led by DMS's Allen Dietrich, M.D., showed that a series of phone calls can significantly improve cancer screening rates among low-income women.

## A close look at costs in the Golden State

Do seriously ill patients fare better in hospitals that spend more money treating them than in hospitals that spend less? Not necessarily—at least not in California—according to a recent study by DMS's Center for the Evaluative Clinical Sciences (CECS). The study, which was published as a web exclusive article by *Health Affairs*, showed that average spending per patient varied by hospital and that as the volume of care rose, both quality and patient satisfaction dropped.

The study, based on Medicare data from 1999 to 2003, compared the performance of 226 hospitals—in Sacramento, San Francisco, Los Angeles, Orange County, and San Diego—in managing seriously ill patients with at least one of 12 chronic illnesses. Two-thirds of them were diagnosed with cancer, congestive heart failure, and/or chronic lung disease.

Among all California hospitals, Medicare spending on hospital care and physician fees ranged from \$24,722 to \$106,254 per patient. About 60% of the variation in the hospital portion reflected the number of days patients spent in the hospital, indicating that volume of care plays a bigger role in driving up Medicare costs than do the institutions' daily rates.

Los Angeles was the most expensive

region, with average Medicare spending for inpatient care of \$43,506 per patient—67% higher than Sacramento, the least expensive region. And Los Angeles had 2.3 times more physician visits, 3.3 times more specialist visits, 2.3 times more days in intensive care, and 1.6 times more days in the hospital. Eliminating what the researchers call “Medicare overcare” by improving efficiency could have saved \$1.7 billion over five years in Los Angeles alone, according to the study.

**Variations:** The team also found variations within hospital systems and among academic medical centers, especially between UCSF and UCLA. UCLA patients spent 45% more days in acute-care hospitals; used 3.5 times more days in intensive care; were 1.5 times more likely to be admitted to an ICU during the hospitalization in which they died; and had 71% more physician visits.

“Chronically ill Americans need a fundamental redesign of care,” stated the paper's authors. But that will require incentives “that reward rather than penalize provider organizations that successfully reduce overreliance on acute hospital care and develop population-based strategies for managing their patients with chronic illness.” The authors were John Wennberg, M.D., M.P.H., director of CECS; Elliot Fisher, M.D., M.P.H.; and others, and the work was underwritten by the California Healthcare Foundation and Robert Wood Johnson Foundation.

CECS will soon report on hospitals in other states. “Our strategy is to be rolling out [the reports] by region,” says Megan McAndrew, communications director for CECS and editor of the *Dartmouth Atlas of Health Care*. She expects the results for New York, New Jersey, and Pennsylvania to be out next, followed by those for the upper Midwest. See [www.dartmouthatlas.org](http://www.dartmouthatlas.org) for updates. LAURA STEPHENSON CARTER



LARRY BRONSTEIN

A new study zoomed in on costs and outcomes in Los Angeles, pictured, and other California cities.

### Performance indicators

Senior citizens usually don't consult hospital performance data when deciding where to have surgery. So found a survey of Medicare patients by researchers at the DMS-affiliated VA Medical Center. Most of those surveyed “relied primarily on the opinions of their referring physician or family and friends in choosing where to have surgery,” wrote Lisa Schwartz, M.D., and colleagues in the *British Medical Journal*. Many said they'd switch hospitals based on mortality data, but since they rely on their physician's opinion, the researchers argued that “performance data should be directed at referring physicians,” not patients.



### Calculating cancer's effect

It's no surprise to learn that breast cancer patients experience mental and emotional distress. A study by DHMC's Comprehensive Breast Program revealed just how common psychological disturbances are among women with early-stage breast cancer.

“We found that 46% of the 185 women that we screened . . . meet or exceed our established thresholds for mental health intervention,” said Caroline Moore, M.P.H., at a recent breast cancer symposium in Texas. About 42% of the women had high stress levels, almost 11% were depressed, and about 9% showed signs of clinical anxiety.



## Airbags blow ill as well as good

A new study reveals that automobile airbags, which have long been shown to save lives and reduce injuries in collisions, may also be the cause of some injuries—in particular, leg injuries.

A team of investigators—including Kenneth Koval, M.D., a professor of orthopaedics and the director of DHMC's orthopaedic trauma service, and Justin Cummins, M.D., a fourth-year resident in orthopaedics—spent two years reviewing thousands of motor vehicle collision (MVC) records. They used the National Trauma Data Bank, a database maintained by the American College of Surgeons.

The researchers analyzed approximately 35,000 MVC records from 1988 to 2004, excluding those with only minor injuries and those with insufficient documentation. They divided the collisions into four groups: those in which a seatbelt was used and the airbag deployed; those in which a seatbelt was used but the airbag did not deploy; those in which no seatbelt was used but the airbag deployed; and those in which neither safety device was used. Then the team reviewed eight different body areas of the crash victims within each group: head, chest, abdomen, spine, the two upper extremities (arms and hands), and the two lower extremities (legs and feet).

**Deploy:** “Seatbelts provided protection for all eight areas, so compared to people who used no restraints, seatbelts provided protection across the board,” Cummins explains. When the researchers reviewed the injuries sustained by crash victims whose airbags had also deployed, they discovered that protection for the head, chest, abdomen, and spine increased. However, the seatbelt-airbag combination provided no extra protection against arm injuries and actually increased the risk for leg injuries by about 35%. “Airbags certainly provide protection in some areas,” Cummins observes, “but there’s a tradeoff—you increase your risk in other areas.” A factor in the finding, he cautions, may be that airbags tend to deploy in more serious collisions.

The study also showed that the seatbelt-airbag combination offers the most safety; the death rate for that group was the lowest—3.3%. The seatbelt-only group had a death rate of 3.6%, while the death rate for the airbag-only group (6.0%) was only slightly less than that for the no-device group (6.2%).

The study, which has been submitted for publication to the *Journal of Bone and Joint Surgery*, the leading orthopaedics journal, is sure to raise some questions. Cummins hopes it may also lead to improvements in airbags. “We need to rethink the design of airbags,” he says. “Instead of transferring the blow from your head to your lower extremities, the addition of knee bolster airbags, or some other design, could help provide protection all the way around.”

Cummins's conclusion is based not only on his research, but also on experience: he himself was involved in a car crash in which an airbag deployed. Happily, he was unhurt. But, he says, “the worst part of the crash, actually, was the airbag deploying.” ANN PATTERSON



JOSEPH MEHLING

**This trio of researchers—from the left, physician Fisher and health-care economists Skinner and Staiger—found wide variations in the cost of post-heart-attack care.**

## Costly care isn't better care

It's worth it” has been the prevailing assumption about the rising costs of treating acute myocardial infarctions (AMIs)—heart attacks. For every 100 elderly heart attack patients, 10 more survived in 2002 than in 1986, thanks to various technological and treatment advances. And every year of life saved cost less than \$25,000, explained three DMS researchers in a recent issue of *Health Affairs*. “But”—and this is a big “but”—“underlying these numbers is tremendous heterogeneity across time and space,” they wrote.

By analyzing Medicare claims data from the nation's 306 hospital referral regions, they found that areas that spent the most on AMI treatment had the lowest gains in survival between 1986 and 2002. Furthermore, improvement in heart attack survival rates stagnated after 1996, though the cost of treatment has continued to grow. The researchers also found that survival gains were lowest in regions where there were more physicians treating each AMI patient.

This message—that spending more doesn't necessarily improve care—has been reinforced time and again by researchers at DMS's Center for the Evaluative Clinical Sciences. CECS physician-researcher Elliot Fisher, M.D., a coauthor of the AMI study, has shown in previous studies that Medicare patients in high-spending regions have neither better outcomes nor more access or satisfaction. But it was unclear until now if this held true in heart attack care, where there have been numerous (costly) technological innovations.

**Measures:** “On average, everyone is better off,” wrote Fisher and his coauthors—Dartmouth health-care economists Jonathan Skinner and Douglas Staiger—“but the regional gains are not correlated with regional spending increases.” The team was careful to note that their study did not evaluate the effectiveness or benefit of high-tech, high-cost treatments. Rather, their findings point to the need to develop “measures of quality and efficiency that can encourage [providers] to adopt low-cost, highly effective care, while discouraging incremental spending with no apparent benefits.”

“Put more simply,” they noted, “the benefits of health spending depend on how one spends the money.” JENNIFER DURGIN



Two Dartmouth researchers mapped anatomical changes in the brains of college freshmen and determined that the brain's structure continues to change significantly after age 18.

## What's the right number of doctors?

Is the U.S. health-care system facing an impending shortage of physicians? The Association of American Medical Colleges (AAMC) and the Council on Graduate Medical Education (COGME) believe it is. Both point to the aging population, trends in physician utilization rates, and economic expansion as contributing factors. One COGME study estimates an 85,000-physician deficit by 2020. In response, the AAMC is recommending that medical schools boost enrollment by 15% over the next decade.

But David Goodman, M.D., and other researchers at Dartmouth's Center for the Evaluative Clinical Sciences have a different view. A study led by Goodman and published in *Health Affairs*, showed that the elderly Medicare population may not be facing a physician shortage.

**Subjects:** Goodman's team studied the ratios of physicians to Medicare patients at 79 academic medical centers (AMCs). All the patients—a minimum of 100 at each center—received the majority of their hospital care during their last two years of life in an AMC. To avoid differences in patients' health-care needs and preferences, which might affect the results,

Goodman limited subjects' health status (all had chronic disease), outcomes (all died during the period 1999-2001), and quality of care (all were treated at integrated academic medical centers).

The results showed large differences among the AMCs in the ratios of physicians to elderly Medicare patients. New York University Medical Center ranked highest in total labor, with 28.3 physician full-time equivalents (FTEs) per 1,000 patients—4.7 times higher than the lowest-ranked institution, Medical College of Georgia, which had 6.0 physician FTEs per 1,000. NYU also had the highest rate of medical specialists (15) per 1,000—6.3 times more than the lowest-ranked institution, Strong Memorial Hospital in Rochester, N.Y.

Many AMCs with low ratios (including DHMC, with 7.7 FTEs per 1,000) are in rural areas, but not all. Several urban AMCs also had low ratios, including the University of Cincinnati Hospital and the University of California at San Francisco; both had the same outcomes and quality of care as high-ratio institutions.

Furthermore, the number of physician FTEs at each AMC correlated closely with the overall number of FTEs caring for Medicare beneficiaries in the region around the AMC.

Most surprising to Goodman was the huge "variation in physician effort, even across academic medical centers, where we would expect . . . commonality in their approach to patient care.

**Efficiency:** "With 45 million uninsured, we need to find opportunities to improve the efficiency of care wherever we can," maintains Goodman. "And medical educational institutions should be investing not in producing more physicians," he continues, "but in improving physician training and investing more in lifelong learning." MATTHEW C. WIENCKE

### Surgical advice

Between one-third and two-thirds of patients undergoing gastric bypass surgery—a treatment for severe obesity—develop gallstones. A study by DMS surgeon Brent White, M.D., found that the most cost-effective ways to prevent them are removing the gallbladder at the time of the bypass and treating the patient with the drug ursodiol for six months after surgery. "Surgeons . . . should consider either using ursodiol or performing a concurrent cholecystectomy," White advised at the annual meeting of the American College of Surgeons.



### Fungal finding

A class of deadly fungal infections called Zygomycoses was the subject of a paper by Jack Brown, Pharm.D. "Zygomycosis appears to have become more common since the mid-1990s," he wrote in the *American Journal of Health-System Pharmacy*, "and has been identified in up to 6.8% of patients at autopsy." Brown summarized the taxonomy, epidemiology, pathogenesis, diagnosis, and treatment of these dangerous fungi. Patients at the highest risk of infection, he reported, are diabetics, intravenous drug abusers, premature infants, recipients of bone marrow transplants, and those who get certain therapies to remove excess iron from the body. ■



Wearing his pediatrician hat, David Goodman sees young patients like this one. But wearing his health policy researcher hat, he studies the physician supply needed for the aging U.S. population.