



Runaway juries aren't to blame for soaring malpractice premiums, found health economist Amitabh Chandra.

Study debunks medical malpractice myth

For many months, the American Medical Association and government officials have been blaming multi-million-dollar jury awards and frivolous lawsuits for ballooning malpractice insurance premiums. But that blame is wildly misplaced, according to a recent study by Dartmouth health economist Amitabh Chandra, Ph.D.

Jury: "This focus on jury awards, or judgments at trial, is very misleading," says Chandra, an adjunct assistant professor of community and family medicine at DMS. "You routinely hear statements about, 'Oh, this jury awarded this person \$20 million, or \$5 million, or something like that.'" But in reality, only a small proportion of malpractice cases make it to trial; the rest are settled out of court. In fact, awards by a judge or jury account for only about 5% of all medical malpractice dollars. Furthermore, the average size of such payments grew only 3.4% from 1991 to 2003, according to Chandra's findings, published in the journal *Health Affairs*. In other words, large jury awards are not driving the explosion of malpractice premiums.

The even more surprising finding—given the national rhetoric—is that medical mal-

practice payments have grown at about the same rate as health-care costs overall.

"The amount of money that we spend on malpractice payments in the United States has grown substantially. There's no disputing that," Chandra explains. "But, as a fraction of all the amount of money we spend on health care, it hasn't grown much." Of every \$1,000 spent on physician and clinical services in 1991, malpractice payments accounted for only about \$10. In 2002, after adjusting for inflation, malpractice payments accounted for about \$11 out of every \$1,000.

And as a portion of total health-care spending, malpractice payments made up an even smaller amount, between \$2 and \$3 per \$1,000 from 1991 through 2002. This suggests that rising medical costs, not excessive jury awards, is driving the growth in malpractice payments.

Premium growth: "A third, more minor, take-away point," says Chandra, "is that the distribution of what payments [are for] has not really changed over time." Also of interest, he and his coauthors noted, is that "states where payments grew dramatically between the early 1990s and the early 2000s were not

the states where premiums grew radically."

Since Chandra's findings conflict so dramatically with the positions of the American Medical Association (AMA) and the White House, the major news media—including the *Los Angeles Times* and National Public Radio—were quick to cover his paper. Critics emerged, too, including the AMA, which charged that the study was based on a flawed registry, the National Practitioner Data Bank (NPDB), which catalogues every payment made on behalf of licensed health-care providers in the U.S. While Chandra admits that the NPDB has many flaws, he says that most of them didn't affect this study because "we didn't use those fields."

The key limitation of this paper, and the databank, Chandra says, "is a loophole called the 'corporate shield,' which allows the name of an individual physician to be dropped from a lawsuit." When that happens, the payment doesn't appear in the NPDB. To see just how disruptive this loophole was to their analysis, Chandra and his coauthors compared NPDB data with data from two state registries that include payments made on behalf of hospitals, as well as on behalf of individual physicians. They found their analysis held true with and without the hospital data.

Link: In their conclusion, Chandra and his coauthors suggested that lower-than-expected returns from investments might be one reason that insurance companies are raising premiums. They did not study that link, however, so it remains only a conjecture.

Next, Chandra plans to investigate the practice of "defensive medicine"—the ordering of unnecessary tests by doctors because they fear being sued. Although he recently left Dartmouth to join Harvard's Kennedy School of Government, Chandra will retain his appointment at DMS and will continue to collaborate with researchers at DMS's Center for the Evaluative Clinical Sciences. "Dartmouth," he says, "is the place to do research that is at the intersection of economics and medicine. It's really the best place in the world to do that." JENNIFER DURGIN



DMS departments whose grant funding ranks among the top 20 of the nation's 125 medical schools are microbiology and immunology at 9th, genetics at 11th, and biochemistry at 15th.

New biomarker for coronary artery disease?

We know high cholesterol is bad. High BNP may be worse. Some day, physicians may be checking our BNP (B-type natriuretic peptide) levels to determine our risk of developing heart disease. BNP is released from cells of the heart wall when it's under stress.

In fact, assessing BNP levels may turn out to be a better way of detecting coronary artery disease (CAD) than the commonly used cardiac stress test, says Robert Foote, M.D., an assistant professor of medicine and of radiology. The stress test—in which an electrocardiogram (EKG) is taken while someone exercises on a treadmill—often fails to detect ischemia, inadequate blood flow caused by constricted or blocked coronary vessels.

In an initial study funded by the Hitchcock Foundation and published in the *Journal of the American College of Cardiology*, Foote demonstrated a correlation between ischemia during exercise and increased levels of BNP. In patients with known CAD, he used nuclear perfusion imaging to accurately measure blood flow to the heart. A radioisotope, given intravenously during a stress test, distributes it-

self through heart muscle in proportion to blood flow. Images taken by a special camera then show which vessels are blocked.

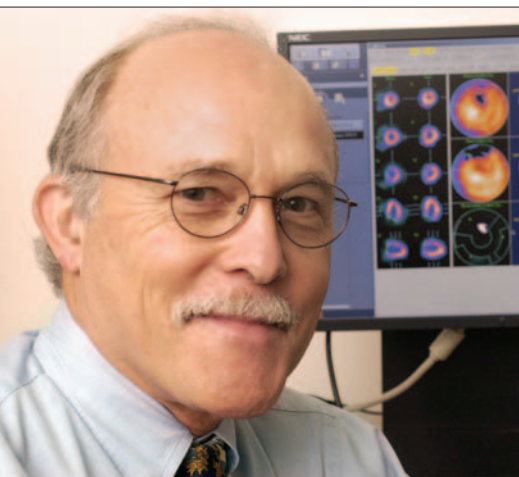
"We have strong evidence that ischemia triggers the release of BNP in the blood stream," says Foote. Of 74 patients with CAD, over 90% showed an abnormal increase in BNP after exercise, while only 37.5% of their EKGs showed abnormal patterns.

An increase in BNP levels can be a good thing when a heart is under stress from hypertension, ischemia, stroke, renal failure, heart failure, and the like. BNP dilates blood vessels, increases blood flow to the kidneys, reduces myocardial oxygen needs, and lowers blood pressure. "The net effect is to reduce cardiac workload," explains Foote. "It has so many good properties that . . . it's been synthesized and it's now being used as a drug to treat severe heart failure."

Tool: But Foote is interested in BNP's value as a diagnostic tool. First, however, researchers must determine what's normal. "BNP levels are a continuum," Foote says. "The higher the level, the higher the risk." He has found average levels of 25 picograms/milliliter (pg/ml) in healthy athletes (members of the Dartmouth women's hockey team), 55 pg/ml in patients with heart disease but no ischemia, 125 pg/ml in patients with ischemia, and more than 1,000 pg/ml in people with heart failure.

Foote will soon conduct a larger study, funded by Roche Diagnostics, to measure BNP in 400 to 500 patients who come to the DHMC emergency department with chest pain of uncertain cause. He hopes to be able to distinguish people with ischemia from those who have other problems, such as indigestion.

"I would not be surprised if [BNP] became a routine part of risk assessment," says Foote. **LAURA STEPHENSON CARTER**



JON GILBERT FOX

A peptide called BNP may be a better biomarker than cholesterol for heart disease, says Foote.

Pedi patterns

More children are admitted to community hospitals than children's hospitals, found DMS pediatrician David Goodman, M.D., and colleagues. According to a study presented at the Pediatric Academic Societies' meeting, 64.4% of hospitalizations for patients aged 1 to 17 were in non-children's hospitals; general hospitals cared for disproportionately high numbers of 15- to 17-year-old females, patients from low-income zip codes, and uninsured patients. Does the U.S. need more children's hospitals or more pediatric expertise at community hospitals? That's a "fundamental question that the health-care community needs to answer," said Goodman.



Back talk

Diagnosing low-back pain can be difficult and problematic, acknowledged Jon Lurie, M.D., of DHMC's Spine Center in a recent paper. The major diagnostic challenge is "to distinguish the >95% [of patients] who have a benign musculoskeletal pain syndrome from the small minority with a serious, specific disease process that requires timely and specific therapy," he wrote in *Best Practice & Research Clinical Rheumatology*. Fortunately, Lurie offered a detailed decision guide to help physicians with this diagnostic conundrum.



A \$9-million birthday present

How would you spend \$9 million if you were 10 years old? For the Toxic Metals Research Program at Dartmouth, the answer is clear: continue to study the impact of arsenic, mercury, and lead on human health. A recent \$9-million grant from the National Institute of Environmental Health Sciences brings the total funding for Dartmouth's Center for Environmental Health Sciences (CEHS), where the toxic metals program is housed, to approximately \$58 million, according to CEHS director Joshua Hamilton, Ph.D. While the goal of the Toxic Metals Research Program hasn't changed since it was founded in 1995, its research is anything but stagnant.

Among the program's key findings have been that even very low levels of arsenic exposure can increase the risk of getting cancer; that arsenic, like mercury, can disrupt normal hormone function in animals; and that large and complex food webs are, interestingly, very resistant to the bioaccumulation of some toxins.

Horn: "We don't like to toot our own horn," says Hamilton, who also directs the toxic metals group and is a professor of pharmacology and toxicology at DMS, "but I have to say that we believe that we are one of the premier research programs in the country, probably in the world, studying arsenic and other toxic metals." The toxic metals program and CEHS are unique because they consist of several scientists studying just a few metals. Currently, there are about 14 CEHS studies underway on arsenic alone. "In the early days, we were one of the few programs studying [arsenic] at all," Hamilton adds. "Over the last five years or so, arsenic has become a very hot topic."

In 2001, Hamilton's research was cited in Congressional testimony by Christie Todd Whitman, the former head of the Environmental Protection Agency, as evidence to support the lowering of the drinking-water standard for arsenic from 50 parts per billion to 10 parts per billion. And Hamilton, as well as DMS epidemiologist Margaret Karagas, Ph.D., served on committees that evaluated the EPA's arsenic standard prior to the change, which goes into effect in 2006. It "feels pretty good," says Hamilton, "to be able to contribute to the national debate and to take our results from the lab directly out into the real world." He estimates that 25 million people in the U.S. will be better protected from the health effects of arsenic under the new standard. CEHS also has an outreach project focused on lead poisoning prevention and awareness in underserved minority populations in Manchester, N.H.

While two-thirds of the CEHS faculty members are from the Medical School, the center also includes faculty from Dartmouth College's chemistry, biological sciences, earth sciences, and environmental studies departments. "Most of the issues we are dealing with are environmental health- and toxicology-related questions," explains Hamilton, "but we really think it's important to partner with people in some of the other sciences [too]." JENNIFER DURGIN



Adachi-Mejia studied PG-13 movies with prominent tobacco brand placements; the *Men in Black II* alien behind her appears in another scene with a Marlboro carton.

Play, even without pay, for tobacco

It's a bird! It's a plane! No, it's Superman . . . zooming past giant billboards plastered with cigarette brands. Not too long ago, tobacco companies paid big bucks to have their products placed prominently in movies—even those aimed at young audiences, like *Superman II*. Although the practice of paying for tobacco brand appearances (TBAs) in movies is now banned, tobacco brands still appear regularly in movies, according to a recent DMS study in the *Journal of the American Medical Association*.

In 1998, an agreement was signed to settle a lawsuit against tobacco companies by state attorneys general. "One of the purposes of the [agreement] was to limit the amount of advertising that kids were being exposed to," says Anna Adachi-Mejia, Ph.D., principal investigator of the study. One provision of the agreement prohibited tobacco companies from paying to place their products in movies.

Hits: To see what effect that provision has had, Adachi-Mejia and her colleagues examined the top 100 box office hits for the four years before and the four years after the 1998 agreement. They found that the total number of movies with TBAs had indeed decreased—from nearly 21% to under 11%—but that the biggest drop was in R-rated movies. The number of PG-13-rated movies with TBAs had not changed significantly.

"It was surprising and alarming to us that there didn't seem to be a change with the youth-targeted movies," says Adachi-Mejia. The number of R-rated movies with TBAs dropped from about 30% before the agreement to 13% after the agreement. But the slight decrease recorded in the percentage of PG-13 movies with TBAs (from 15% to just under 12%) was not considered statistically significant.

"We know that kids are really affected by what they see," explains Adachi-Mejia. Two of her colleagues—Madeline Dalton, Ph.D., and James Sargent, M.D.—have published studies showing that the more children are exposed to smoking in movies, the more likely they are to begin smoking. Superman will be back on the big screen next summer in *Superman Returns*. Adachi-Mejia hopes that this time he'll steer clear of tobacco billboards. KRISTEN GARNER



DMS geneticist Victor Ambros, Ph.D., received the 2005 Lewis S. Rosenstiel Award for Distinguished Work in Basic Medical Research, for his discovery of the first microRNA gene.

Simulators can improve sedation safety

At DHMC, patient simulators are being used as “crash-test dummies” to see how well health-care teams respond to pediatric sedation emergencies. There are medications that can alleviate the pain and anxiety that children experience when undergoing procedures such as bone marrow biopsies or spinal taps. However, complications like respiratory depression, the slowing or stopping of breathing, may occur as a result.

In a recent paper published in *Anesthesia and Analgesia*, George Blike, M.D., and colleagues showed that patient simulators—high-tech mannequins—can be used to assess medical teams’ ability to rescue sedated patients from life-threatening complications. That lets them identify and thus correct errors.

Previous studies by Blike and a fellow DHMC anesthesiologist, Joseph Cravero, M.D., have shown that clinicians “were undertreating pain” in children, explains Blike. That’s because while doctors want to make children as comfortable as possible, they of course are reluctant to risk serious complications or even death.



Anesthesiologist Blike demonstrates use of emergency airway equipment on a simulated patient.

“If we were going to get people to be more aggressive and not undertreat pain any longer, we had to address the fear of overdose and the fear of sedation complications,” says Blike. He reasoned that if the rescue response could be studied and improved, then doctors would feel more comfortable using sedating medications.

With the simulator, “we don’t have to wait for you to have an accident and then try to look at it after the fact,” says Blike. The mannequin can be programmed to generate specific sedation-related complications. Then caregivers’ responses can be observed and, if necessary, improved before they have to handle such emergencies in real patients.

Signs: In this study, a life-like pediatric mannequin was programmed to respond like a four-year-old child experiencing respiratory depression as a result of having been sedated. The “patient” showed low blood-oxygen levels and a slowed heart-beat. If the team managed the respiratory depression appropriately by opening the airway and providing ventilation in a timely manner, the simulator’s vital signs improved. If the team failed to resuscitate the “patient,” its vital signs remained low. In a real patient, that could lead to brain damage or death.

“We are not as prepared for critical incidents related to sedation as we might think,” says Cravero. Problems identified by the study included not having emergency airway equipment set up and not calling for help soon enough. The researchers also found that caregivers who perform this type of rescue regularly had more success.

“Powerful technology,” like specially programmed simulators, “gives you a wealth of information about your vulnerabilities so you can take corrective action—and that’s how you create safety,” concludes Blike. **KRISTEN GARNER**

How low should we go?

Lowering the threshold for what’s considered abnormal in the most common prostate cancer-screening test “would be a mistake,” said three DMS researchers in a paper in the *Journal of the National Cancer Institute*. Some doctors feel prostate-specific antigen scores as low as 2.5 should be flagged as abnormal. But doing so, wrote H. Gilbert Welch, M.D., et al., would double the number of men defined as abnormal and subject about 1.35 million more men aged 40 to 69 years to unnecessary biopsies. “It is easy to diagnose more prostate cancer,” the authors wrote. “It is not easy to know who has clinically important disease.”



Much ado about melanoma

Another paper by the same team, this one in the *British Medical Journal*, concluded that a dramatic increase in melanoma is “largely the result of increased diagnostic scrutiny and not an increase in the incidence of the disease.” Welch et al. examined 15 years of Medicare data and found that “the incidence of early-stage disease has risen rapidly, whereas the incidence for late-stage disease and mortality have been relatively stable.” Since it’s unlikely that treatment advances exactly keep pace with the rising incidence, they argue, “overdiagnosis” is the most plausible explanation.



Study used pediatricians to screen mothers

Pediatricians usually focus on kids and leave the welfare of their mothers to ob-gyns. But Ardis Olson, M.D., an associate professor of pediatrics at DMS, believes that identifying signs of depression in mothers is a vital step in protecting the health and well-being of children.

According to Olson, the children of mothers with persistent depressive symptoms are four times as likely to exhibit behavior problems. Such children are also more prone to experience sleep problems and injuries. And, as they grow up, they are at increased risk of depression themselves. Among children with one parent who is clinically depressed, 40% are likely to develop symptoms of depression by age 20. That number increases to 60% by age 25.

Questions: In a study published in the June issue of the *Journal of Developmental and Behavioral Pediatrics*, Olson and her coauthors found that asking two key questions during well-child visits can help pediatricians identify at-risk mothers. “This is part of a move to screen all adults for depression, as recommended by the U.S. Preventive Services Task Force,” explains Olson, adding that mothers of young children generally have more contact with a pediatrician than with any other health-care provider.

Designed to test the efficiency of screening in this setting, as well as the relative efficacy of different types of screening, Olson’s study was conducted at four practices in rural communities in New Hampshire and Maine. A total of 473 mothers, with children ranging in age from two weeks to 16 years, took part. (The number of fathers accompanying children to visits was so small that their results were not included.)

The questions recommended by the Preventive Services Task Force—“In the past couple of weeks, have you been in a depressed mood most of the time?” followed by “During the past couple of weeks, have you often had little interest or pleasure in doing things?”—

were posed in two different formats. In one group, 250 mothers were interviewed by the pediatrician, who asked the questions in the context of a scripted discussion about family issues. In the second group, 223 mothers were given a paper questionnaire, which described depression as “a common but treatable illness in parents,” explained the importance of screening for it, and then asked participants to check “yes” or “no” in response to the same two questions.

Among those interviewed in person, 5.7% screened positive—that is, they answered yes to both questions, indicating that they were at high risk for depression. That interview screen, plus subsequent discussions triggered by it, revealed depressive symptoms or other mental health concerns in a total of 8.8%. The detection rate among mothers responding to the paper questionnaire was significantly higher. In that group, 22.9% screened positive, with subsequent discussions revealing depressive symptoms or other mental health concerns in a total of 27%.

Specific: The primary reason for the difference, Olson suggests, is that adults are generally more comfortable revealing sensitive information on paper or to a computer than during a face-to-face interview. But the study showed that either method of screening is more effective than the pediatrician merely observing a depressed affect, which missed 54% of the mothers who had a positive screen. Similarly, asking general questions about stress and mood was not as useful as asking these two specific questions.

The 11 participating pediatricians felt the screenings were well worth the one or two minutes they took to administer. All four practices were prepared to follow up positive screens with referrals and other resources. The pediatricians saw their role as educating and motivating mothers, not diagnosing a depressive disorder. About 40% of the screen-positive mothers in both groups who were not already being treated accepted a referral for



Pediatrician Ardis Olson found that well-child visits are a good setting to screen for maternal depression.

further assessment or mental health care.

“Many parents don’t recognize that they’re depressed,” Olson says. “They think it’s normal to feel stress and have difficulties. They’re not aware of crossing the line into depression.”

Earlier studies have shown that depressed mothers don’t do well at parenting. “One of the main problems is that they’re inconsistent,” Olson explains. “Sometimes they are withdrawn, and sometimes they are overly obtrusive. The children don’t know what to expect.” Depressed mothers often lack the energy to interact positively with their children—by reading to them, for example. Thus it isn’t surprising that the children often grow into depressed adults, as well. As Olson points out, “Their behavior models are depressed people.”

Follow-up: Olson is now working on a six-month follow-up of the practices involved in this study, and she looks forward to conducting further assessments of the processes and outcomes of maternal screening in a variety of settings.

CATHERINE TUDISH



DMS microbiologist Deborah Hogan, Ph.D., was one of only 15 researchers nationwide selected as a 2005 Pew Biomedical Scholar. She studies model systems for host-pathogen interactions.

Study explores Native surgical outcomes

American Indian and Alaska Native military veterans are more likely to die within 30 days of surgery than their Caucasian counterparts. That was the finding of a study by DMS surgeon Lori Alvord, M.D. The results—some of which are conflicting—contribute to a growing list of health disparities between Native peoples and the general U.S. population.

The study, which was published in the *Journal of the American College of Surgeons*, included 2,155 American Indian (AI) and Alaska Native (AN) male veterans and 2,264 Caucasian male veterans. Those are small numbers compared to many surgical studies, which often include hundreds of thousands of patients. Nevertheless, it “is the largest study of Native outcomes in surgery ever,” says Alvord, who is herself a Navajo and DMS’s associate dean for student and multicultural affairs.

Surprise: To compare postoperative mortality (deaths) and morbidity (complications) in the two groups, Alvord’s team used data from the Veteran Affairs National Surgical Quality Improvement Program (NSQIP). They found that AI/ANs had a 50% greater risk of dying within 30 days of selected surgeries than the Caucasians. However, to their surprise, they saw no difference in morbidity between the two groups—a perplexing finding, given the difference in mortality.

“We may have a problem in the way that the study measures morbidity,” explains Alvord. “The study measures morbidity basically by assigning a morbidity score if you have any one of 21 complications. It’s a binomial distribution. There’s ‘no complications’ and then the other category is ‘one or more complications.’” Alvord and her colleagues chose this classification system because they modeled their study on a larger NSQIP study in which the binomial system had been validated. “It worked for a huge number of

patients, like over 500,000,” says Alvord, “but if you’re working with only a couple thousand in each group, maybe some other things become more important.”

Samples: For example, it’s possible that the AI/AN patients had more severe complications. Or that their complications were not accurately assessed. Or, as with any study based on population samples, that the mortality disparity was due to chance. Or some combination of those factors. Alvord aims to find out the reasons for the inconsistency in her next study, by developing a more precise morbidity classification system and by adjusting for socioeconomic factors.

Alvord, who is relatively new to research, just completed a two-year fellowship through the National Institutes of Health and the University of Colorado that trains minorities to conduct research about minorities. The program seems to have launched Alvord as a researcher. She’s begun a third study, too, on Native perceptions of surgery and their effect on outcomes. Alvord picked her topics because of DMS’s strength in outcomes. “And because I am Native,” she adds, “surgical outcomes in American Indians really made sense.” JENNIFER DURGIN



Alvord is studying comparative surgical outcomes.

Devilish mechanism

Two DMS researchers have revealed the insidious process by which a molecule called Smad7 helps pancreatic cancers grow out of control. Smad7—which is present in half of human pancreatic cancers—thwarts the usual checks and balances of cell growth and allows the proliferation of cells and blood vessels



that feed tumors. “It’s a devilish mechanism,” says Murray Korc, M.D., chair of medicine at DMS and coauthor of the Smad7 paper for the *Journal of Biological Chemistry*. “Smad7 not only prevents TGF-beta molecules from slowing the cancer down, but enables them to multiply at a high rate, and thus gives the cancer another growth benefit.”

Platelet parameters

The FDA currently allows platelets—blood cells that aid in clotting—to be stored no more than five days before being given to patients. But new research by DMS pathologist James AuBuchon, M.D., suggests that platelets could be stored for seven days with no significant effect on outcomes, thanks to new bacterial detection methods. “Extension of platelet storage and concomitant use of a bacterial detection system would provide logistical advantages by reducing outdated and improving patient care,” wrote AuBuchon in the journal *Transfusion*.



Bon (hydroxyl)apatite

The mineral portion of bones and teeth is a substance called hydroxylapatite. There is more of it in teeth, which makes teeth harder than bone. It has an unusual property in that when it is exposed to ionizing radiation, it instantly forms a free radical—the carbonate anion. Free radicals can be detected and quantified by a technique called electron paramagnetic resonance (EPR) spectroscopy. Most biological free radicals are extremely short-lived, but the carbonate anion is stabilized in the crystal structure of hydroxylapatite, making it exceptionally long-lived. In fact, it is detectable centuries after it has been formed and has been used for the archeological dating of ancient teeth in human and animal remains.

But the substance has a very contemporary purpose as well. Dartmouth radiologist Harold Swartz, M.D., Ph.D., has found it a useful marker for measuring radiation exposure—an application of interest in military and counterterrorism as well as in medical settings.

Record: Swartz first used the technique on extracted teeth in 1968, but advances in EPR now allow the measurements to be made in teeth that are still attached to their owner's jaw. That makes an individual's teeth a permanent record of exposure to cosmic radiation, dental x-rays, and other sources of radiation.

However, Swartz and his team are especially interested in assessing doses that are orders of magnitude larger than the sum of these everyday exposures—such as might be encountered during the detonation of a “dirty” bomb or the meltdown of a nuclear reactor. Such exposures make people physically ill and often require treatment. The sign most often used to triage victims of exposure to dangerous levels of radiation is vomiting, which is indicative of damage to the gastrointestinal tract. But vomiting is one of the most nonspecific of all medical complaints. Another sign is depression of the white blood cell count, indicating damage to the bone marrow. But the drop may not occur for several critical days.

So Swartz's group is developing an instrument that can be used in the field to allow triage of patients into those who do not need treatment, those who need only supportive care (such as fluids and electrolytes), and those who will need bone marrow transplantation. Their pilot model requires wheeled transportation, but eventually they hope to develop a hand-held instrument that could be widely available in case of radiological emergencies.

Irradiation: The methods will be tested and the instruments calibrated on DHMC radiation oncology patients whose treatment targets include appropriate doses to the teeth. They will be further refined at the University of Rochester Medical Center, on patients receiving whole-body irradiation for disseminated cancers. The work is being supported by the counterterrorism unit of the National Institute for Allergy and Infectious Disease—which one could say makes the agency Swartz's tooth fairy.

ROGER P. SMITH, PH.D.



FLYING SQUIRREL GRAPHICS

Charles Brenner, right, and Pawel Bieganski, center—pictured with grad student Huan Liu—were authors of a *Journal of Biological Chemistry* “Paper of the Week.”

Protein paper is picked from pack

Of the more than 6,600 articles published in the *Journal of Biological Chemistry* (*JBC*) each year, fewer than 100 are featured as a “Paper of the Week.” One of the papers recently selected for that honor features work from the lab of Dartmouth researcher Charles Brenner, Ph.D. The paper focuses on a particular protein associated with a rare neurological disease.

“We want to feature the exciting work our authors publish,” says Robert Simoni, Ph.D., deputy editor of the *JBC* and chair of biological sciences at Stanford. “Reviewers are asked to nominate papers they judge to be in the top one to two percent of papers to be published in the *JBC* each year.” Brenner's paper was selected, he adds, because of its “broad interest, novelty, and impact.”

“We were the first people to identify an enzymatic activity of the Aprataxin protein,” says Brenner, an associate professor of genetics and of biochemistry and a researcher at Dartmouth's Norris Cotton Cancer Center. It was already known that certain mutations in the gene that codes for Aprataxin result in malfunctioning versions of a protein that cause a rare inherited neurological disease called ataxia-oculomotor apraxia syndrome 1 (AOA1). AOA1 is characterized by loss of control over the movement of the head, eyes, and limbs.

Genes: But until now, no one understood how this protein worked. Then Brenner and his research colleagues—postdoctoral fellows Heather Seidle, Ph.D., and Pawel Bieganski, Ph.D.—recognized similarities between a family of cancer-related genes and the ataxia-producing gene and decided to investigate further. They found that mutated Aprataxin lacks a certain enzymatic function and that the “loss of that enzymatic activity leads to changes in the developing brain that produce the ataxia,” Brenner explains.

Brenner hopes the attention generated by the “Paper of the Week” designation will “stimulate research into this very interesting protein in order to identify other molecules that are regulated by Aprataxin.” Some of the molecules, he believes, “may turn out to be drug targets to treat the kids that are born with this disease.” KRISTEN GARNER



Calcium may do more than build strong teeth. A DMS study showing a possible protective effect against colon polyps was presented at a meeting of the American Association for Cancer Research.

Tackling the mechanisms of head injuries

In hard-hitting sports like football, helmets don't always protect players from mild traumatic brain injuries, a.k.a. concussions. "Concussions are a major area of concern in all levels of football," says Jeffrey Frechette, Dartmouth's head athletic trainer. They "range from headache to feeling dizzy to being knocked out."

But little is known about what actually causes concussions. This fall, the Dartmouth football team is helping several DMS researchers find some answers.

Safer: "If more were understood about exactly how concussions are caused, then there might be better medical care for those with the brain injury," says DMS psychiatrist Thomas McAllister, M.D., one of the researchers on the project. "There might also be better safety equipment, better preventative measures, and safer techniques taught in sports."

Enter Head Impact Telemetry (HIT) helmets, which can keep track of hits that players sustain. The HIT system was conceived in the early 1990s by Richard Greenwald, Ph.D., an adjunct faculty member at Dartmouth's engineering school and founder of Simbex, a Lebanon, N.H.-based R&D firm, and Brown Med-

ical School researcher Trey Crisco, Ph.D. Early on, sensors that measure head acceleration were affixed to the outside of helmets worn by jumpers on the U.S. Ski Team, since they sometimes hit their heads and suffer concussions. Since then, Simbex has developed the HIT system for use on the gridiron—with funding from helmet-maker Riddell and the National Institutes of Health.

In the DMS study, 40 Dartmouth football players are wearing HIT-equipped helmets. Tiny accelerometers, embedded in specialized pads in the helmets, are linked to an encoder that wirelessly transmits data—such as head acceleration and impact magnitude and the number, location, and direction of hits—to a laptop computer on the sidelines. Trainers also wear pagers that sound when players receive potentially concussive hits.

"The system is an extra set of eyes to pick up a kid who we might otherwise have not known about," says Frechette.

Data: It's the data that's of most interest to the DMS team: McAllister; surgeon Ann-Christine Duhaime, M.D.; and neuropsychologist Arthur Maerlender, Jr., Ph.D. They will conduct neuropsychological assessments of the players with the HIT helmets—such as functional MRI scans and tests of their working memory—and will compare these findings to the HIT data. For example, they will compare the effects of one major impact to the cumulative effects of many smaller hits.

"The idea is to see whether multiple sub-concussive impacts [affect] cognitive function," says McAllister.

The researchers hope soon to expand the pilot study to include more football players as well as other athletes. Once scientists understand the biomechanics, manufacturers may be able to engineer helmets that will make concussions a distant memory. MARK P. LAWLEY



CHRIS MILLMAN

This season, the helmets of 40 Dartmouth football players are mini mobile neuropsychology labs.

Picking up parental habits

"Honey, have some smokes," said a 6-year-old boy to a doll. The boy was one of 120 youngsters pretending to grocery shop as DMS researchers observed. Led by Madeline Dalton, Ph.D., the team found that children were more likely to "buy" cigarettes if their parents smoked and to



"buy" alcohol if their parents drank at least monthly. "Our study is the first to demonstrate that preschool children possess social cognitive scripts of adult social life in which the use of alcohol and tobacco play central roles," Dalton et al. wrote in the *Archives of Pediatric and Adolescent Medicine*.

Reproductive immunity

Hundreds of scientific articles on the immune system of the female reproductive tract were recently summarized by five DMS researchers in the Departments of Physiology and of Microbiology and Immunology. The goal of the summary, published in *Immunological Reviews*, was "to define the innate immune system in the female reproductive tract and, where possible, to define the regulatory influences that occur during the menstrual cycle." It's essential that the tract's immunological processes be considered "in the design of vaccines for the protection against microbial diseases," concluded the authors. ■

