



DMS's Henry Bernstein, D.O., published in the journal *Pediatrics* the first prospective study of post-childbirth discharge decisions; 17% of patients were deemed not ready to go home.

A simple recipe for cerebral disaster

What do you get when you mix a pinch each of normal prions and polyanions with a dash of copurified lipid molecules? A brew of infectious prions.

A DMS team led by biochemist Surachai Supattapone, M.D., Ph.D., has published the first report of spontaneous generation of infectious prions in a test tube. The paper was in the June *Proceedings of the National Academy of Sciences*.

Prions are normal proteins found in the brain that become infectious when they misfold. As they slowly convert from the normal to the infectious form, they can cause rare, deadly brain disorders called transmissible spongiform encephalopathies, such as mad cow disease in cows, scrapie in sheep, and Creutzfeldt-Jakob disease (CJD) in humans.

Rare: The Dartmouth work provides a biochemical model of the naturally occurring, but very rare, sporadic CJD, says Supattapone. And, adds his lab manager Nathan Deleault, the first author on the study, "it gives us a glimpse as to how this process occurs in the brain."

The findings, Supattapone notes, also provide the best support to date for the protein-only hypothesis—that unlike other pathogens, which rely on nucleic acid

containing DNA or RNA to replicate, a prion can propagate without nucleic acid. Some scientists are critical of this idea and think prion diseases are caused by an as-yet-unidentified slow virus. But others—like Supattapone, who trained in the lab of Nobel Laureate Stanley Prusiner, M.D., a prion pioneer at the University of California, San Francisco (UCSF)—prefer the protein-only hypothesis.

The study was also important in that it was "the first time that an infectious agent has been created from noninfectious components," says Supattapone. It was "very surprising." Surprising enough that he wanted to be sure the samples hadn't been contaminated with infectious prions from other research. So his team ran the experiments again in a colleague's prion-free lab—and reproduced the results.

At DMS since 2001, Supattapone has been slowly unraveling the mysteries of prion disease. Next, his team hopes to determine how the interaction between polyanions—molecules with repeated, negatively charged ions that are found naturally in the brain—may contribute to spontaneous infectious prion formation.

Patent: Prion researchers are seeking ways to prevent, diagnose, and treat prion disease. And they're trying to "develop ways to break the transmission cycle," says Supattapone. He and Prusiner recently received a patent for an antiseptic compound they developed at UCSF. Called PrioX, it can inactivate infectious prions on surgical blades and other surfaces.

Still, Supattapone is modest about his achievements. So far, he says "all we've done is create a biochemical model, which mimics what occurs naturally in the brain." But he doesn't plan to stop there. LAURA STEPHENSON CARTER



JON GILBERT FOX

Deleault, left, and Supattapone generated prions in the lab.

Affected by CF

DMS scientists have identified a gene named *cif* that, with its corresponding protein, may contribute to cystic fibrosis (CF). The group previously reported that *Pseudomonas aeruginosa*, a pathogen that often colonizes CF-affected lungs, secretes a protein (the one just identified) that may contribute to the disease. Writing in *Infection and Immunity*, principal investigator George O'Toole, Ph.D., and colleagues "demonstrate that the *cif* gene is expressed in the cystic fibrosis lung," and propose a model by which *P. aeruginosa* colonizes a CF lung.



Bone of contention

A hip fracture increases an elderly person's risk of dying, but only in the first six months after the injury, a DMS study concluded. After six months, pre-fracture frailty and illness are more important predictors of death than the fracture itself or age, sex, race, or socioeconomic status. "Our study indicates that fracture prevention may be of limited benefit in extending overall life expectancy," wrote Anna Tosteson, Sc.D., and colleagues in *Osteoporosis International*. Since "hip fracture is one of the most highly visible and devastating consequences of osteoporosis," they note, the finding has implications for the "economic value" of "costly new osteoporosis treatments."





Dartmouth transplant surgeon David Axelrod, M.D., analyzed the cost of transplanting “marginal” versus “ideal” donated livers. On average, marginal organs cost \$84,000 more.

Long-term study puts folate to the acid test

Folic acid, a B vitamin credited with building strong spines in infants, may have a dark side for colorectal health in adults. A decade-long study by the Polyp Prevention Study Group (PPSG), a consortium of researchers at Dartmouth and several other medical centers, found that people who took supplemental folic acid had at least as many adenomas—precursors of most colorectal cancers—as those who took a placebo.

Tumors: Epidemiological and animal studies have suggested that folic acid may inhibit the formation of tumors in the large intestine. Testing that hypothesis, the investigators discovered instead that giving folic acid to people with a history of adenomas had no more preventive effect than a placebo—and maybe less. The *Journal of the American Medical Association (JAMA)* published the study in its June 6 issue and also made it the subject of a JAMA Reports video news release.

Of 1,021 men and women aged 21 to 80 who enrolled in the study in 1994, almost 97% had a colonoscopy within three years. At least one adenoma was found in 44.1% of those taking 1 mg a day of folic acid, and in 42.4% of those taking the placebo. The incidence of an advanced lesion was 11.4% on folic acid and 8.6% on placebo. A few years later, the gaps between the two groups had widened.

DMS epidemiologist John Baron, M.D., the study’s lead investigator, calls the double-blind trial “very strong” in showing that folic acid does not decrease the risk of adenomas in people with previous tumors. But he said the results did not unequivocally show that folic acid increases adenoma risk. The paper, whose lead author was DMS’s Bernard Cole, Ph.D., said “evidence for an increased risk of adenomas . . . requires further research.”

The interest in further study stems from a 1996 U.S. law that mandated folic

acid fortification of enriched flour and uncooked cereal grains by 1998. Canada passed similar legislation in 1998. There has been strong evidence that the laws’ goal—reducing neural tube defects, spina bifida, and anencephaly in newborns—is being met. Some scientists had posited that fortification might also help reduce colorectal and other cancers.

However, an observational study in the July issue of *Cancer Epidemiology, Biomarkers & Prevention* offers compelling support of the PPSG conclusion. This study overlaid the timelines of folic acid fortification and of colorectal cancer incidence in the U.S. and Canada. It found that a steady decline in such cancers before fortification turned to an increase after that point. The finding didn’t surprise Baron. “Folate is a food for cancer,” he says. “Some of the earliest chemotherapeutic regimens [were designed to] block folate utilization.”

Range: So how much folate is too much? Baron chooses not to be an alarmist. “For most people, I’m guessing that fortification won’t be harmful,” he says. “But suppose you get a guy who eats breakfast cereal, likes bread, and takes multivitamins [with folic acid]? Now you’re getting to a range . . . [with] relatively little margin for safety.”

JAMES DICLERICO



Folic acid doesn’t foster colon health, found Baron.

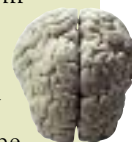
Breast stroke

Pre-menopausal women with very dense breasts are twice as likely to develop ductal carcinoma in situ (DCIS), an early form of breast cancer, as pre-menopausal women with scattered-density breasts. That’s according to a DMS-led study of data in the New Hampshire and Vermont mammography registries. “Our study,” wrote the investigators in *Cancer Causes and Control*, “is the first prospective assessment of breast density in relation to risk of DCIS, and the only study to separately examine the influence of density in premenopausal and postmenopausal women.”



Chemobrain question

A study in rats has shed light on “chemobrain”—the mild cognitive impairment that many cancer patients feel after chemotherapy treatment. Working with DMS faculty, Dartmouth College grad student Jill MacLeod examined the effects of a standard breast cancer chemo regimen on learning and memory in rats. She found that rats treated with cyclophosphamide and doxorubicin had difficulty remembering some types of information. Her results, published in *Behavioural Brain Research*, suggest the drugs “may have toxic effects on the hippocampus” and cause “specific learning deficits shortly after treatment has ended.”





DMS's Department of Genetics, according to data from the Association of American Medical Colleges, ranks in the top 10% nationwide in terms of grant funding per faculty member.

A new ally against multiple myeloma

Kenneth Meehan, M.D., has taken on a formidable adversary. His foe is multiple myeloma, an incurable cancer of the blood. To improve the survival of patients with the disease, he is trying to take advantage of one of the strongest weapons patients have against cancer—their own immune systems. In a recent DHMC clinical trial, Meehan combined immunotherapy—stimulating the immune system to fight a disease—with standard treatments for multiple myeloma.

Stem: A typical treatment regimen for multiple myeloma begins with high doses of chemotherapy. Such doses destroy not only the cancer cells but also patients' bone marrow—where all blood cells, including those that make up the immune system, are made. That requires giving patients an autologous stem-cell transplant. "In a sense, we have to rescue them by giving them their own cells back," says Meehan, who heads DHMC's Bone Marrow Transplant Program. Hematopoietic stem cells, cells that can give rise to all the different types of blood cells, are isolated from patients before they're given the chemo regimen. After the treatment, the patients get back their own stem cells, which then repopulate the bone marrow.

Yet even after the chemo and the transplant, multiple myeloma recurs in most cases. That indicates, says Meehan, "that after the transplant something more is needed." Even if only a few cancer cells survive the chemo, they will continue to divide and patients will eventually relapse. So Meehan decided to try stimulating patients' own immune systems to kill any remaining cancer cells.

He gave patients in the trial Interleukin-2 (IL-2) and granulocyte macrophage colony stimulating factor (GM-CSF) right after the transplant. These substances, produced naturally in the body, increase the production of immune cells. Meehan hoped this would accelerate the post-treatment recovery of the immune system. Other studies have found that patients whose immune systems recover more quickly after a transplant show better overall survival.

Trial: The purpose of the Phase I/II trial was to assess the safety of the treatment, to determine the optimal dosages, and to determine if the treatments elicit a response in the immune system. The results, published in the journal *Bone Marrow Transplantation*, show that IL-2 and GM-CSF were well tolerated and elevated levels of cytotoxic T cells—immune cells thought to be important in killing cancer cells. In addition, blood from participating patients was able to kill myeloma cells grown in the lab.

Meehan hopes the immune response will lead to longer survival. The trial has laid the groundwork for future clinical trials, in which he plans to use more types of immunotherapy, including some that are even more specific for the tumor cells. He also hopes to use the concept to gain insight into the exact mechanism by which immune cells kill tumor cells—maybe unleashing a powerful warrior that's been there all along. KRISTEN GARNER



MARK WASHBURN

Meehan has joined forces with the immune system.

Watery worry

Arsenic—at levels commonly found in contaminated wells in the United States—can interfere with numerous important biological pathways. Molecular epidemiologist Angelina Andrew, Ph.D., and other Dartmouth investigators observed in mice that arsenic altered signaling pathways important in angiogenesis, lipid metabolism, oxygen transport, apoptosis, the cell cycle, and immune responses. Publishing in *Toxicological Sciences*, Andrew and her colleagues expect that their research "will help guide investigations into mechanisms of arsenic's health effects and clarify the threshold for biologic effects and potential disease risk."



Complex matters

A team of DMS biochemists recently took some of the mystery out of how organelle membranes merge within a cell. Membrane merging is essential for moving and sorting proteins and has been known to include a protein complex called SNAREs, as well as the Rab family of proteins.

By detailing how SNAREs and Rabs interact to drive membrane mergers and to protect organelles from lysis, the paper earned principal investigator William Wickner, M.D., and his coauthors "feature article" placement in the August 21 *Proceedings of the National Academy of Sciences*. ■

