JON GILBERT FOX

Dartmouth epidemiologist John Baron chaired the committee that called a halt to the controversial Vioxx trial.

DMS's John Baron was at eye of Vioxx storm

Timing can be everything, especially in clinical drug trials. That's one lesson of the recent worldwide withdrawal of Vioxx, a multibillion-dollar anti-inflammatory medication for arthritis and acute pain. Vioxx's manufacturer, Merck, voluntarily pulled the drug after results of an ongoing study showed that its prolonged use could double the risk of heart attack and stroke. The news was startling, especially for a drug that had been on the market since 1999. Why was such a significant risk not known before?

Data: "If you did a study that lasted 18 months, you would have seen exactly nothing [based on] our data," explains John Baron, M.D. He is a professor of medicine at DMS and chaired the steering committee for the study, known as the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial. Baron is not an employee of Merck but was paid to offer advice on protocols and to serve as the top liaison between the data-safety monitoring committee, which was responsible for the safety of participants and which made the initial recommendation to halt the study, and the steering committee, which made the final decision to discontinue the trial.

APPROVe began in 2000 and was designed to judge Vioxx's potential to prevent a recurrence of colon cancer, Baron's area of research specialty. The doubling of cardiovascular risk emerged only after 18 months, he explains. And since participants entered the trial at different times, the trend did not appear conclusively until September 2004, nearly five years after the study began. The Food and Drug Administration (FDA) had approved the drug based on studies with shorter time frames.

Vioxx belongs to a class of drugs that target COX-2, an enzyme responsible for inflammation, while avoiding another closely related enzyme, COX-1, which has a protective effect on the stomach. Though comparable to aspirin in relieving pain, COX-2 inhibitors are not as damaging to the stomach and digestive tract. "After the discovery of COX-1 versus COX-2 and the different enzymes, these drugs were developed very quickly," says Baron.

Trial: Since COX-2 is over-expressed in many cancers, researchers wondered if such drugs could be used to treat cancer. The prospect was "very exciting, almost delicious," says Baron. In the APPROVe trial, participants were divided into two groups of 1,293 each. One group received a placebo, while the other received 25mg a day of Vioxx. In the placebo group, there were 25 confirmed cardiovascular events—heart attacks or strokes. In the Vioxx group, there were 45 events. Those numbers represent 1.9% and 3.5% of participants, respectively, and translate into a near doubling of risk.

And because "people who get into clinical trials tend to be healthy," says Baron, researchers worried what would happen in "a more real-world situation, where the rate of cardiovascular disease depends on age and sex and smoking and all those other factors."

In fact, Vioxx had been in a "real-world situation" for five years. It was being taken by 20 million people in the U.S. and millions more worldwide. According to one FDA estimate, Vioxx may have been responsible for as many as 27,785 heart attacks, fatal and non-fatal, in this country between 1999 and 2003. Though the risk of Vioxx causing a heart attack in an individual patient is small, the elevated risk is significant because of the drug's widespread use. Its withdrawal spurred hundreds of lawsuits against Merck.

Coverage: Meanwhile, the coverage of the withdrawal in the lay press and even in scientific journals has been "loud and deceptive and sometimes ill-informed," believes Baron. Merck's response was "quite impressive and very fast," he contends. "There was absolutely no push-back."

While the controversy surrounding Vioxx is unlikely to be resolved soon, he sees lessons to be learned from the situation. The discovery of COX-2 inhibitors was "really a marvel of modern science," says Baron, but "the promise of molecular medicine has some limitations." It would be safer to evaluate all drugs for longer periods before approval, he says, "but you can easily imagine that people would be complaining" that the FDA is bureaucratic and slow. Balancing rapid approval of potentially useful drugs against possible long-term or delayed side effects "is a difficult issue for a society to handle," he says. "It's not going to be easy." JENNIFER DURGIN

The DMS COOP Project, a network of private physicians established in 1972 to do practice-improvement studies, is the oldest practice-based primary-care research network in the U.S.

Researcher calls vaccine results "stunning"

Diane Harper, M.D., M.P.H., was busy at her computer as usual one recent afternoon. There was a palpable electricity in her small office, however. The day before, *The Lancet* had published the results of an international clinical trial she'd led, testing a vaccine against two strains of human papillomavirus, HPV-16 and HPV-18, viruses that cause 70% of cervical cancer. Harper has studied the HPV-cervical cancer connection for 20 years.

Randomized: "The results of this trial are actually stunning," Harper says. The vaccine increased the body's immune response to the viruses to 80% to 100%. Conducted between 2000 and 2003, the study included 1,113 women aged 15 to 25 from the U.S., Canada, and Brazil. In the double-blind, randomized trial, 560 received the vaccine and 553 received a placebo. Participants got three vaccinations over a period of six months and follow-up testing for 27 months.

"Among 'the perfect people,'" Harper says—that is, women who got all three injections and all follow-up tests—"the vaccine was 100% effective against persistent HPV-16/18 infections." Even among less-than-perfect subjects—those who got one or two injections—it was 91% effective. "Usually the data aren't so good for the group that doesn't fully comply with the protocol," she observes, "but even this group saw a significant benefit."

HPV is transmitted by skin-to-skin contact, usually through sexual activity. Of the more than 100 strains of HPV—most of which do not cause serious health problems—about 30 are linked to cancer of the cervix. Most HPV infections, even from high-risk strains, are resolved by the body's immune system, but some progress to cancer. Worldwide, 230,000 women die of cervical cancer annually—the vast majority in developing countries, where screening and treatment are not widely available. Even in the U.S., more than 13,000 women are diagnosed with the disease and 5,000 die of it each year.

The vaccine tested in the study—a virus-like particle (VLP)—was designed by GlaxoSmithKline Biologicals of Belgium to prevent infections, cell abnormalities, and precancerous lesions, all of which can advance to cancer. The VLPs, Harper explains, are "little hollow globes, a coating with nothing inside." Scientists are able to snip out a piece of the HPV DNA that contains the genetic code without the virus. This is used to create the VLPs, which mimic the virus but contain nothing harmful. When the particles are injected, the body sees them as HPV and begins producing antibodies.

Phase III: Harper and her colleagues are now beginning a Phase III trial, which will enroll 15,000 women worldwide, including 300 at DHMC, and run through 2009. If all goes as expected, the vaccine could be available in the U.S. by 2010.

She receives no money from GlaxoSmithKline, Harper adds. "The study and its protocols were planned by independent physicians," she says, though she feels industry has a role to play in "excellent science that can be translated into improved clinical care." CATHERINE TUDISH

JON GILBERT FOX

Diane Harper led a worldwide HPV vaccine trial.

Country fare

"We need to think about veterans who live in rural settings as a special population," explains DMS psychiatrist William Weeks, M.D. Weeks and colleagues at the White River Junction, Vt., Veterans Affairs Outcomes Group conducted the first nationwide comparison of the health status of rural versus urban VA patients. The study, published in the *American Journal of Public Health*, found that rural veterans are in much poorer health then their suburban and urban counterparts. The authors had some advice for policy makers: establish more clinics in rural areas and coordinate VA services with Medicare.

Water, water, everywhere . . .

A new federal standard for arsenic in drinking water—set to take effect in 2006—is 10 parts per billion. That may still be too high, according to a team of DMS researchers that has been examining the effects of arsenic on rat cells. Led by physiologist Jack Bodwell, Ph.D., the team published its findings in *Chemical Research in Toxicology*. The researchers described how arsenic disrupts hormone signaling and regulation—causing reproductive problems and other abnormalities—and confirmed that even concentrations of arsenic well below the new standard can cause such problems.

Journal is devoted to field conceived at DMS

Getting a paper published is something any academic appreciates. So consider the prestige of having an entire issue of a journal devoted to a field you founded *and* getting papers by several colleagues as well as yourself into it. In October, a special online issue of the journal *Health Affairs*—titled "Variations Revisited"—featured the work of several Dartmouth physicians and economists, notably John Wennberg, M.D., director of Dartmouth's Center for the Evaluative Clinical Sciences (CECS).

Landmark: The issue explored variations in patterns of clinical practice from one region of the country to another. In an introductory note, John Iglehart, the editor of *Health Affairs*, wrote that in the 31 years since Wennberg and Alan Gittelsohn published a landmark paper in *Science* on clinical practice variation, "one can only marvel at how little variations . . . have been reduced."

Asked how he accounts for the persistence of such variation, Wennberg says, "It is very hard to change economic systems. Our system is not yet designed to punish waste and reward efficiency."

The issue's lead article, by Wennberg, uses Medicare data to evaluate better-performing hospitals. Concentrating on events in the last six months of life, the study followed 90,616 patients with solid-tumor cancers, congestive heart failure, or chronic obstructive pulmonary disease (COPD)—comparing the number of physician visits, hospitalizations, and ICU stays in 77 well-known academic medical centers (AMCs). A second part of the study focused on seven hospitals named by *U.S. News & World Report (USN&WR)* as the best U.S. geriatric hospitals in 2001.

Among the 77 AMCs, rates of use varied wildly. Looking at cancer patients, for example, the number of days in the hospital ranged from a low of 8.5 to a high of 23. Days in the ICU for COPD patients ranged from 1.8 to 13.1. And for patients with congestive heart failure, the number of physician visits ranged from 15.2 to 99.3. Within each hospital, however, the study found a high degree of consistency. In other words, hospitals with high use rates for one condition were likely to have high use rates for other conditions.

Even among the seven "best" geriatric hospitals, there were striking differences. Patients at New York's Mount Sinai Medical Center spent, on average, twice as many days in the hospital during the last six months of life as patients at Mayo Clinic hospitals. The number of ICU days at UCLA Medical Center was three times higher than at Massachusetts General Hospital. And patients at Mount Sinai and UCLA averaged more than twice as many physician visits as those at Duke University Hospital.

Outcomes: Other studies by Wennberg and his CECS colleagues have shown that more care and higher spending do not correlate with better patient outcomes. In fact, the opposite may be true: more care can result in worse outcomes. Why does *USN&WR* give high rankings to hospitals that fare poorly under a study like this? "We are using different kinds of measurements," Wennberg explains. The criteria for making the *USN&WR* list include factors such as numbers of beds and of nurses per bed, plus intangibles such as reputation. "They look at process and structure," says Wennberg, "but . . . they can't predict outcomes."

Elliott Fisher, M.D., M.P.H., a professor of medicine at DMS and codirector of the Veterans Affairs Outcomes Group in White River Junction, Vt., questions in a related paper whether the increased intensity of care at AMCs results in better outcomes. His study tracked mortality rates for Medicare patients who had had heart attacks, colorectal cancer, or hip fractures in 300 hospitals from 1994 to 1996; he followed their care for five years. The hospitals were ranked according to five intensity levels, based on such criteria as frequency of specialist consultations and number of procedures. The data confirmed that more services, and more spending, did not improve outcomes. "Conservative practice looks just as good as, if not better than, a more aggressive, high-intensity practice pattern," he concluded.

FLYING SQUIRREL GRAPHICS

John Wennberg, right, and Elliott Fisher, left, had work featured in a recent special issue of *Health Affairs*.

Wake-up call: Fisher, too, found striking variations in practice patterns. "It's more than a little surprising that there is so much difference in major medical centers across the U.S.," he says. "Having academic medical centers differ so profoundly should be a wake-up call."

The issue's 21 papers included several others with lead authors from Dartmouth—orthopaedic surgeon James Weinstein, D.O.; pediatrician David Goodman, M.D.; surgeon Justin Dimick, M.D.; and economist Katherine Baicker, Ph.D.—plus an essay by and an interview with Wennberg.

The work is having an impact: at a press conference the day of the journal's release, the commissioner of the Food and Drug Administration described steps that Medicare is taking to reduce unwarranted variations in care nationwide. CATHERINE TUDISH

DMS researchers William Wade, Ph.D., and Ronald Taylor, Ph.D., are making progress on identifying a vaccine for cholera, according to papers in recent issues of *Infection and Immunity*.

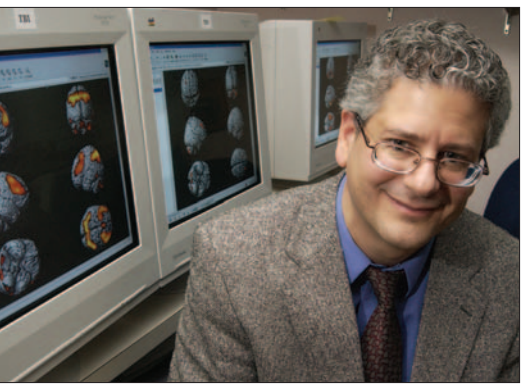
Memorable findings from imaging study

It's unnerving but normal for people to have occasional memory lapses as they get older. Yet some people insist that their forgetfulness is more serious than such "senior moments," even though they do fine on memory performance tests.

MRI scans tell a different story, however. They can detect brain abnormalities in people with these perceived "cognitive complaints"—those who, "on detailed clinical interviews and questionnaires, . . . really feel their memory and other cognitive functions are showing changes," says Andrew Saykin, Psy.D., a professor of psychiatry and of radiology. He reported this unexpected finding, based on a study of 120 older adults, at the Ninth International Conference on Alzheimer's Disease and Related Disorders.

"I thought at first if we saw complaints it would be associated with depression, because people who are depressed tend to feel their cognitive function isn't very efficient," Saykin says. After excluding subjects with clinically significant depression, "it turned out that we were looking at something very specific to the memory system and that we found neural correlates for what people were telling us."

A combination of anatomic and functional MRI, or magnetic resonance imaging, can detect changes in the brains of people with diagnosed memory problems—from mild cognitive impairment (MCI) to Alzheimer's disease. Typically, the hippocampus, the walnut-sized part of the brain that is critical in learning and memory, begins to atrophy in early stages of cognitive disorders. Functional MRI, which maps changes in blood oxygenation during brain activity, showed that fewer brain cells are activated during memory exercises in people who are cognitively impaired than in people whose memory is normal. Subjects with "cognitive complaints" did well on memory tests, but their brains showed changes characteristic of MCI: atrophy of the hippocampus and reduced signaling in the frontal lobes.



JON GILBERT FOX

Andy Saykin uses imaging to diagnose dementias.

Early: The finding may mean the cognitive complaint group could benefit from early intervention for Alzheimer's. About 50% of people with MCI go on to develop Alzheimer's or another dementia, says Saykin, though it's too soon to tell what percentage of those with "cognitive complaints" will do so.

In a different study—this one with only 18 patients, nine of them cognitively healthy and nine diagnosed with MCI—Saykin tested a drug called donepezil. While lying in an MRI scanner, subjects take a test that involves listening to a string of consonants and pressing a button when they hear certain patterns. They take the test without the drug and again after being on it for 10 weeks. "What we found was that in comparison to the control group, the people on drug basically were able to activate their frontal lobes," says Saykin, and that "correlated with better cognitive task performance."

In addition, data from a large trial suggests that the medication can delay the transition from MCI to Alzheimer's.

But while all the results are promising, Saykin cautions that much more study is needed. LAURA STEPHENSON CARTER

Changing view of MS

The "recognition of new 'players'" in the causes and progression of multiple sclerosis (MS) has been one of the biggest changes in MS research in recent years, according to a literature review by two Dartmouth neurologists. MS is predominantly an autoimmune disorder, they explain, but "recent studies have challenged this existing paradigm, supporting the role of other immune cells and factors (even nonimmune)." They concluded that the future of MS therapy is in novel approaches that target "a multifaceted spectrum of immune activity." The paper was published in *Frontiers in Bioscience*.

Inflammatory insight

In a review of the published research on glucocorticoids (GCs)—steroids with metabolic and anti-inflammatory effects—a DMS team found a big gap between the literature and clinical practice. "It seems clear that the long-held clinical view that GCs act solely as anti-inflammatory agents needs to be reassessed," the authors wrote. "Varying doses of GCs do not lead simply to varying degrees of inflammation suppression, but rather GCs can exert a full range of effects from permissive to stimulatory to suppressive." The paper appeared in the journal of the Scandinavian Society of Anaesthesiology and Critical Care Medicine.

Bringing rigor to education, too

It's baffling, really. Medicine, a field rooted firmly in research, has never applied the same degree of rigor to evaluating the way physicians are trained. "If medicine has a high threshold for evidence of clinical care, why is there no corresponding threshold for educational effectiveness?" ask the DMS authors of a September article in the *Journal of the American Medical Association (JAMA)*. "For example, what is the basis for the Liaison Committee on Medical Education (LCME) and Accreditation Council for Graduate Medical Education (ACGME) accreditation requirements?"

"There isn't any!" insists Patricia Carney, Ph.D., assistant dean for educational research at DMS and was the lead author of the *JAMA* article. "What happens," she says, "is that the accrediting bodies all get together and they decide what medical schools ought to be doing, mostly based on what they, themselves, do." In the article, she and her coauthors call for medical schools around the country to channel resources into what they've dubbed "educational epidemiology"—the science of studying the training of doctors. While a lot of papers about medical education are published, the number in which "an actual design is applied to the evaluation and a hypothesis is identified and tested . . . is actually pretty low," says Carney. What is published is largely qualitative rather than quantitative, the authors contend.

Data: But a handful of institutions, including Dartmouth, hope to change that. DMS was also one of eight medical schools invited to write about such research for the October issue of *Academic Medicine*. Medical education research began at DMS in 1995 with data collected on index cards. Carney and family physician Allen Dietrich, M.D., used the cards to track students' experiences in their primary-care rotations. What diseases were they seeing? What procedures were they performing? Then, in 1998, Carney and several colleagues launched ClinEdDoc, a computer-based documentation system.

"To me, ClinEdDoc was a Phase I trial that showed that collecting such data was feasible," says Carney. The system yielded eight published papers, including one comparing the educational experiences students get at academic medical centers, affiliated residency sites, and community-based practices. ClinEdDoc also allowed students to track their own learning and identify any gaps.

Today, DMS students use a different computer-based tool, the Dartmouth Medical Encounter Documentation System (DMEDS). They can record a wide variety of data on DMEDS, from diagnoses they encounter to communication skills they employ.

Better ways of assessing medical education are essential "unless we plan to go to five-year programs," says Carney. "We have got to figure out what older parts of the curriculum don't need to stay, because medicine is evolving. The science of health care, not just medicine but the whole shooting match, is so complicated that we have got to figure out what belongs and what doesn't." JENNIFER DURGIN

MARK WASHBURN

Dartmouth cardiologist David Malenka led a study that has policy implications.

Heart study raises policy questions

Should hospitals without heart surgery programs be allowed to offer invasive though nonsurgical heart procedures like angioplasties and stent implantations? A recent study headed by DMS cardiologist David Malenka, M.D., offers new insight into this controversial question. By comparing Medicare data from over 600,000 patients who underwent any of several nonsurgical procedures classed as percutaneous coronary interventions (PCIs), Malenka and colleagues revealed disparities between hospitals with and without surgical backup.

The study was based on 943 hospitals with a heart surgery program and 178 without one. Overall, patients who had PCIs in hospitals without such programs were 29% more likely to die within 30 days than those treated in hospitals with on-site heart surgery. Patients who had PCIs on a nonemergency basis fared even worse; they were 36% more likely to die in hospitals without than those with surgical backup. But no difference in mortality was seen between the two kinds of hospitals when PCIs were performed on an emergency basis—which the researchers defined as procedures done the same day patients were admitted for a heart attack.

The puzzling nature of this latter finding was noted in an editorial accompanying the paper, which was published in the *Journal of the American Medical Association*. "It seems unlikely that the interventional cardiologist would be a poor operator for one kind of procedure and a superior operator for the other," said the editorial.

Implications: Nevertheless, the findings have important implications. "If PCI programs are allowed to develop in centers without on-site cardiac surgery, patients being treated by [emergency] PCI will likely benefit," concluded the paper's authors. But, they cautioned, policies aimed at increasing access to emergency PCIs by making them available at hospitals without cardiac surgery "may inadvertently lead to an overall increase in mortality related to PCI," since 78% of PCIs performed at such hospitals are done on a nonemergency basis.

While Malenka headed the study, the lead author of the paper reporting the results was David Wennberg, M.D.C.M., an adjunct associate professor at Dartmouth Medical School. JENNIFER DURGIN

On December 1, World AIDS Day, Dartmouth received $2 million to combat pediatric AIDS. The funds are going to a collaborative project run by DMS and Muhimbili University in Tanzania.

Hedgehog pathway presents many puzzles

"To me, signal transduction is like a puzzle, except there is no picture that comes with it," says David Robbins, Ph.D., an associate professor of pharmacology and toxicology. Robbins studies how proteins transmit signals from the outside to the inside of a cell in order to turn a target gene on or off. His lab is interested in a specific signaling pathway called Hedgehog, which plays a role in both early development and cancer.

The Hedgehog gene (or Hh, as it's abbreviated) was first studied in fruit flies. It acquired its name because during embryonic development, its mutant in flies is covered with pointy denticles, so resembles a hedgehog. Three mammalian versions of Hh were subsequently discovered —Desert, Indian, and Sonic; the latter is named after a video game character with a row of blue spikes down its back.

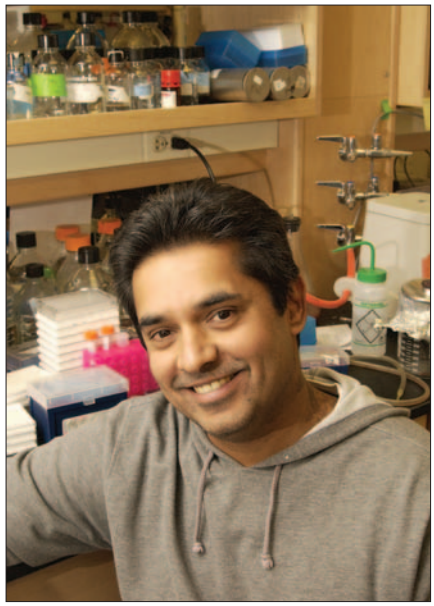
Agent: A key reason for studying these pathways, explains Robbins, is their implications for drug development. In the past, drugs were discovered empirically. "If someone ate something and survived," Robbins says, the substance became a new therapeutic agent. "Now drugs are developed more mechanistically," he says, to target specific steps in signaling pathways. This method has yielded many effective medications, and understanding the Hh pathway could lead to the identification of more drug targets to treat cancer and developmental disorders.

The mechanism of Hh signaling is largely unknown, however, so Robbins and his colleagues have been trying to learn more about it. They are interested in what happens both inside and outside the cell. Evidence has suggested the existence during development of a diffusible form of Hh—one capable of sending, over long as well as short distances, signals that cause cells to become specialized tissues. Robbins's lab has succeeded in identifying a native, diffusible form of Hedgehog thought to play this role.

Target: Meanwhile, inside the cell, the Hedgehog Signaling Complex (HSC) has been shown to play an important role in this pathway. One of Robbins's key contributions to the field was the discovery of HSC. It consists of several proteins, including the transcription factor responsible for activating the target genes of the Hh pathway. The HSC acts as a "middleman" between the binding of Hh to its receptor and the activation of target genes inside the cell. Understanding the exact mechanism by which this occurs is Robbins's next goal; his lab's preliminary discoveries show the process to be very complicated. For example, there may be two forms of the HSC and three forms of the transcription factor.

So there are still many missing pieces to this intricate puzzle. But the fact that Robbins has "always liked puzzles" augurs well for his ability to eventually put them all together. KRISTEN GARNER

JON GILBERT FOX



David Robbins studies cell-signaling mechanisms.

Stentorian note

Building muscle is usually good—but not in your arteries. In fact, according to Michael Simons, M.D., chief of cardiology at DHMC, the growth of smooth muscle along the lining of arteries is the most common cause for the failure of stents—mesh tubes that reopen blocked blood vessels. A team led by Simons reported in *Circulation* that smooth muscle can proliferate in arteries after mechanical injury, such as from angioplasty or stenting. So stents coated with smooth muscle inhibitors are the treatment of choice, the authors concluded.

Pancreatic promise

Two recent studies show promise for combating pancreatic cancer, one of the most aggressive and deadly cancers. In a trial led by Murray Korc, M.D., chair of medicine, researchers injected a protein "sponge" into mice with human-derived pancreatic tumors. "The protein sponge completely suppressed pancreatic tumor growth," Korc reported. "In all the tumors tested, there was a marked decrease in blood vessel formation, which is very exciting." The other study—led by a postdoctoral fellow in Korc's lab, Nicole Boyer Arnold, Ph.D.—described a pathway that is responsible for pancreatic cancer's ability to become resistant to traditional chemotherapy.

Phone is key to novel psychiatric approach

"Reach out and touch someone" ran a 1980s Bell System jingle that urged phone customers to call a loved one. Using the phone to connect people is also at the heart of a new treatment for depression that was developed by Dartmouth family physician Allen Dietrich, M.D., and a team of researchers across the country.

The new approach is called RESPECT-Depression—short for Re-Engineering Systems for the Primary Care Treatment of Depression. It integrates work by a primary-care clinician, who diagnoses and manages the patient; a care manager, who provides telephone support; and a psychiatrist, who supervises the care manager and offers treatment suggestions to the clinician.

Trial: Five U.S. health-care organizations, encompassing 60 affiliated practices, participated in a clinical trial that compared the new model to standard care. After six months, 60% of RESPECT-Depression patients (106 out of 177) had responded substantially to treatment, versus 47% of standard-care patients (68 out of 146). In addition, 90% of patients treated using the new model rated their care as good to excellent (they noted that they especially appreciated the telephone support), compared to only 75% of patients in the control group. All five organizations have taken steps to sustain use of the new model, and one, Highmark Blue Cross Blue Shield of Pittsburgh, Pa., decided to make the changes permanent. The trial results were published in the *British Medical Journal* in September 2004.

"This is a big step forward for patients, for clinicians, and for insurers," says Dietrich, who was the lead author of the paper. "Other studies have provided guidance on steps to enhance primary care of depression. But this study shows how to translate such actions from the page to routine practice." The model was developed by the MacArthur Initiative on Depression and Primary Care, a national collaborative that Dietrich cochairs, with John Williams, M.D., of Duke. Dartmouth psychiatrist Thomas Oxman, M.D., is its associate chair.

Under the new model, if a patient shows warning signs of depression—such as daily fatigue, eating disorders, low self-esteem, or thoughts of suicide—the clinician administers a patient health questionnaire, the PHQ9, to assess the severity of the depression. The clinician then talks with the patient about how the treatment plan will be structured in terms of psychiatric counseling, use of antidepressants, and interactions with the care manager. The primary-care clinician also does a suicide assessment and introduces the patient to the idea that the process will take at least a few months.

A care manager then calls all patients monthly to help them stay on their medication, answer questions about side effects, help them schedule counseling visits, and support them in taking self-management steps such as planning exercise and social activities. "Patients with depression often have trouble showing initiative or being active, and so the follow-up [by the care manager] to make sure they're moving forward and to give them emotional support I think is very important," says Dietrich.

Process: The care managers are nurses, social workers, or people with backgrounds in public health and most often are hired from within the sponsoring health-care organization. Care managers administer the PHQ9 each month and report to the supervising psychiatrist, who then gives suggestions to the clinician about changes in treatment. This process continues monthly until the patient achieves remission.

Magellan Health Services, Inc., one of the largest national behavioral-health managed-care organizations, is in the pilot phase of applying the new model and is working with other health plans to develop the use of it in community primary-care practices. In addition, RESPECT-Depression is being adapted by the Department of Defense for a pilot program at Fort Bragg, to treat soldiers who return from Iraq and Afghanistan with symptoms of post-traumatic stress disorder (PTSD). The *New England Journal of Medicine* reported in July 2004 that rates of PTSD and major depression were much higher among returning troops in 2003 than in earlier military campaigns.

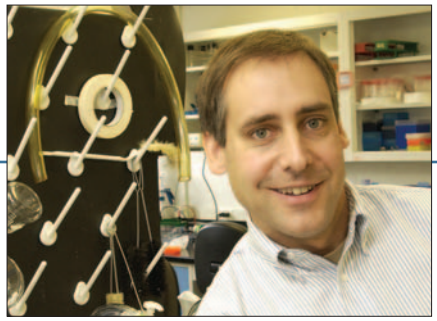
JON GILBERT FOX

Family physician Allen Dietrich is helping primary-care colleagues nationwide treat depressed patients.

Depression: According to the World Health Organization, depression was the fourth-highest cause of disability and premature death worldwide in 1990 and will be the second-highest by 2020. In the U.S., clinical depression affects more than 19 million people each year, yet fewer than half of them seek treatment. Dietrich and Oxman believe that the new approach can help. "Family physicians are good at treating depression," explains psychiatrist Oxman. "The problem is they are so busy. . . . But when you have a system for them, then people don't fall through the cracks."

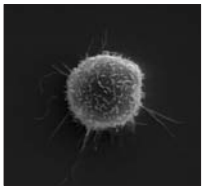
MATTHEW C. WIENCKE

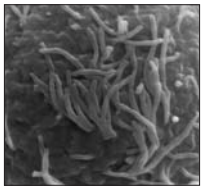
His eye's on microvilli



JON GILBERT FOX

Higgs, above, studies lymphocyte microvilli, below.





Lymphocytes are "guys in white hats" in more ways than one. They are circulating white blood cells and play a key role in battling villains like infections and inflammatory diseases. It's long been known that lymphocytes have numerous finger-like projections called microvilli. Over the past five years, it has become clear that microvilli serve a critical physiological function. Among those helping to advance understanding of the role of these "good guys" is Henry Higgs, Ph.D., an assistant professor of biochemistry at DMS.

Microvilli are believed to be important in guiding lymphocytes out of the rapidly moving blood stream into locations in the body where they are needed—a process called extravasation. The emerging picture is that tissue inflammation triggers the migration of molecular receptors from the interior membrane of the endothelial cells that line blood vessels to the cells' surface. When these receptors are exposed to slower-moving blood at the margin of a vessel, they appear to interact weakly with lymphocytes' microvilli.

Receptors: Imagine a tumbleweed being blown up a narrow canyon, its outer stems catching on obstructions that gradually slow it down. Finally, it has been slowed enough to put down roots. Similarly, the tips of microvilli are almost certainly the initial contact with endothelial receptors that slow lymphocytes' momentum. But the anchoring mechanism is believed to be located at the base of microvilli. It seems likely, therefore, that there are two different kinds of docking apparatus involved in extravasation. The anchoring step causes the lymphocyte to flatten and elongate. Next, the lymphocyte worms its way between the tightly fitted endothelial cells, finally emerging on the tissue side of the blood vessel.

At that point, evidence suggests that the lymphocyte reassumes its normal shape and proceeds to the site of the inflammation to do immunologic battle. Even in the absence of inflammation, lymphocytes routinely migrate to and patrol lymph nodes, apparently seeking out abnormalities that failed to elicit an alarm. It's not known what part, if any, microvilli play in other immunologic functions, such as antibody production, but Higgs is convinced they do have other roles.

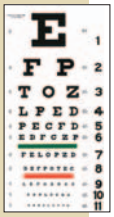
Many details remain to be worked out, but there is hope that extravasation can be exploited clinically. For example, the body's inclination to reject a tissue transplant is mediated largely by lymphocytes. Today, rejection is controlled with powerful but toxic immunosuppressant drugs that interfere with lymphocytes' function. If extravasation could be blocked or slowed, the body might more readily accept the foreign tissue—without the toxic effects of immunosuppressants.

There are other potential therapeutic applications. For example, if the migration of lymphocytes to arterial plaques containing cholesterol could be blocked, it might prevent the rupture of those deposits—a common cause of heart attacks and strokes. And many cancer cells share aspects of the extravasation process, accounting for their ability to metastasize, meaning the malignancy of some cancers could be reduced by destroying their microvilli. So the body's "white hats" may yet help investigators do battle with other bad guys. ROGER P. SMITH, PH.D.

Annual research funding to Dartmouth Medical School has increased by 58% since fiscal year 2001. For more on the most recent fiscal year's research income, see page 19 in this issue.

Visionary work

Zinc plays a critical role in the blinding disease retinitis pigmentosa, according to a group of researchers from DMS. The team determined that a zinc deficiency can cause malformation of a light-receptor protein called rhodopsin, which is essential for vision but is dysfunctional in those with the disease. The discovery reveals a possible "pharmacological approach for the treatment of select retinitis pigmentosa mutations," wrote the paper's authors. Their report was the "Paper of the Week" in the *Journal of Biological Chemistry*. Since the disease affects an estimated one million people worldwide, the public health implications of the work are promising.



Another look at Botox

In addition to treating wrinkles, severe underarm sweating, and certain neurological disorders, Botox may also be a safe and effective treatment for gastroparesis—a debilitating gastric disorder that causes nausea and vomiting and often affects diabetics. The finding came from a small study led by DHMC gastroenterologist Brian Lacy, M.D., Ph.D. The eight subjects were all type I diabetics. Before the treatment can be added to the list of Botox's approved uses, however, a double-blind, placebo-controlled trial is in order. ■