

**Patient compliance is vital in clinical trials. Of 23 sites in the National Lung Screening Trial, which is comparing x-rays with spiral CT scans, DHMC has one of the highest compliance rates.**

## On the record about off-label drug use

**W**hen a doctor says “take two and call me in the morning,” patients tend to assume there’s sound evidence backing up the recommendation. But that may not be the case, according to a study led by David Radley, M.P.H., a Ph.D. student at DMS’s Center for the Evaluative Clinical Sciences.

**Uses:** Using a national database, Radley and colleagues analyzed 725 million prescriptions written in 2001. They found that 79% were for uses approved by the Food and Drug Administration (FDA), while 21% were “off-label”—for uses not approved by the FDA.

Off-label prescribing is not necessarily cause for alarm, notes a DMS pharmacologist. “A lot of the time, using a drug in a way that’s not FDA-approved is very good treatment,” says David Nierenberg, M.D., who was not involved in the study. But there must be “good papers in the peer-reviewed journals that are unbiased that show that the drug is safe and effective” for the off-label use. Herein lies the most disconcerting finding of Radley’s study.

Of the 725 million prescriptions he analyzed, 15% were written without evidence of safety or effectiveness. In other words, these drugs were not approved by

the FDA for the condition they were prescribed for *and* there were few or no reports in the scientific literature supporting the use. Psychiatric and allergy drugs were the most common ones in this category. “This issue of sneaking off of FDA approval into another area can be very dangerous,” observes Nierenberg.

“By definition, off-label uses receive less scrutiny than labeled ones do,” Radley says. “This doesn’t mean that all of them are bad. This doesn’t mean that they are not carefully considered by the physician prescribing the drug. But it does imply that off-label uses may carry greater unknown risks compared to approved uses.”

Concerns about patient safety are what first inspired Radley to begin researching prescribing patterns, when he was an M.P.H. student at Yale. Although his study—published in *Archives of Internal Medicine*—does not assess patient safety, it provides a foundation for further inquiry. “Our study was innovative in that it was the first” to comprehensively examine off-label prescribing, says Radley.

He is also concerned about the wastefulness of prescribing practices with little or no scientific evidence. “The efficiency with which we provide care,” says Radley, “is something that everybody should be thinking a lot about.”

To address both concerns, he and his coauthors call for “more extensive post-marketing surveillance to identify non-evidence-based prescribing practices that lack FDA approval.”

**Evidence:** And at the individual level, Radley encourages patients to ask their doctors about the evidence behind prescriptions they write. “Patients should be asking their doctors, ‘Is this going to work for me? Is it going to put me at risk?’” Radley advises. “That holds not just for off-label medication use, but for all medication use.”

JENNIFER DURGIN

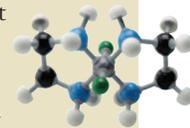


MARK WASHBURN

**A recent study found that 15% of U.S. prescriptions do not have sound evidence behind them.**

### A mast-er regulator

Mast cells—the cells responsible for making allergy sufferers miserable—have important, beneficial roles to play in tissue transplants, DMS immunologists recently reported in *Nature*. Lead researcher Randolph Noelle, Ph.D., and his team found that mast cells regulate specific T-cells



that are “essential to establish and sustain self-tolerance” of a transplant. “Even though recent studies have underscored the plasticity of mast cells in regulating acquired immune responses,” Noelle and colleagues wrote, the finding “that mast cells may be instrumental in orchestrating T<sub>Reg</sub>-cell-mediated peripheral tolerance is unprecedented.”

### Talk therapy

Just three phone calls a year from a nurse-educator can significantly improve emotional and physical functioning in patients with chronic pain and psychosocial problems. That was the primary finding of a controlled

trial by researchers in DMS’s psychiatry department. The nurse-educators assessed patients’ pain, psychosocial problems, and treatment preferences; reviewed self-management strategies with them; provided problem-solving approaches; and gave rapid feedback to the patients’ primary-care physicians. The paper was published in *Annals of Family Medicine*.





The Association of American Medical Colleges reported that DMS's Department of Microbiology and Immunology ranks 6th out of 126 medical schools in research income per faculty member.

## “Dramatic” finding from a casual chat

It's not often that a casual chat leads to a research project with important implications. But at DMS, at least one study began that way.

Microbiologist George O'Toole, Ph.D., explains that the project—on biofilm infections associated with catheters—grew out of a conversation between Robert Shanks, Ph.D., a postdoctoral fellow in microbiology, and DHMC nephrologist Martha Graber, M.D. And *that* conversation was stimulated by a chat Graber had had with ophthalmologist Michael Zegans, M.D., about biofilm-related eye infections. As Graber listened, she wondered if some of the *Staphylococcus aureus* infections she was seeing in the dialysis unit might be biofilm related. Biofilms, which are bacteria in communities rather than in free-swimming or planktonic form, are more resistant to antibiotics.

Later, Graber had lunch with Shanks and other biofilm researchers. And *that* led to a collaboration with O'Toole, Shanks, and others to investigate whether heparin, an anticoagulant commonly used in dialysis procedures, has an impact on the ability of *S. aureus* to form biofilms.

“The answer to that question is most definitely yes,” O'Toole says. The finding that heparin stimulates the formation of

bacterial biofilms was reported in the journal *Infection and Immunity* in 2005. A follow-up study published this year in *Nephrology Dialysis Transplantation* reported that sodium citrate—an anticoagulant used widely in Europe, but not in the U.S., to prevent clotting in catheters between uses—can inhibit biofilm formation.

Patients with failing kidneys must undergo dialysis several times a week. They are connected to a machine via a catheter placed in a large neck vein or via a fistula, a surgically created connection between an artery and vein in the arm. The machine removes, purifies, and returns blood to the patient. Fistulas are less likely to become infected but cannot be used until the surgery site heals.

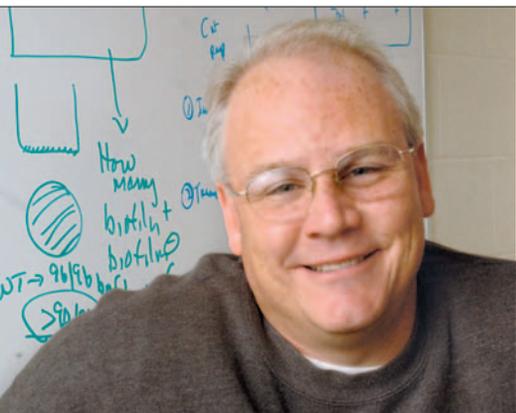
There are 400,000 vascular catheter infections a year in the U.S., caused mostly by *S. aureus*. “Bugs get in through the hole where the blood goes,” Graber says. “It's the Achilles' heel of catheters.”

And so is heparin. Although it's effective at preventing clotting in catheters, it can leave patients vulnerable to hard-to-treat biofilm infections.

**Staph:** In order for biofilms to form, “you need cells attaching to a surface and cells attaching to each other,” O'Toole explains. “Heparin seems to stimulate the ability of staph to bind to itself.”

Shanks, who is now on the faculty at the University of Pittsburgh, is studying the mechanism by which heparin does this. And at DMS, O'Toole's lab is investigating how sodium citrate works and is testing alternatives. Sodium citrate is not widely used in dialysis in the U.S. because of fear of accidental infusion of highly concentrated forms. DHMC uses heparin.

The heparin-biofilm association was unknown until the Dartmouth papers. “This was such a clear finding—it was so dramatic,” says Graber. “I was incredibly surprised.” LAURA STEPHENSON CARTER



JON GILBERT FOX

George O'Toole's lab studies biofilm formation.

### Fat chance

One could say that breast cancer cells are addicted to fat—or, rather, to a protein called S14 that allows the cells to manufacture their own fat. “This makes sense, as fat is a crucial fuel for breast cancers,” explains William Kinlaw, M.D., an associate professor of medicine at Dartmouth. He recently published three papers revealing potential for S14 as a new anticancer target. “We're now working to examine this idea rigorously in cancer-prone mice engineered to lack S14 in the mammary gland,” adds Kinlaw, “and to find areas on the S14 protein that might be suitable for attack with a drug.”



### Brain teaser

Exposure to nonylphenol—a prevalent environmental pollutant derived from herbicides, pesticides, polystyrene plastics, and paints—may harm a developing brain, a team of Dartmouth researchers recently reported. “Our results suggest that this environmental estrogen, if present at elevated levels, . . . may have deleterious effects on neuronal differentiation,” wrote Leslie Henderson, Ph.D., et al. in the journal *Endocrinology*. “Because nonylphenol bioaccumulates, our results may be broadly applicable to a wide range of . . . terrestrial species that are higher in the food chain,” not just the aquatic organisms they studied.





A paper in the electronic edition of the journal *Science* by DMS geneticist Jay Dunlap, Ph.D., and colleagues has suggested the cellular clock has an anticancer as well as a time-keeping role.

## Some movie smoking is still rising

There is good news and bad news from Hollywood. The latest DMS study—in a nine-year effort to quantify the effects of movie smoking on young people—showed that across all ratings movies now contain less smoking. That’s good news, since 80% of smokers begin before age 18.

“Because movie smoking is linked to adolescent smoking, it was important to us to clearly and quantitatively understand how and when cigarette use is depicted on-screen,” says James Sargent, M.D., a professor of pediatrics and director of cancer control at Dartmouth’s Norris Cotton Cancer Center. The new study was released by the American Legacy Foundation, an organization devoted to keeping young people from smoking.

**Depictions:** A closer look reveals disquieting news rooted in the movie rating system, which classifies films for age-appropriate content—primarily language, violence, and sex. Sargent’s team reviewed the 100 highest-grossing movies each year from 1996 to 2004. Most box-office hits carried ratings of G, PG, or PG-13. These movies are seen by three times as many youths as R-rated movies. And 75% of the films produced and rated for young people still contain depictions of tobacco. Although the percentage of youth-rated

movies with tobacco use has gone down, the absolute number of such movies has risen as studios gear more and more films to the young. This is the bad news.

“This trend may have implications for youth exposure, because, as the movie industry has shifted toward releasing a higher proportion of its movies with a youth rating, so has a higher share of movie smoking become youth-rated,” the report said. The authors also proposed a solution: “Since movies are financed and produced with a target audience in mind, an R-rating for smoking would assure that movies intended for youth audiences would be smoke-free.”

Sargent explains the recommendation: “The assumption is that the industry would strip the smoking from movies that are intended for the G to PG-13 range rather than risk an R rating, because they want to retain the adolescent segment of the viewer market.” His team’s report gives the Legacy Foundation and other groups fodder to continue lobbying studio heads, since any decision to alter the rating system rests primarily with them. “There are many public-health activists at state and local levels working on this issue,” Sargent says. “We need to bring pressure to bear on the movie industry.”

**Effect:** In addition to continuing to measure movie smoking, the DMS team has also started looking at another aspect of the issue. For that purpose, social psychologist Keilah Worth, Ph.D., joined the group a year ago. “I’m trying to get an idea of which kids are most vulnerable to the [movie] effect, why the effect might be happening,” she says. “The psychological mechanism behind it is exactly what we’re trying to figure out now. It is not the case that kids who are just going to smoke anyway watch these movies—that it doesn’t matter because they’re going to smoke anyway.”

ROSEMARY LUNARDINI



ION GILBERT FOX

Smoking in youth-rated movies gets Sargent even more exercised than this vintage Camel poster.

### Seek and ye shall find

DMS researchers have shown once again that when it comes to cancer, the harder you look, the more you find. “The incidence of thyroid cancer in the United States more than doubled over the past 30 years,” wrote Louise Davies, M.D., and H. Gilbert Welch, M.D., M.P.H., in the *Journal of the American Medical Association*.

But most of the cancers were two centimeters or smaller, and “mortality [from thyroid cancer] remained stable during this period,” suggesting “that increased diagnostic scrutiny has caused [the] apparent increase.”

### Etude in D minor

Watchful waiting, though a time-honored practice for many conditions, may not be the best choice for patients with minor depression who seek help. Only 9% to 13% of patients improved after a month of watchful waiting in a small study conducted by Dartmouth psychiatrists and psychologists. The findings also suggest that encouraging “regular engagement in active pleasant events” and discouraging “avoidant coping styles” may be beneficial interventions. “Developing evidence-based self-help materials along with aggressive dissemination measures could have a significant impact,” they concluded in their paper, published in *General Hospital Psychiatry*. ■

