



JON GILBERT FOX

Thérèse Stukel headed a study whose conclusion was that many heart-attack patients don't get optimal care.

High-tech care may not be best for heart attacks

Drug therapy can be as beneficial as expensive, high-tech cardiac procedures in prolonging survival after a heart attack, according to a recent Dartmouth study. Furthermore, the treatment that patients get varies widely by geographic region. “What we found was . . . a bit of a surprise,” says Thérèse Stukel, Ph.D., lead author of the study, which was published in the *Journal of the American Medical Association*. “We really are not prescribing drugs optimally.”

Survival: Every year, more than 280,000 Medicare patients are admitted to hospitals with heart attacks—and 18% of them die within 30 days. The researchers examined seven years of data on 158,000 Medicare patients who were hospitalized after a first heart attack in 1995 or 1996. The study focused on how the treatment that patients got—medical management versus invasive management—affected their survival.

Medical management involves the administration of drugs, such as aspirin, that thin the blood; drugs that reduce blood pressure; and thrombolytics, drugs that prevent the formation of clots. Invasive management includes cardiac catheterization, a diagnostic procedure whereby a thin tube is threaded through the arteries to find blockages; angioplasty, a therapeutic procedure whereby a

balloon-tipped catheter is inserted into a blocked vessel to improve the blood flow; and bypass surgery, where a new vessel is grafted onto an artery to circumvent a blockage.

Stukel and her colleagues found that patients who received invasive therapy lived no longer than those who received optimal medical therapy. “So what we are doing is exposing patients to these high-tech, high-risk procedures that are very costly without getting the benefit,” she explains.

Some cardiologists disagree with the study's findings, saying clinical trials have shown that invasive treatments improve survival. Stukel, however, points out that those trials were performed on ideal patients in facilities where experienced doctors “perform the procedures within 12 hours of the heart attack.” But, she adds, “this is by and large not the case in the real world.”

The problem is that “the public wants the latest, high-tech service and feel that care is being rationed if they're not receiving it,” she says. “It's very difficult to tell a patient that this may not improve their survival, whereas taking their cardiac medications might.”

Supply: Patients are more likely to get invasive procedures if they live in areas of the country that have a greater supply of high-tech cardiac services. “There is a strong rela-

tionship between how much technology is available and the likelihood of these patients getting it,” says one of Stukel's coauthors, David Wennberg, M.D., M.P.H., an adjunct associate professor of community and family medicine at DMS.

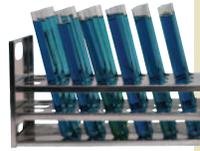
“It's very difficult to turn your back on a piece of technology that's just down the hall,” Stukel points out.

The study also confirmed previous work showing that older, high-risk patients, who are more likely to benefit from invasive care, are *less* likely to receive it. Ironically, doctors may fear that invasive therapy is too dangerous for these patients. “What tends to drive that treatment practice is possible physicians' misconceptions about risk/benefit trade-offs,” Stukel says. “Typically, they direct the therapy to lower-risk and younger patients.”

Risk: So if drugs aren't being prescribed optimally and invasive therapy is being given to the wrong patients, what's the solution? “What we are recommending is a systems-minded approach, such as standing orders at hospitals and electronic medical records, so that every eligible heart-attack patient is immediately stratified into high-risk or low-risk and receives the cardiac drugs, unless the physician orders” otherwise, says Stukel.

In addition, some experts propose regional cardiac centers but disagree on the model. Some argue that all heart attack patients should be transported as quickly as possible to such a center. Others, like Stukel, think patients should go to a local hospital to get immediate thrombolytics and medical therapy, and if necessary later be referred to regional centers specializing in intensive heart treatments. “Time is muscle,” Stukel says. “Heart-attack patients need to have thrombolytics . . . as fast as possible.”

The authors hope the results will improve the care patients get. “What I would hope is that the seduction of high-tech medicine will be tempered by the finding that really good basic medicine is as important [as], or more important than, these high-tech type of activities,” says Wennberg. SION E. ROGERS



According to the the latest data available from the Association of American Medical Colleges, DMS is 21st among the nation's 125 medical schools in grant income per basic-science faculty member.

Pleas are persuasive, but are they positive?

After seeing or hearing celebrity pitches for cancer screening, Americans are more likely to get screened, found a DMS study. But the authors of the paper, published in the *Journal of the National Cancer Institute*, say the well-meaning, passionate pleas of people like Katie Couric, Rosie O'Donnell, and Norman Schwarzkopf may not be good for the public.

"Celebrity endorsements of cancer screening tests typically consist of one-sided messages either asserting that the celebrity's life was saved by a cancer screening test or suggesting that the life of a loved one was lost due to a failure to be screened," says Steven Woloshin, M.D., coauthor of the study.

Two-edged: But the decision to undergo screening is more complex than such ads imply. "Early detection of cancer will help some people, but it can create problems for others, such as unnecessary testing and treatment," the authors explain. "Consequently, screening is increasingly recognized as a two-edged sword." (For more on this subject, see page 40.)

To find out *how* influential celebrity messages about cancer screening are, the researchers surveyed a nationally representative sample of 360 women aged 40 or older and 140 men aged 50 or older. They asked the women if they'd "seen or heard celebrities like Rosie O'Donnell and Nancy Reagan talk about getting mammograms"; 73% said they had. Men were asked if they'd "seen or heard celebrities like Norman Schwarzkopf talk about getting PSA tests"; 63% said they had. And men and women over 50 were asked if they'd "seen or heard celebrities like Katie Couric talk about getting a sigmoidoscopy or colonoscopy"; 52% said they had.

Next, those who responded "yes" to the first questions were asked if the messages had made them more likely to have the screening test, less likely, or neither. It

turned out the effect was significant—"more likely" responses totaled 25% for mammography, 31% for PSA, and 37% for sigmoidoscopy or colonoscopy.

Likely: "There's not a lot out there that can get 25% of people to say that they are more likely to get screened," says Robin Larson, M.D., M.P.H., lead author of the paper. The same team also just published a study on advertising by academic medical centers (see the facing page).

"Screening is really a complex issue," says Larson. "Americans are very enthusiastic about screening, and they don't perhaps understand that there are downsides." She and her coauthors are also concerned about the effect of celebrity endorsements on doctor-patient relationships. "It makes it harder for you," she says, "when you do go to your doctor and try to have a balanced conversation about something when you have this emotional, influential person saying, 'Go get screened. I might not be alive now if I hadn't.'"

The goal of messages about screening "should not be to persuade but to inform," the authors conclude. "Thus, we see no obvious role for celebrity endorsements of cancer screening." JENNIFER DURGIN

Appeals by celebrities like the one below are effective—but a DMS study questions their effect.

Risk assessment

Many female reproductive factors—such as taking oral contraceptives, having children at a given age, or receiving estrogen replacement therapy (ERT)—do not seem to affect a woman's risk of developing pancreatic cancer, says a study by DMS's Eric Duell, Ph.D. But the findings, published in the *American Journal of Epidemiology*, did suggest that women who reach menopause at age 45 or older may be more likely to get pancreatic cancer, as well as that oral contraceptives and ERT may lower the risk for current and former smokers.



Oh, oxygen

Many preemies need respirators because their lungs can't process enough oxygen from the air. But high concentrations of oxygen inhibit lung-cell growth and, a new DMS study shows, protein synthesis. In the *American Journal of Physiology*, a team led by Jeffrey Shenberger, M.D., revealed the mechanisms by which hyperoxia—too much oxygen—hinders the creation of proteins that are essential for lung development. "Whereas a great deal has been learned regarding the activation of cell cycle checkpoints and DNA repair pathways by hyperoxia," the paper said, "little attention has been paid to the process whereby hyperoxia impairs translation." Until now.



Academic medicine meets Madison Avenue

Top academic medical centers appear to be guilty of some of the same advertising practices—such as using emotional appeals and failing to present balanced information—that have earned pharmaceutical ads a bad rap. In a study published in the *Archives of Internal Medicine*, four Dartmouth physician-researchers reviewed 122 newspaper advertisements from the 17 academic medical centers that were named to the *U.S. News & World Report* “Honor Roll” of best hospitals in 2002.

Concern: “Many would think that advertising by academic medical centers is just kind of mismatch, so it was interesting to find that almost all of them are doing it,” says the paper’s lead author Robin Larson M.D., M.P.H., an instructor in medicine who just completed a fellowship in outcomes research. And “what’s more interesting, or concerning, is the way that they are doing it.”

Of the 122 ads that the team analyzed, 75 of them used what Larson and her colleagues categorized as emotional appeals. For example, an ad promoting a women’s heart center included the text “Researchers find the leading killer of women to be indifference.” Another read “The [medical center name] restored my eyesight. And my ability to dream.”

Further, 58 of the ads promoted free or inexpensive services that the authors believed were “likely to lead to further business,” such as a free symposium on fertility or complimentary health screenings.

Although 36 of the ads simply promoted the hospital and 65 of them promoted groups of related services, such as cancer centers, many pushed cosmetic services and procedures whose benefits remain unproven, such as total-body CT scans.

“When the public sees ads from academic medical centers, I think they really assume that it’s something that’s a good idea and it’s safe or proven,” says Larson. But that may be a false assumption, according to the study. “Of the 21 ads for single services, two pro-

moted a widely accepted procedure (dialysis),” the authors wrote. The remaining 19 single-service advertisements were for “procedures considered cosmetic,” such as Botox injections and LASIK eye surgery; procedures having “limited (or no) efficacy data,” such as deep-brain stimulation and total-body CT scans; or procedures “lacking consensus,” such as prostate-specific antigen (PSA) and digital rectal examination cancer screening tests. (For more on the debate surrounding cancer screening, see page 40.) And only one such ad mentioned potential harms associated with a service.

Although any advertisements that are aimed at recruiting research subjects for clinical trials must first be approved by a medical center’s institutional review board, in order to ensure that their messages are accurate and objective, none of the centers in the study had “a comparable process for advertising to attract patients,” the authors noted in the paper. “Why should patients get less protection than research subjects?” asked Larson and her collaborators—Lisa Schwartz, M.D.; Steven Woloshin M.D.; and H. Gilbert Welch, M.D., M.P.H.

Assumption: All four authors are members of the DMS faculty, internists at the VA Medical Center in White River Junction, Vt., and members of the VA Outcomes Group, a collaboration of physician-researchers and fellows who are concerned with how medical information is communicated to the public and who question the assumption that patients always benefit from more care. The same authors also recently published a paper about the effect celebrity endorsements have on the public’s willingness to be screened for cancer (see the facing page).

Although the authors were critical of academic medical center advertising, they did acknowledge the “growing financial challenges” facing such centers, “as providers of a disproportionate amount of care to the poor and uninsured as well as many unprofitable



Larson shows samples—on her computer screen and on a tear sheet—of the ads that a recent study analyzed.

but necessary services.” The reality is that attracting new patients helps academic medical centers stay afloat and fulfills a tremendous public service—providing care regardless of an individual’s ability to pay. DHMC, for example, provided \$87.7 million in uncompensated care in 2004. (Dartmouth-Hitchcock was not included in the study, however; although it’s ranked by *U.S. News & World Report* in several categories, it’s not listed in enough specialties to make the magazine’s “Honor Roll.”)

Sensitive: Yet in order to also serve their mission to “improve the health of their communities and the larger society in which they reside,” academic medical centers should focus their advertising on “evidence-based services, or at least those likely to improve overall public health,” the authors of this study contend. Overall, academic medical centers need to be “more sensitive to the conflict of interest between public health and making money,” they assert. JENNIFER DURGIN



DMS geneticist Victor Ambros, Ph.D., presented data at a meeting in Europe on the use of a new assay for profiling microRNA in samples of the human brain cancer glioblastoma multiforme.

A look at metabolism in breast tumors

If being a resident is like learning to ride a bike—you're pushing the pedals but are supported by training wheels or a parent running alongside—then resident Jennifer Quinn, M.D., M.P.H., will soon be trading one training bike for another.

Skills: Quinn, who is about to complete her residency in internal medicine, will stay on at DHMC as a Tiffany Blake Fellow. The fellowship, underwritten by the Hitchcock Foundation, funds a year of supervised study and research to help a physician develop the skills to become an effective investigator and to compete for independent grant support. Quinn will be working at Dartmouth's Norris Cotton Cancer Center in the lab of William Kinlaw, M.D., studying the role of glucose metabolism and progesterone in the development of breast tumor cells.

Quinn began her medical career in Boston, in the office of an ophthalmologist, where she worked with people who had degenerative eye diseases. In 2002, she graduated from the Tufts University combined M.D.-M.P.H. program.



LEE MCDAVID

Quinn looks forward to investigating how tumors grow, as well as to mentoring undergraduates.

She will suspend her clinical duties next year while she investigates sugar-to-fat metabolism and how it might promote breast cancer growth. Specifically, she'll look at a protein called CHREBP—a sugar sensor found in cancerous breast tissue but not in normal breast cells—and the role it plays in the synthesis of lipids, or fats, and in the growth and survival of breast cancer cells. She will also investigate the role CHREBP plays in how progesterone modulates sugar signaling. "It's one part of a very big story," she says.

Quinn hopes her studies will shed light on why breast tumors have a high rate of fat synthesis, which encourages breast cancer. "These tumors are hypermetabolic and gobbling up sugar," she notes. "Is that somewhere we can intervene?"

Grassroots: Most of Quinn's training has been clinical, and most of her research has been epidemiological—related, that is, to the incidence and control of disease in broad populations—so she now wants to beef up her laboratory experience. "I convey information much better if I understand it at a grassroots level myself," she says. "I don't like to just quote evidence to patients. I like to know where that evidence came from."

As a Tiffany Blake Fellow, Quinn will be able to develop the skills and contacts required to do independent clinical research, but she is also looking forward to mentoring Dartmouth College undergraduates—including at least one student participating in the Women in Science Program. She enjoys the role of mentor and teacher, as well as researcher. "If I had my druthers, my ideal career would be one where I could be both a physician and a scientist," she says. "Ultimately, the goal is to do something that will help people. . . . I think I see where [my research] could do that. Not tomorrow, not in a year, but maybe down the road." LEE MCDAVID

Protein of pain

DMS researchers recently demonstrated how a receptor protein in the central nervous system, dubbed TLR4, contributes to neuropathic pain—a debilitating condition resulting from damaged or dysfunctional nerves. The finding, published in the *Proceedings of the National Academy of Sciences*, reveals new therapeutic possibilities for treating chronic pain. "The results of this study are significant because they demonstrate the potential for very novel drug targets," says the lead researcher, Joyce DeLeo, Ph.D., director of the Neuroscience Center at Dartmouth.



Modeling disease

Human autoimmune pancreatitis (AIP)—a rare and poorly understood disease—may become less mysterious and more treatable thanks to a DMS study published in the *American Journal of Pathology*. The research team, led by pathologists Daniel Longnecker, M.D., and William Hickey, M.D., figured out how to induce a disease analogous to AIP in rats, thereby creating "an immunologically intact animal model to dissect basic immunological mechanisms" of the disease. "Furthermore," they wrote in the paper, "this model represents a novel means for the study of organ-specific autoimmunity in general."



Can “chemobrain” be mitigated?

Have you ever locked your keys in the car? Forgotten an appointment? Sure, everyone has memory lapses from time to time. But for some cancer patients who undergo chemotherapy, such slips happen all too often. “Chemobrain,” as patients call the condition, is characterized by memory problems, trouble concentrating or multitasking, and difficulty summoning the right word in conversation.

Persist: “For some people these are acute side effects of the treatment, and for some people these side effects actually persist long after the treatment,” says Tim Ahles, Ph.D. The director of DMS’s Center for Psycho-Oncology Research, Ahles studies the effects of chemotherapy on long-term cognitive function. “We are very interested in why some people have these long-term cognitive defects,” he says. He and his collaborators want to know what factors make some patients more vulnerable to these effects than others.

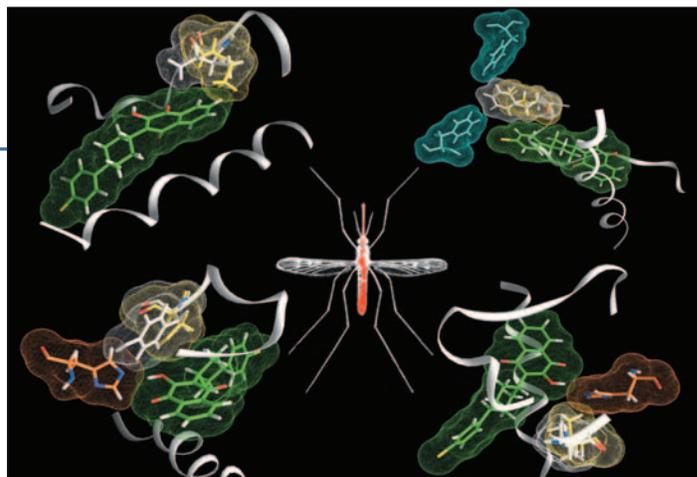
Currently, the researchers are assessing the cognitive function of patients with lymphoma and breast cancer, both pretreatment and posttreatment. They are then evaluating associations between the development of long-term cognitive defects and several other variables. The variables they are looking at include the types and doses of chemotherapy the patients have received and the genetic differences among the individuals. For example, are patients who receive a particular regimen of chemotherapy more likely to develop long-term cognitive defects? Or is there a particular gene that triggers vulnerability to these side effects?

One particular gene the group is examining is called APOE. One version, or allele, of this gene, E4, has been associated with Alzheimer’s disease and traumatic brain injury. Recent research by Ahles’s team suggests that the carriers of APOE’s E4 allele may have a higher risk of developing long-term cognitive defects after receiving chemotherapy.

Side effects: Most patients who experience chemo-related cognitive defects find that they return to normal shortly after they finish their regimen, but “for some people these side effects actually persist long after the treatment,” explains Ahles. His group has published data showing that lymphoma and breast cancer survivors who received chemotherapy experience more cognitive defects five years after the conclusion of their treatment than do similar patients who received only nonsystemic treatment, such as surgery or local radiation.

Chemotherapy confers an increased chance of survival, of course, as well as an increased risk of cognitive defects. But these problems do affect long-term quality of life for some patients. Could it one day be possible to get the benefit without the risk? Ahles and his colleagues hope so. Their ultimate goal is not just measuring the problem but mitigating it. “If we really understood the mechanism,” he says, “there will hopefully be drug interventions that may either prevent or reduce the negative cognitive impact of chemotherapy.”

KRISTEN GARNER



This graphic shows a mosquito, the vector for malaria, surrounded by molecular models of the antimalarial atovaquone as it loses potency against resistant strains.

Researchers take a swat at malaria

When battling any kind of resistance—even drug resistance—it pays to know thy enemy. In the case of the antimalaria drug atovaquone, DMS researchers recently confirmed the identity of “the enemy”—five specific mutations in an enzyme of the parasite that causes malaria. With this new understanding, the team hopes “to develop a drug that malaria cannot become resistant to,” says biochemist Bernard Trumpower, Ph.D. “Malaria has become resistant to every drug that has been targeted to it.”

Complex: Trumpower, who heads the lab that made the discovery, has spent years studying the cytochrome bc1 complex—the enzyme on which atovaquone acts—but only lately has he looked at its tie to malaria. About five years ago, a University of Michigan researcher phoned Trumpower to ask for his help studying atovaquone resistance in *Pneumocystis pneumonia*, once a major cause of death in AIDS patients. Soon Trumpower and his team learned that similar problems of resistance plagued the drug’s effectiveness against malaria, too.

“In the case of *Pneumocystis* and malaria, there was evidence indicating that the resistance was due to mutations in the gene which codes for one of the proteins in this enzyme,” Trumpower says. “That evidence was genetic coincidence.” In other words, they’d found particular mutations in resistant *Pneumocystis* and in resistant malaria parasites. Trumpower’s lab modeled each of these mutations in yeast and then tested their resistance. The enzyme without the mutations was sensitive to the drug, while the enzyme with the mutations was resistant. “So we biochemically confirmed, or proved, what was suspected from genetic, coincidental, guilt by association,” he says.

Atovaquone is a “relatively difficult compound to chemically synthesize,” notes Trumpower. As a result, the drug (which goes by the brand name Malarone) is expensive and thus is taken mostly by Westerners who travel to regions where malaria is prevalent. Trumpower, however, believes a drug his team is developing, with the help of Dartmouth chemistry professor Gordon Gribble, Ph.D., will be easier to synthesize, cheaper, and better. “If we are going to succeed, we will know in a three- to five-year period,” he adds.

JENNIFER DURGIN



DMS pediatrician David Goodman, M.D., in a Web exclusive for the journal *Health Affairs*, concluded that the evidence supporting claims of a physician workforce shortage is questionable.

Steroids may have elevated effect on teens

The recent Congressional hearings on anabolic steroid abuse by professional athletes helped to shed light on the dangers of performance-enhancing drugs. And ongoing research at Dartmouth is helping to illuminate how prolonged use of steroids may trigger irreversible molecular changes in the brain, especially in adolescent females.

Abuse: Anabolic-androgenic steroids (AAS), synthetic derivatives of testosterone, are controlled substances used by some athletes to build muscle and increase body size. “These are increasingly used drugs of abuse,” says Leslie Henderson, Ph.D., a professor of physiology and of biochemistry at DMS. “In particular, the use among junior high and high school kids has been escalating.” The Centers for Disease Control and Prevention reported in 2001 that 5% of all high schoolers had used steroids without a prescription.

“The most common side effects associated with chronic steroid abuse,” Henderson says, “are changes in aggression, anxiety, and sexual behaviors.” These changes have been known for some time, but there has “not been a lot done to try and understand the underlying basis” for them.

Henderson, in collaboration with Ann

Clark, Ph.D., a professor of psychological and brain sciences at Dartmouth College, has reported that AAS use affects behavior and interferes with the expression of signaling molecules in the brain. Henderson’s lab looks at how these steroids affect a neurotransmitter receptor, the gamma-aminobutyric acid type A (GABA_A) receptor. The GABA_A receptor, an ion channel in the brain, allows negatively charged chloride ions to flow rapidly into neurons. The inward flow of chloride ions inhibits nerve-cell activity by preventing the generation of electrical signals that travel along neurons.

In the short term, AAS use exploits this natural process by allowing GABA_A receptors to remain open longer. The increased chloride ion flow dampens activity in the central nervous system and may contribute to the antianxiety effect that is reported with initial AAS use.

But long-term AAS use can produce very different effects, including increased anxiety or aggression. In mice, chronic steroid exposure alters the expression of some GABA_A receptor subunit genes. One kind of steroid decreased expression of these genes in areas of the brain important in reproduction and aggression in female but not male mice; it also had more effect on adolescents than adults.

Awareness: Henderson and Clark hope their work will heighten public awareness of the risks of AAS use among adolescents, girls in particular. They also hope a better understanding of the underlying mechanisms may lead to new therapies. For example, DMS’s Hillary White, Ph.D., has shown that androgens may ameliorate symptoms of fibromyalgia.

Henderson says their own work is far from the clinical stage, but that “overall understanding of how these drugs affect transmission in the brain could have broad repercussions.” SION E. ROGERS



ION GILBERT FOX

Henderson studies steroids’ basic mechanisms.

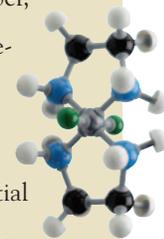
Sedation scale

A new tool for assessing pediatric sedation practices has been developed and validated by a team of Dartmouth anesthesiologists. In a recent issue of *Anesthesia and Analgesia*, the researchers, led by Joseph Cravero, M.D., explained that the Dartmouth Operative Conditions Scale (DOCS) “will allow a more detailed analysis of sedation techniques.” For example, they wrote, “two techniques for bone marrow biopsy . . . could be compared not only for ‘was the procedure completed?’ but also for what the child’s behavior, degree of movement, and pain was like during the procedure.”



Burden of proof

Two researchers who headed a recent international clinical trial on a vaccine that could prevent 70% of cervical cancers are cautioning policy-makers “to avoid scaling back” the use of Pap smears. In a paper published in *Vaccine*, Dartmouth’s Diane Harper, M.D., M.P.H., and her coauthor detailed the cervical cancer burden worldwide—especially in developing countries—as well as the potential of the vaccine. “Any premature relaxation of cervical cancer control measures already in place,” they concluded, “will bring a resurgence of the disease to the unacceptable levels of the not-too-distant past.”



Treating the trauma of war in women vets

Veterans of World War I and II, all of them men, experienced aftereffects of combat known then as “shell shock.” In the wake of the Vietnam conflict, the condition acquired a new name—post-traumatic stress disorder (PTSD)—but most of its victims were still men. In today’s military, however, women as well as men suffer psychological effects related to the trauma of combat.

Dartmouth psychiatry researcher Paula Schnurr, Ph.D., is determined to help the women who are serving on the front lines in Afghanistan and Iraq and thus are returning home in need of treatment for PTSD. She is leading the the first Veterans Affairs study to focus exclusively on female GIs and PTSD; it is also the largest individual psychotherapy trial ever done on PTSD.

PTSD is an anxiety disorder that develops after a traumatic event, whether it be engaging in combat, surviving a natural disaster, or experiencing sexual assault. Its symptoms can include nightmares, depression, emotional numbness, outbursts of anger, and feelings of intense guilt. By testing two forms of cognitive behavioral therapy, Schnurr and her colleagues hope to determine the most effective, lasting treatment for women, as well as men, at VAs across the country.

Schnurr, one of the study’s principal investigators, is deputy executive director of the VA National Center for PTSD in White River Junction, Vt. Her team plans to start analyzing the data in November 2005 and to publish the results in February 2006.

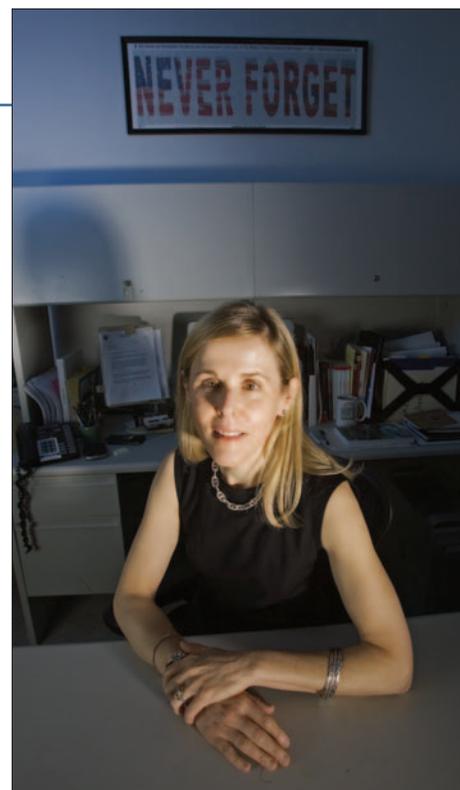
The study has enrolled 283 women diagnosed with PTSD—aged 22 to 78, both active-duty personnel and veterans—from 12 sites: nine VA hospitals, two community VA centers, and Walter Reed Army Medical Center in Washington, D.C. While only a handful of the subjects have served in Iraq or Afghanistan (most enrolled in the study in 2002, before many troops started returning), of the 283 women, 198 (70%) have experienced sexual trauma, either in childhood, in

the military, or since their discharge. “Although there are unique experiences for the women currently in Iraq, especially the exposure to hostile fire and use of weapons in ways that many women in the military—even in a war zone—haven’t experienced, many other issues are quite similar. The event that we are really focusing on in the treatment [in this trial] is sexual trauma, and you don’t have to be in a war zone, unfortunately, to experience that,” says Schnurr.

Grand opera: The study employs nearly 120 people—therapists, supervisors, monitors, and investigators at the 12 participating sites, plus data analysts and a biostatistician at a data-coordinating center in Palo Alto, Calif. “This is the grand opera of treatment research,” says Schnurr’s DMS colleague and coprincipal investigator, Matthew Friedman, M.D., Ph.D. “We’ve been very fortunate having some excellent people working with us to coordinate all this.”

The women in the trial were split into two groups. Half are being treated with exposure therapy and half with present-centered therapy. In exposure therapy, the premise is that reliving a traumatic experience “can help reduce the fears, the emotional distress associated with that experience,” says Schnurr. “You’re trying to allow them to remember without being overwhelmed by the pain.” Patients relive the trauma through imaginary formats in therapy, as well as by going into real situations they may be avoiding because of their fears. “The goal is to uncouple the memory itself—which is never going to disappear—from all of the emotional baggage,” adds Friedman. In present-centered therapy, patients talk about current problems in their daily lives—how the disorder affects their relationships, children, jobs, and so on—rather than about the past trauma.

Schnurr and Friedman believe both therapies will do well in the trial but that exposure therapy may do better, in part because the therapists are very enthusiastic about it.



CHRIS MILLMAN

Schnurr is heading the largest individual psychotherapy trial ever done on post-traumatic stress disorder; the poster behind her commemorates the trauma of 9/11.

Most had to be trained in the technique for the trial, which was a good simulation of how it would work in a real VA setting. The team chose exposure therapy because data suggested it would work in a wide range of patients—women and men, young and old.

“If the hypothesis is that the active ingredient, the thing that makes exposure therapy so effective, is the confrontation with the traumatic material in the safety of a therapist’s office, then the comparison [present-centered] therapy has to be absolutely without that ingredient,” says Friedman.

Role: But present-centered therapy may have a role as well. “It has all the non-specific components of trust, of therapeutic relationships . . . that any good psychotherapy consists of, so if the prolonged exposure beats it in this horse race, it will really be good evidence that it’s the ingredient of the exposure itself that is the crucial difference,” says Friedman.

Once the researchers know which therapy is more effective, they’ll start implementing it in the VA system. MATTHEW C. WIENCKE



A team led by Dartmouth cognitive neuroscientist Michael Gazzaniga, Ph.D., received a \$22-million grant from the National Science Foundation to study brain mechanisms involved in learning.

“A time to be born, and a time to die”

To everything there is a season,” says Ecclesiastes 3, including “a time to be born, and a time to die.” Though understood in the Biblical sense to apply to human affairs, the concept appears in the biological sense to be built into the simplest life forms. In multicellular organisms, even in the absence of outside threats to survival, certain cells are destined to die during the life of the organism.

Biologists call this process apoptosis, or programmed cell death. The remarkable thing is the precision with which the cells march to their demise. But it is for the good of the organism that apoptotic cells fulfill their function and then expire.

Unraveling the sequence of events in apoptosis is the goal of DMS geneticist Barbara Conratt, Ph.D. She and colleagues recently reported a new finding about the process in *Nature*: a role for mitochondria, the cellular power plant, in prompting cells to self-destruct.

An example of apoptosis in mammalian development includes the purging of

nearly half of the brain neurons formed during embryogenesis, because they failed to establish the correct synaptic connections. Mice unable to undergo apoptosis are born with swollen heads because faulty neurons were not eliminated.

Stages: Scientists are still unsure exactly what triggers apoptosis, but they’ve determined that in its terminal stages, proteolytic enzymes called caspases are activated to digest the cell from the inside. It’s also been known that mitochondria were involved in the intermediate stages—they appeared to fragment—but it wasn’t clear whether this was a critical step in apoptosis or a result of the process.

Conratt and her colleagues use a small worm, *C. elegans*, for their studies. It carries the concept of “programmed” to a new level. During each worm’s development, exactly 1,090 cells form and precisely 131 undergo apoptosis. It is the only model organism in which the time and place of doomed cells’ extinction is known, making it an important experimental tool.

The first step in their latest work was showing that, as in mammals, *C. elegans* mitochondria fragment during apoptosis. More importantly, it turned out that either inducing or preventing mitochondrial fragmentation respectively enhanced or impeded apoptosis. Thus mitochondrial fragmentation was shown to be a determinant and not a result of apoptosis.

Role: The next step for the lab will be looking at the role this fragmentation plays. Previous work has shown that a key event in apoptosis is the release of cytochrome c from mitochondria, but there is little agreement on how that occurs; the fragmentation may be what triggers it.

Since apoptosis is important in cancer and autoimmune diseases, a lowly worm may one day suggest new treatments by showing that there is “a time to kill, and a time to heal.” ROGER P. SMITH, PH.D.

TB or not TB

Current tuberculosis screening guidelines for HIV patients in the developing world may not be adequate, according to new findings from a Dartmouth-Tanzania research collaborative known as DARDAR. Publishing in the journal *Clinical Infectious Diseases*, the authors of the study point out that “tuberculosis is the leading cause of death among persons with HIV infection in the developing world,” but a substantial number of TB cases may go undetected. “Some cases can only be identified by sputum culture,” they said, a technique not available in many resource-poor settings.



Beer pressure

Adolescents who own t-shirts, backpacks, and other items with alcohol brand names or logos are more likely to drink alcohol than their peers, according to a study led by DMS pediatrician Auden McClure, M.D. In a survey of 2,400 Vermont and New Hampshire middle-schoolers, McClure and her colleagues found a strong correlation between owning branded paraphernalia and alcohol use. The authors of the study, which was presented at the annual meeting of the Pediatric Academic Societies, are urging alcohol companies to voluntarily stop producing such goods—as the tobacco industry did in 1998. ■



JON GILBERT FOX



How cells die is the focus of Conratt’s research.