A PREVIEW OF CHANGES TO HEALTH-CARE LAWS

STARTING IN 2014, businesses with 50 or more full-time employees will be required either to provide an insurance option to their employees or pay a fee for not doing so. This provision of the 2010 Affordable Care Act (ACA), often referred to as the employer mandate, provoked sharp resistance during the debate over the legislation and continues to face resistance today.

"This policy will lead to layoffs, reduced working hours, and dropped coverage for employees," warned Kansas Senator Jerry Moran recently. "Congress should repeal this damaging mandate."

But according to research by Carrie Colla, a Geisel health economist, such fears may be overblown. Colla has studied the implementation of a similar mandate in San Francisco and found that the ordinance increased access to health care without having a negative effect on employment. These findings, she says, may shed light on what will happen at the national level after implementation of the federal provision.

In a study published in *Health Affairs*, Colla outlined the details of the San Francisco plan and what happened in the two years following its implementation in 2008. The ordinance had two components. One was the creation of a public health-care option called Healthy San Francisco, which gave enrollees access to a limited number of providers in the city. It's not formal insurance, Colla notes, but it does give people who would otherwise be uninsured some medical coverage.

The second part of the ordinance is the employer mandate, which penalizes employers with 20 or more employees if they do not provide a health insurance option. Healthy San Francisco is paid for in part by fees collected from those employers. As with the employer mandate provision of the ACA, the San Francisco ordinance required that the coverage provided by employers meet a minimum level per employee.

Colla and her coauthors were interested in examining whether the mandate caused employers to withdraw private insurance offerings, to offer a mini-medical plan, or to expand insurance coverage. To find out, they surveyed employers both within San Francisco and, as a comparison, in surrounding counties where the ordinance did not apply.

IF NOT FOR THE ORDINANCE, COLLA CONCLUDED, ANOTHER 10% OF WORKERS WOULD BE WITHOUT EMPLOYER-PAID HEALTH BENEFITS.

In 2007, before the ordinance went into effect, 93% of employers in San Francisco who would later become subject to the mandate offered health insurance. The mandate went into effect in 2008. By 2009, the percentage of firms offering insurance had increased to 96% in San Francisco. In counties surrounding San Francisco, the percentage dropped from 94% in 2007 to 90% in 2009.

During the same period, there was little difference in the increase in premiums between San Francisco and surrounding counties, but there were significant differences in who paid for those premiums. In San Francisco, employers increased their contributions to premiums by 17%. At the same time, the cost for employees rose only 9%, from $56 to $61. In surrounding counties, the cost of premiums paid for by employees rose by 50%, from $52 to $78. And if not for the ordinance, Colla concluded, another 10% of workers would be without employer-paid health benefits.

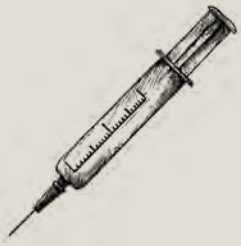
Despite the initial controversy surrounding the policy, including criticism from local business groups and a lawsuit that charged that the mandate was overly burdensome, by 2009 64% of employers supported the mandate, according to the survey.

"I think the main lessons are that it's feasible, that employers support it, and that—most important to us—it actually expanded coverage among workers," Colla says. She adds that these findings might bode well for the implementation of the employer mandate portion of the ACA next year. "I think some of the resistance will die down when employers learn more about it and as it becomes the norm," she says. "I'm hopeful that it will be implemented smoothly. But we'll see."

AMOS ESTY

UNDERSTANDING DIVISION

Writing in the journal *Science*, Geisel researchers from the Department of Biochemistry reported the key role played by the protein INF2 in the division of mitochondria, the organelles that produce energy for cells. The finding may lead to a better understanding of the development of neurodegenerative diseases, such as Huntington's disease and Alzheimer's disease.



HARNESSING A PROTEIN'S POWER

A novel approach to attacking chronic myeloid leukemia (CML) seems to offer the possibility of treating the disease in patients whose cancers are resistant to the standard treatment. In a paper published in the *Proceedings of the National Academy of Sciences*, assistant professor of pharmacology and toxicology Manabu Kurokawa described research he carried out as a postdoc at Duke University. Rather than inhibiting BCR-ABL, the protein that causes the disease, Kurokawa harnessed the protein to force apoptosis in cancer cells. As BCR-ABL is not present in normal cells, this technique could be used to target only cancer cells.

Jon Gilbert Fox

Research led by William Kinlaw was recently put to the test in a clinical trial.

CUTTING CANCER'S FOOD SUPPLY

WILLIAM KINLAW, A GEISEL PROFESSOR OF MEDICINE, has been exploring new ways to prevent cancer cells from making the fat they need to grow and spread.

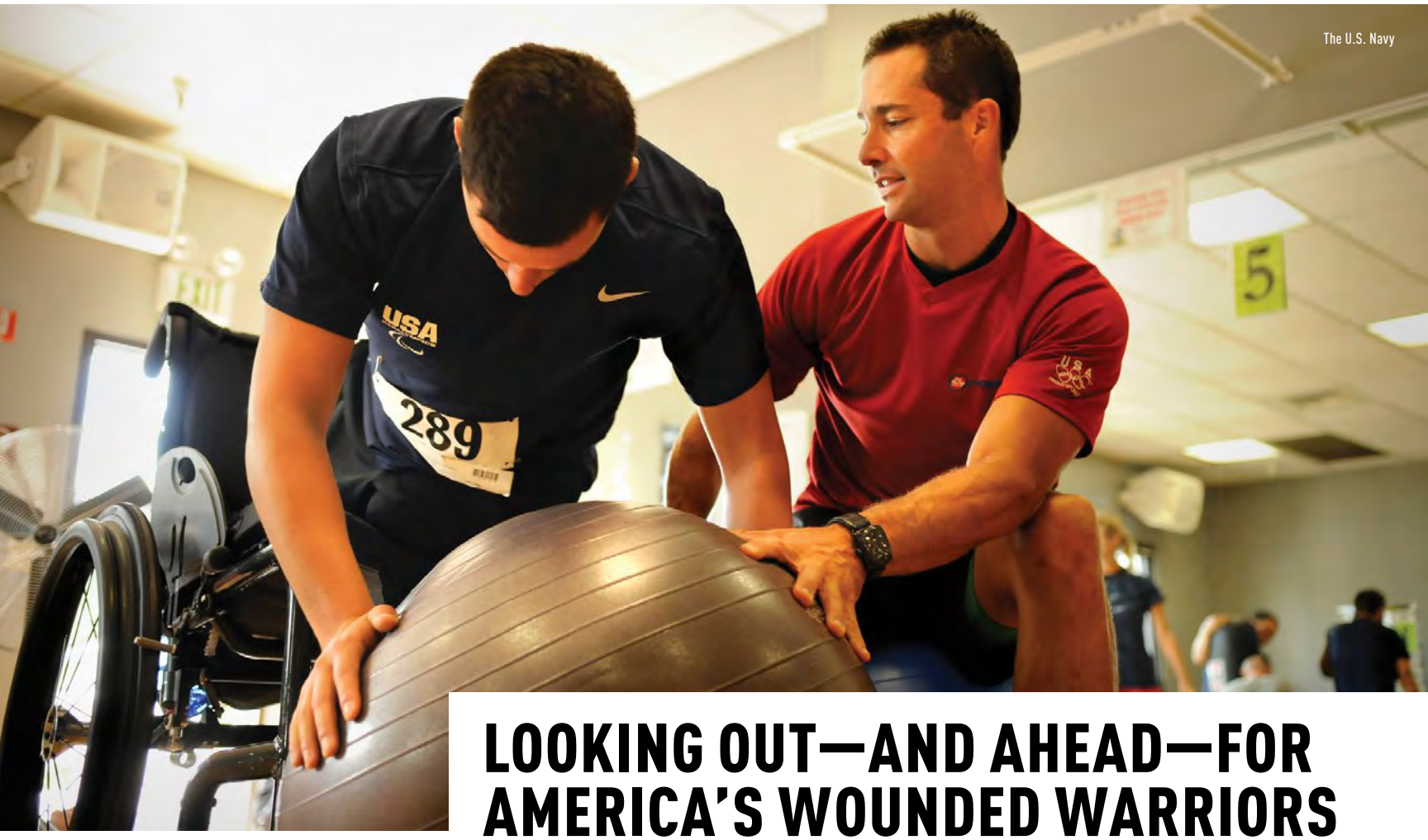
Working with several other researchers, Kinlaw recently completed a clinical trial that shows how treatment with conjugated linoleic acid (CLA)—a dietary supplement that is sold in health-food stores and used for weight loss—targets key genes involved in fatty acid synthesis, which may significantly reduce the growth of invasive breast cancer tumors. The results of the trial were published in *Breast Cancer Research and Treatment*. According to Kinlaw, this is the first clinical trial to use conjugated linoleic acid as a cancer therapy in patients.

The researchers enrolled 24 women with stage I to stage III breast cancer. All the women took CLA during the 10 to 12 day period between the time they had a biopsy and surgery. The researchers examined biopsy tissue samples (pre-CLA) and surgically removed tissue samples (post-CLA).

The most significant finding was that a gene named *Spot-14*—which cancer cells use to get the fatty acids they need to survive—was suppressed in the patients' tumors after taking CLA for 10 to 12 days. CLA also suppressed Ki-67, a protein found in the nucleus of cancer cells that is commonly used as an indicator of the aggressiveness of a tumor. The reduction of Ki-67 levels seems to indicate that the tumors were becoming less aggressive.

Kinlaw was encouraged by the findings. "I think CLA is probably not going to end up being a drug itself," he says, "but it certainly could be a prototype, and this study is a proof of principle that targeting these pathways in human tumors might be a useful thing to do."

MATTHEW C. WIENCKE



The U.S. Navy

A Marine injured in Afghanistan works with a trainer. The prevalence of serious injuries among veterans of the wars in Iraq and Afghanistan has raised concerns about long-term health-care costs.

LOOKING OUT—AND AHEAD—FOR AMERICA'S WOUNDED WARRIORS

TREATING VETERANS OF PAST WARS at the White River Junction VA Medical Center got James Geiling thinking about the future. "One thing that struck me at the VA, where I'm taking care of Vietnam-era vets, is the long-term medical effects of war injuries," he says. "And I started to think about what that means for today's vets."

In a recent article published in the journal *Military Medicine*, Geiling, a Geisel professor of medicine; Joseph Rosen, a Geisel professor of surgery; and health economist Ryan Edwards discussed the potentially enormous long-term costs of caring for veterans of the wars in Iraq and Afghanistan and what might be done to reduce those costs.

Over 2.3 million active-duty military personnel and reservists have served in Iraq or Afghanistan through September 2011. The Congressional Budget Office (CBO) has estimated the health-care costs for veterans of these wars will be about $40 billion to $55 billion through 2020, and estimates of the total health-care costs over the next 30 to 40 years range from $600 billion to $1 trillion.

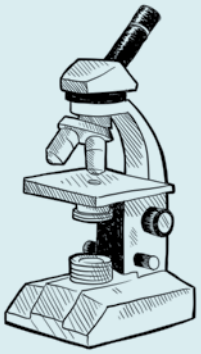
Geiling and his coauthors note that patterns of injury and a higher survival rate than in previous conflicts both play a role in these estimates. Many veterans of the recent wars survived injuries that might have killed them in previous conflicts. The prevalence of improvised explosive devices (IEDs) in these wars has led to many polytraumatic injuries, such as the loss of multiple limbs, severe facial injuries, traumatic brain injury (TBI), blindness, deafness, or some combination of these injuries. There is also the potential for post-traumatic stress disorder (PTSD), which can be expensive to treat. According to the CBO, about one-fourth of veterans treated from 2004 to 2009 were diagnosed with PTSD.

About 50,000 men and women have been wounded in action while serving in Iraq or Afghanistan, and hundreds of thousands of veterans have received treatment from the Veter-

OVERHEARD

As a society, we hand out antibiotics like candy, tossing one life preserver here, one there, assuming the supply is never ending. But it turns out we are, in fact, running out of antibiotics. This will in turn affect our son, who has never taken an antibiotic in his life.

—TIM LAHEY, MD, ASSOCIATE PROFESSOR OF MEDICINE, WRITING IN *THE ATLANTIC*



SIGNATURE FINDING

Research led by associate professor of genetics Michael Whitfield identified gene expression signatures that can accurately identify patients with scleroderma who will respond positively to a particular treatment. There is no known cure for scleroderma—a rare autoimmune disease—and only some patients respond to the one drug often used to treat it. Finding a way to identify those patients who do not stand to benefit could help them avoid unnecessary treatment.

ans Health Administration. By 2035, these veterans will be middle-aged, with health issues similar to those Geiling now sees in Vietnam veterans.

Geiling, who is a 25-year veteran of the Army, argues that being aware of these issues should lead to preventive measures. "We should help an amputee to reduce his cholesterol and maintain his weight at age 30 to 40 rather than treating his coronary artery disease or diabetes at age 50," he says. "If we treat a veteran's PTSD at age 21 with counseling and lifestyle interventions, we may help her to reduce suicidal thoughts and avoid the use of tobacco or alcohol. This will save us from having to fund her treatment for chronic obstructive pulmonary disorder or alcoholic liver disease."

Geiling believes that drawing attention to these issues is important. "Today's veterans are clearly at risk for long-term illness, and there's data to show that," he says. "We just need to think about these things and keep them in mind today so we might prevent them from appearing in 2035."

NANCY FONTAINE

GLOBAL GRANT

OVER THE NEXT FEW YEARS, George O'Toole, a Geisel professor of microbiology and immunology, will be part of an international team of researchers that takes a new approach to a longstanding problem in biology: how bacteria form colonies called biofilms. The collaboration is the result of a $1.6-million grant awarded to O'Toole and three other researchers—one each from UCLA, the University of Oxford, and the University of Cologne—by the Human Frontier Science Program, an organization based in France.

Biofilms can be found just about everywhere, and in the wrong setting they can pose significant medical challenges. Bacteria in biofilms are often much more difficult to kill with antibiotics than are free-swimming bacteria, making them very difficult to eradicate when they form on medical devices or in the lungs of people with cystic fibrosis, for example.

O'Toole has spent years studying biofilms, with a particular focus on biofilm formation. "We've used a number of different tools, mostly bacterial genetics and biochemistry, to try to understand at a macroscopic level what's happening," he says. That work has led to a better understanding of how, at a group level, bacteria form biofilms.

The new collaboration—which includes experts in biophysics, microscopy, and fluid dynamics—will lead to a better understanding of the mechanics of biofilm formation among individual bacteria cells, including how the components of a single cell attach to a surface when joining a biofilm. The researchers will also examine how manipulating the genetics of bacteria affects the ability of individual bacteria cells to join biofilms. "It's bringing to bear a number of different disciplines to tackle a question that has been out there in the field for a while but that no one has been able to really understand at a detailed, mechanistic level," O'Toole says.

Jon Gilbert Fox

Microbiologist George O'Toole is part of an unusual collaboration that will offer a different perspective on his research.

O'Toole is excited to be part of this diverse team of researchers. "Science is really moving in the direction of trans-disciplinary work, where you're stretching yourself in new directions and each person brings a discrete expertise to the table," he says. "One good way for making new breakthroughs in a field is by bringing in people with novel perspectives."

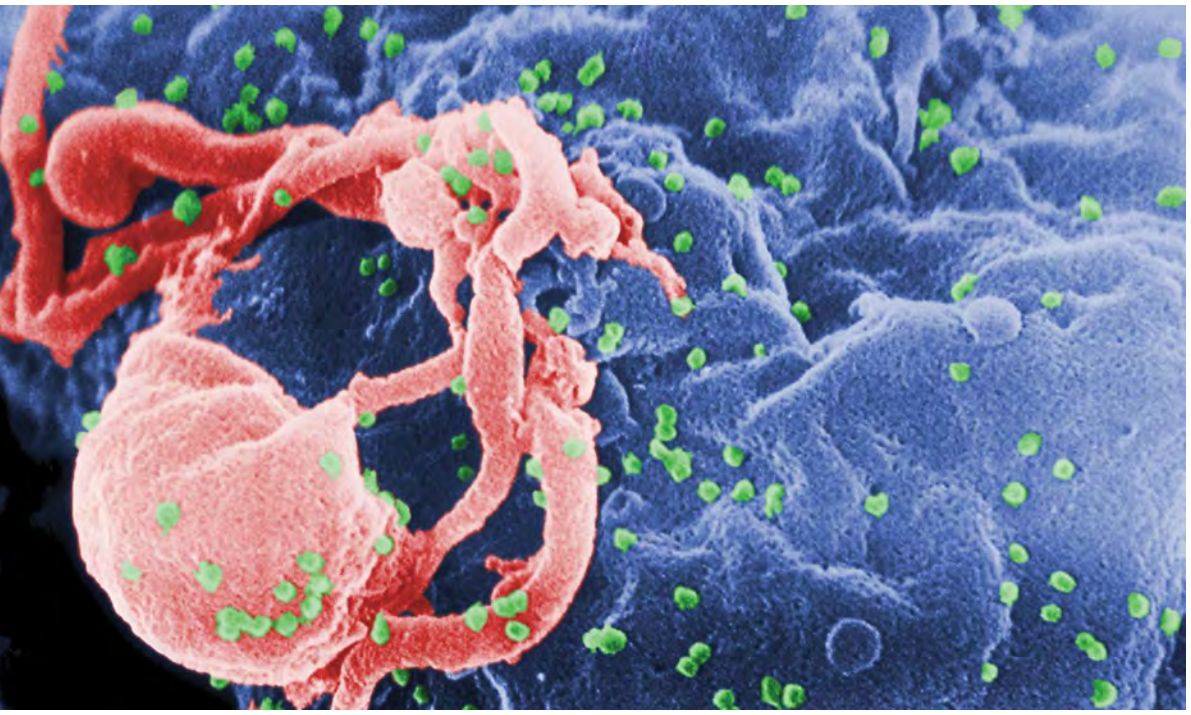
AMOS ESTY

OVERHEARD

Older adults with mental health disorders have greater disability than those with physical illness alone, as well as poorer health outcomes and higher rates of hospitalization and emergency department visits, resulting in per-person costs that are 47% to more than 200% higher. Yet mental health services account for only 1% of Medicare expenditures.

—STEPHEN BARTELS, MD, PROFESSOR OF PSYCHIATRY, WRITING IN THE *NEW ENGLAND JOURNAL OF MEDICINE*

CDC/C. Goldsmith, P. Feorino, E. L. Palmer, W. R. McManus



A cell infected with HIV releases HIV particles (green).

LOOKING CLOSER AT HIV INFECTION AND IMMUNITY

FOR MORE THAN 20 YEARS, ALEXANDRA HOWELL, a Geisel professor of medicine and of microbiology and immunology, and a researcher at the White River Junction VA Medical Center, has been working to understand the mechanics of HIV infection. Her particular focus has been studying the conditions in the female reproductive tract that either contribute to or inhibit infection. She notes that although the likelihood that a woman will become infected with HIV following sexual contact with an infected partner is fairly low, in the range of 1 in 400 to 1 in 1000 encounters, certain conditions can increase susceptibility. Worldwide, the number of women with HIV has grown steadily in recent years.

Howell wants to identify the conditions that promote or prevent infection in the hope of developing more effective measures to decrease the risk for women. An early step for Howell was to examine the role of the reproductive hormones estradiol and progesterone, which fluctuate during the menstrual cycle, pregnancy, and menopause. By studying blood cells *in vitro*, she found that high levels of estradiol protected cells against infection, whereas high levels of progesterone seemed to promote it. Then, about four years ago, her research team took their investigation to the next level by studying how to block infection regardless of hormonal conditions. "We wanted to block expression of the proteins that HIV needs to get into a cell," Howell says. To infect a cell, HIV has to bind to two proteins: CD_4 and CCR_5. She hoped that by blocking the expression of those proteins, the virus would be prevented from entering the cell and the immune system would be able to destroy the virus.

The researchers attempted to block production of CD_4 and CCR_5 in mice with a humanized immune system using a method called RNA interference. This technique involves using small pieces of short interfering RNA (siRNA) that bind to the messenger RNA (mRNA) that codes for CD_4 and CCR_5, blocking production of the proteins.

Howell and her team put the siRNA that blocks CD_4 and CCR_5 into the vaginal tracts of the mice, waited three days, then infected the mice with HIV and monitored the bloodstream for evidence of infection. A control group of mice received siRNA that was "irrelevant"—it was the same size as the CD_4 and CCR_5 siRNA, but it didn't bind to any mRNA in the cells.

"WE WERE SCRATCHING OUR HEADS, WONDERING WHAT WAS GOING ON."

As they had hoped, the researchers found that the siRNA that blocked expression of CD_4 and CCR_5 inhibited the transmission of HIV very effectively. But what surprised them, she says, was that the control group—mice that received the irrelevant siRNA—were also protected from HIV infection. "We were scratching our heads, wondering what was going on," Howell says. The receptors should not have been suppressed, yet the control mice also had very low levels of infection compared to mice that were not treated at all.

To tease out the reason the mice that received the ostensibly ineffective siRNA were protected, the researchers added siRNAs to human

OVERHEARD

"The idea that you have one rule for screening, that everybody gets screened at the same rate using the same threshold for the same period of time, doesn't make sense."

—H. GILBERT WELCH, MD, PROFESSOR OF MEDICINE, QUOTED ON NPR

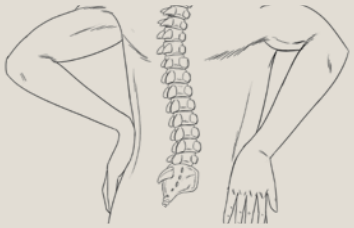
blood cells in the lab. They discovered that the short pieces of siRNA looked like the genome of HIV to the immune cells. "This made sense, since HIV uses RNA for its genome," says Howell. They found that the cells were taking up siRNA and responding as if it were a virus, secreting innate immune factors. "It didn't matter what the sequence of the siRNA was, it was inducing these same protective immune cytokines," she says—namely, a cytokine called interferon-alpha. Howell's group hypothesized that Toll-like receptors, or TLRs, were becoming activated in the immune cells that took up the siRNA, because they knew that some TLRs are specific for small pieces of RNA.

In a recent study published in the journal *AIDS Research and Human Retroviruses*, Howell and her team tested whether the specific TLR that becomes activated by RNA, TLR7, was involved by using a compound called gardiquimod, a drug known to bind to and activate TLR7. What they found was "strange," says Howell: "The cells treated with gardiquimod were almost impossible to infect with HIV." Why? They confirmed that the cells were cranking out interferon-alpha. But even when they blocked production of interferon-alpha, the cells were still resistant to infection, albeit less so. What Howell discovered is that gardiquimod also stops the action of an HIV enzyme called reverse transcriptase, which the virus needs to convert its RNA to DNA, preventing its replication machinery from being inserted into the chromosome of the cell, thus preventing infection.

Now that the researchers have made this discovery, Howell thinks it's possible that eventually gardiquimod or a similar compound might be used as a microbicide. But first she wants to find out exactly how gardiquimod works.

"The discovery part is interesting—that's the sizzle with your steak," she says. But, she adds, what's really important is understanding infection, and figuring out how to prevent it.

LAUREN ARCURI WARE



THE SECRET TO SATISFACTION

Experiencing improvements in function is more important than a decrease in pain for patients with chronic disabling back pain, according to research led by Rowland Hazard, a professor of orthopaedics and of medicine and the director of the functional restoration program at DHMC. The study followed patients enrolled in the functional restoration program. Before beginning the program, patients were asked to record goals to achieve over the next three months. They were later surveyed about their satisfaction with the program and about how fully they felt they had achieved their initial goals. "At least three months after the treatment, functional goal achievement had by far the greatest impact on patient satisfaction," the researchers concluded in *The Spine Journal*.

STUDYING NATURE *AND* NURTURE

THANKS TO A $12-MILLION GRANT FROM THE NATIONAL INSTITUTES OF HEALTH (NIH), the Geisel School of Medicine has established a multidisciplinary center for the study of molecular epidemiology. Over the next five years, the grant, part of the NIH's Institutional Development Award program, will fund research devoted to understanding how environmental exposures interact with genetics to affect human health. The new center is the fourth Center of Biomedical Research Excellence (COBRE) created at Geisel.

"Epidemiology is becoming increasingly valued for its contribution to illuminating the causes, and, in turn, prevention of human disease," says Margaret Karagas, a professor of community and family medicine and the principal investigator on the grant.

The center will have four primary projects. Brock Christensen, an assistant professor of community and family medicine and of pharmacology and toxicology, is investigating the relationship between epigenetic changes and the risk of developing breast cancer.

Diane Gilbert-Diamond, an assistant professor of community and family medicine, is leading an investigation into the relationship between *in utero* vitamin D and immune function in early childhood.

Building on her research in premature babies with cystic fibrosis, Juliette Madan, an assistant professor of pediatrics, is investigating bacterial colonization in pre- and full-term infants and its connection to infection and allergy risk.

Using advanced imaging techniques, Tracy Punshon, a Dartmouth College research assistant professor of biological sciences, will study the transfer of metals from mothers to infants and examine whether the mother's genotype contributes to the risk of transferring metals.

In addition, the creation of a biorepository will allow for the long-term storage and study of specimens, facilitating research by participants in the COBRE and other researchers at the medical school.

EPIDEMIOLOGY IS BECOMING INCREASINGLY VALUED FOR ITS CONTRIBUTION TO ILLUMINATING THE CAUSES OF HUMAN DISEASE.

Karagas is excited about the work being done by these and other researchers. "We have an extraordinarily talented group of early career faculty conducting state-of-the-art epidemiologic research," she says. "We hope this new infrastructure will serve not only the institution, but the region and beyond."

SUSAN GREEN