Medicine@Yale

Advancing Biomedical Science, Education and Health Care

Volume 5, Issue 2 March/April 2009

Doing the right thing: can neuroscience research make it easier?

Yale undergraduate believes that healthy messages can be made more persuasive

Despite the health risks, about 1.1 billion people smoke tobacco worldwide, and cigarette manufacturers spend more than $8 billion annually on product promotion. But what if advertising aimed at rooting out smoking was as effective as ads that encourage it?

For Emily Yudofsky, the idea of using powerful marketing techniques to influence behavior for the better is more than just a dream. A Yale College junior majoring in psychology, Yudofsky established her own "neuromarketing" company, Applied Resonance Research, in 2007, with the goal of using imaging technologies to enhance the effectiveness of public-service advertising.

With funding from the Yale Interdisciplinary Research Consortium on Stress, Self-Control and Addiction (IRCSSA), Yudovsky is now using the medical school's functional MRI (fMRI) facility to study how product branding influences the brain.

While in high school in Houston, Yudofsky attended neuroimaging conferences. Having developed a strong interest in the field, she secured a summer position with a team of neuroscientists and behavioral scientists at Baylor College of Medicine's Human Neuroimaging Laboratory. A study taking place in the lab at that time, the results of which were published in the journal *Neuron* in 2004, reported that subjects' preference for a popular soft drink increased when drunk from cups bearing the drink's logo, and that brain regions involved in decision-making and memory were more stimulated when sips of

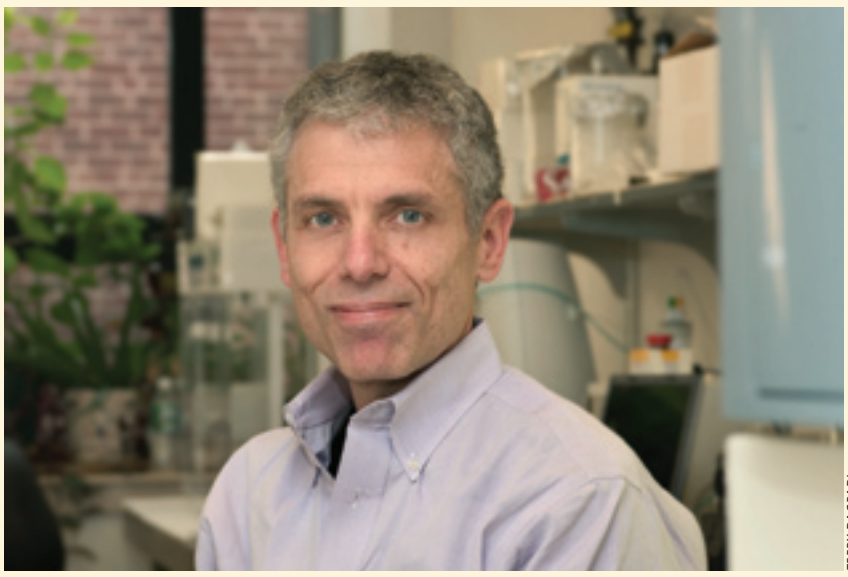
Neuromarketing, *page 4*

MICHAEL MARSLAND

Psychology major Emily Yudofsky is conducting research aimed at enhancing the effectiveness of public-service advertisements that promote healthy behaviors.

$5 million grant funds dyslexia study

Probing the 'lexinome' in hopes of a genetic test for reading disorders



TERRY DAGRADI

With support from The Manton Foundation, Jeffrey Gruen has embarked on a new exploration of the genetics of dyslexia.

Jeffrey R. Gruen, M.D., a School of Medicine scientist whose discovery of a gene involved in dyslexia was named one of the top 10 scientific breakthroughs of 2005 by the journal *Science*, has received a $5.2 million grant from the New York-based Manton Foundation to further his research on the genetics of dyslexia.

The Manton Foundation was established in 1991 by Sir Edwin Manton and his wife, Lady Manton, the former Florence V. Brewer. Born in England in 1909, Edwin Manton, known to friends and colleagues as "Jimmy," was successively director, executive vice president and senior advisor at American International Group. For his role as a major benefactor of Tate Gallery in London, Manton was knighted in 1994 by Queen Elizabeth II of England. The foundation supports education, the arts, conservation, health care and medical research.

Gruen, associate professor of pediatrics, investigative medicine and genetics, will use the grant monies to launch a new study that will compare the complete genomes of 1,000 dyslexic children with those of 1,000 fluent readers to obtain a fine-grained view of genes that are known to play a role in reading disabilities, and possibly to identify new genes that confer a risk of developing dyslexia. The ultimate goal of Gruen's work is to devise a practical genetic test for dyslexia, making it possible for parents and teachers of children with dyslexia to begin educational interventions early in life, the time when researchers have shown those interventions to have the most significant and lasting impact on reading ability. In addition, the new study will enroll children of non-European ancestry, who have been underrepresented in research on the genetics of dyslexia, Gruen says.

"I have a folder full of e-mails from desperate parents who've read

Dyslexia, *page 7*

Philanthropists aid a young scientist's innovative research

Alison P. Galvani, PH.D., assistant professor of epidemiology at the Yale School of Public Health, who at age 29 was one of the youngest-ever recipients of a Guggenheim Fellowship, combines psychological, economic and medical insights to generate mathematical models of disease transmission and control.

Miriam Burnett (1922–2008)

Galvani's research on the epidemiology of infectious diseases has enjoyed the generous support of the late Miriam Burnett and that of her son Charles Burnett III, who have contributed more than $650,000 to support Galvani's work. "The gifts from Miriam and Charles Burnett have been wonderful in facilitating my research," says Galvani.

While growing up in San Francisco, Galvani was always keenly interested in math and science, and

Galvani, *page 4*

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TERRY DAGRADI

A leader of the National Institute of Diabetes and Digestive and Kidney Diseases' IBD Genetics Consortium, Judy Cho is uncovering genetic factors that raise the risk of developing Crohn's disease and ulcerative colitis.

Intestinal fortitude

Yale physician–scientist advances the genetics of inflammatory bowel disease

In 1932, *JAMA*: *The Journal of the American Medical Association* published "Regional Ileitis: A Pathologic and Clinical Entity," which described 14 patients who had been treated at New York's Mount Sinai Hospital for fever, abdominal pain, diarrhea and emaciation. Despite its rather understated title, the article was soon recognized as a classic, and its first author, Burrill B. Crohn, M.D., has been immortalized by that honor peculiar to medicine, his name forever conjoined to an illness.

Today, Crohn's disease and ulcerative colitis fall under the broader clinical umbrella of inflammatory bowel disease, or IBD. According to Judy H. Cho, M.D., associate professor of medicine and one of the world's leading experts on the genetics of IBD, both diseases are chronic autoimmune conditions with similar symptoms, primarily distinguished by the regions of the gastrointestinal tract on which they wreak their havoc.

When Cho entered medical school at The Ohio State University in her hometown of Columbus, she planned to become a surgeon. But "when I saw the neurosurgeons standing in the OR for twelve hours," she says with a laugh, "I decided it wasn't for me." Instead, after her residency at Northwestern University, Cho completed a fellowship in gastroenterology in 1991 at the University of Chicago. She got great satisfaction caring for IBD patients, she says, because the disorder's chronic nature allowed her to build close relationships that approached those enjoyed by a primary care physician. Some cases of IBD can be successfully managed with immunosuppressant drugs, but up to two-thirds of patients require hospitalization or surgical treatment at some point in their lives.

But 60 years after Crohn's *JAMA* paper, the causes of IBD remained a scientific mystery. "In about 1993," says Cho, "I was sitting in a lab flipping through *Science* and saw a paper from Bert Vogelstein's lab [at Johns Hopkins] which ultimately led to the identification of a whole new class of genes that, when mutated, cause a hereditary form of colon cancer." Because IBD is also a familial disease, Cho recalls, "it clicked in my mind at that moment that genetic research was a perfect melding of clinical relevance and basic science."

Lifelines
Judy Cho

Soon after, Cho collected her first DNA samples from her patients. In 2001, before moving to Yale, Cho and colleagues at the University of Michigan were the first to establish a genetic vulnerability, in a gene known as *NOD2*, for Crohn's disease.

Now, in addition to directing Yale's Inflammatory Bowel Disease Program, an interdisciplinary group of gastroenterologists, radiologists, surgeons and pathologists, Cho chairs the steering committee of the IBD Genetics Consortium, a group of seven academic centers devoted to unraveling causes of the disease. This January, Cho and other members of the consortium linked regions on two chromosomes with ulcerative colitis.

But the successes in IBD genetics thus far are "low-hanging fruit," Cho says, adding that further progress will require careful classification of IBD patients, whose symptoms and clinical course can vary wildly from case to case.

"The major reason to do genetics is to develop new therapeutic targets and to refine our understanding of the disease" she says. "We're not lacking for potential targets, but we're lacking an understanding of how the immune mediators associated with IBD combine to cause disease. Part of this means figuring out how to follow patients better over long periods of time, which our present research system doesn't do very well."

With an eye to the future, Cho acts as a mentor to young physician–scientists through the Yale Center for Clinical Investigation. "Human translational work is much more complex than classic basic science," she says, largely because the lives of human patients don't unfold in the tightly controlled confines of the lab. So Cho sets her sights with a wide range. "It will be very challenging to develop a novel therapy," she says, " but the intermediate goal is to somehow classify people a little bit better."

Skin cancer expert is appointed new Smith Professor

David J. Leffell, M.D., deputy dean for clinical affairs, chief executive officer of Yale Medical Group and professor of dermatology and surgery, has been named the David Paige Smith Professor of Dermatology.

Leffell specializes in the diagnosis and treatment of melanoma and other skin cancers. He is an expert in Mohs surgery, a technique in which skin cancers are removed layer by layer and studied immediately under a microscope using a frozen section method. The Mohs technique allows removal of the entire tumor, providing the highest cure rate and minimizing scarring. The Cutaneous Oncology Unit that Leffell founded in 1988 treats more than 3,500 patients per year.

David Leffell

His research focuses on non-melanoma skin cancer, wound healing and cancer epidemiology. Leffell and colleagues discovered the skin cancer gene *PTCH* in 1996, and he has conducted collaborative research clarifying the role of ultraviolet radiation in skin cancer and skin aging. Other research includes the role of the *p53* gene in skin cancer and the development of innovative diagnostic devices.

As deputy dean of the School of Medicine, Leffell has been responsible for the growth and development of the school's clinical practice.

David Paige Smith, who joined Yale's medical faculty in 1873, was a grandson of Nathan Smith, a premier physician in post–Revolutionary War New England. Nathan Smith was a central figure in the establishment of the Medical Institution of Yale College, as the School of Medicine was known at the time.

Newest research building is recognized for environmental features

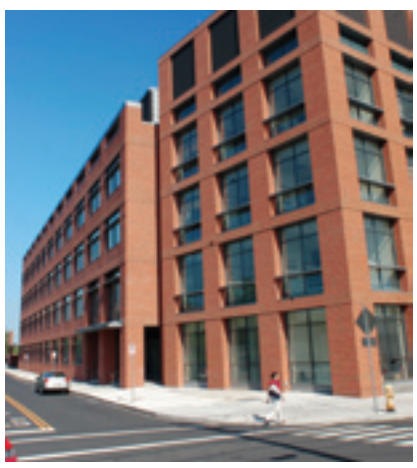
The research building at 10 Amistad Street in New Haven has been awarded the LEED Gold certification by the U.S. Green Building Council's Leadership in Energy and Environmental Design.

Completed in 2007, the building houses the School of Medicine's program in Vascular Biology and Therapeutics, the Yale Stem Cell Center and the Human and Translational Immunology program.

"Right from the outset the team was charged with incorporating green attributes in alignment with Yale's sustainability strategy, which includes striving for outstanding environmental performance in the design, renovation and construction of its facilities," says Virginia Chapman, the medical school's director of construction and renovation.

The 120,000-square-foot building has many green attributes, ranging from its accessibility to transportation and the materials used in its construction, to its waste management and energy conservation systems.

Many of the materials used in the building's construction were produced locally and selected for their high recycled content, and recycling of debris reduced the amount of construction waste by 70 percent. A lab waste recycling program has also been incorporated.



TERRY DAGRADI

Water collected on the roof of the research building at 10 Amistad St. is used in ultra-low-flow lavatories and dual-flush toilets.

Medicine@Yale

Peter Farley, *Managing Editor*

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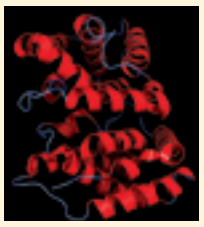
Advances

Health and science news from Yale

Versatile molecule protects against IBD

Immune system signaling molecules known as cytokines are believed to play a major inflammatory role in autoimmune diseases, in which the body's immune defenses somehow turn on its own cells.

Things aren't so simple in the case of the cytokine interleukin-22 (IL-22; below), which promotes the inflammation of skin cells seen in psoriasis but appears to protect cells in inflamed livers. Scientists from the laboratory of Richard A. Flavell, PH.D., Sterling Professor of Immunobiology, and Regeneron Pharmaceuticals have now found that IL-22 also plays a protective role in inflammatory bowel disease (IBD; see related story, p. 2). As reported in the December issue of *Immunity*, mice that were deficient in interleukin-22 had more severe forms of colitis and higher mortality.



Postdoctoral associate and first author Lauren A. Zenewicz, PH.D., says the discovery could lead to IBD treatments without the side effects of current immunosuppressive therapies, which include increased susceptibility to infections.

Aspirin for the heart, now for the liver?

The popular pain and fever reliever acetaminophen, best known as Tylenol but sold under many other trade names, is usually thought of as an aspirin alternative. But a new Yale study suggests that adding a bit of aspirin to acetominophen might deal with the risk of liver toxicity that is one of the drug's most problematic side effects.

In an article published online in the *Journal of Clinical Investigation* in January, Associate Professor of Medicine Wajahat Z. Mehal, PH.D., and colleagues describe how acetominophen-induced liver damage (which can progress to acute liver failure) is caused by a biochemical double whammy: first liver cells die, then their death triggers an inflammatory response mediated by the coordinated activation of two components of the innate immune system, TLR9 and Nalp-3. The team showed that liver damage could be headed off in mice either with TLR-blocking drugs or by using aspirin to tamp down the Nalp-3 response.

These results may have wide application, says Mehal. "Many agents such as drugs and alcohol cause liver damage, and we have found two ways to block a central pathway responsible for such liver injury," he says. "Our strategy is to use aspirin on a daily basis to prevent liver injury, but if it occurs, to use TLR antagonists to treat it."

Yale Netcast
"Aspirin May Save Lives and Livers"

Finding new ways to calm storms in the brain

For more than four decades, the Yale Epilepsy Program has led the way in research

When Dennis D. Spencer, M.D., a tall, soft-spoken man with an Iowa drawl and a mostly gray beard, speaks about his many colleagues in the Yale Epilepsy Program (YEP), he lists name after name, but always comes back to the word "team." Much like the interdependent cells of the brain, YEP members all play roles vital to the success of the group as a whole. And the parts fit together very well: throughout its 42-year history, the program has been a leader in the field.

Dennis Spencer, chair and Harvey and Kate Cushing Professor of Neurosurgery, is the YEP's surgical director, and his wife, Susan S. Spencer, M.D., professor of neurology and neurosurgery, directs the program's medical side. The program's two halves are a synergistic marriage in which neurological research centered on the causes, nature and treatment of epilepsy enables further surgical advances, and vice versa.

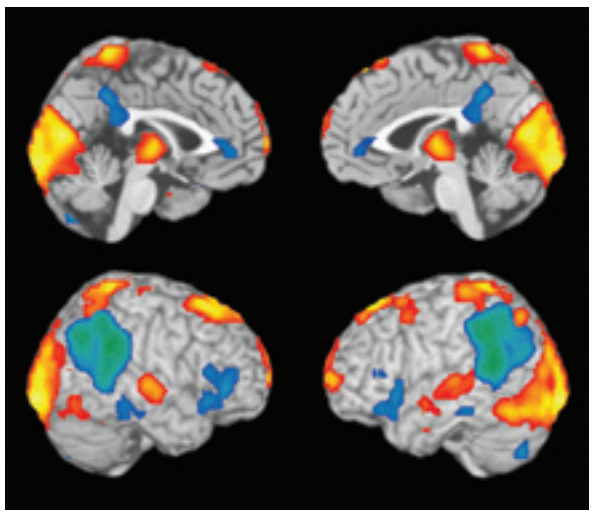
Founded in 1967 at the Veterans Administration Hospital in West Haven, Conn. (now the VA Connecticut Healthcare System), the YEP has evolved and expanded as the scientific and medical understanding of epilepsy and its causes has broadened. Yale's team—which now includes more than 20 faculty from the Departments of Neurology, Neurosurgery, Neurobiology and Diagnostic Radiology—has pioneered a number of advances widely viewed as milestones in the field (see "Covering All the Bases," p. 6).

Epilepsy is a chronic neurological disorder, affecting about 50 million people worldwide, in which abnormal or excessive activity in the brain's cortex results in unprovoked seizures. References to epilepsy date back to fifth-millennium B.C. Mesopotamia, when the disorder was thought to have been caused by evil spirits; it was only later that ancient physicians, like Atreya and Hippocrates, began to suspect that seizures originated within the brain.

Most seizures are less than two minutes long, but confusion afterward may last longer. In extreme cases, convulsions may occur. Most cases of epilepsy can be managed, but not cured, with medication. However, in about 20 to 30 percent of patients, seizures cannot be controlled with medications, and about half of these patients are referred for neurosurgical treatment.

One factor critical to the successful neurosurgical treatment of epilepsy is the precise localization of seizure foci; such knowledge enables surgeons to isolate and operate on only those parts of the brain that cause seizures and thereby preserve surrounding normal tissue that supports important neurological functions.

In the late 1960s, Richard H. Mattson, M.D., the YEP's first director and a leader in the pharmacological treatment of epilepsy, set up closed-circuit television (CCTV) cameras to videotape patients while simultaneously recording their brain activity with electroencephalography (EEG). The two recordings could be easily superimposed to show how behavioral changes correlated with changes in brain activity, a process that would have been quite cumbersome with film technology. Before Mattson's innovation, people didn't fully know what seizures looked like within the brain, nor did they fully understand the correlation between brain function and the behavioral aspects of seizures, says Dennis Spencer.



COURTESY OF HAL BLUMENFELD

Changes in brain activity of a 12-year-old girl during absence seizures, as measured by functional magnetic resonance imaging (fMRI). Abnormal increases are shown as warm colors, and decreases as cool colors. Activity increases in the thalamus, located in the center of the brain, along with a mixture of increases and decreases in the cortex, may explain why absence seizures cause loss of consciousness.

Change was rapid in the early 1970s. It was a time, Spencer says, when "people were breaking away from the concept that you recorded from the scalp with EEG and got kind of a general localization" of seizure activity. As a medical student at Washington University in St. Louis, Spencer had learned to monitor the brain more directly with electrode arrays placed on the dura, a thin, leathery covering of the brain just beneath the skull. On his arrival at Yale as a neurosurgery resident in 1971, Mattson's CCTV/EEG technique was the main tool for monitoring seizure activity, but Spencer oversaw the replacement of scalp electrodes with intracranial electrodes, both arrays and depth electrodes inserted into the cortex.

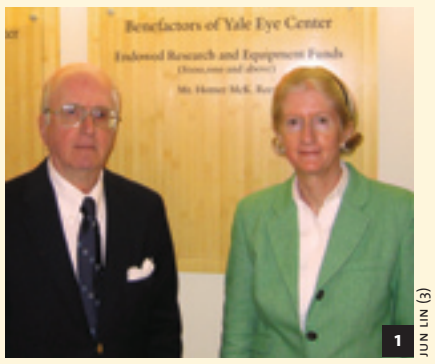
Spencer and Yale colleagues soon discerned that most seizures in the brain's temporal lobe—the most common site of origin for "partial" seizures, those that begin in a localized place—originate in the hippocampus, a structure deep in the brain that plays an important role in managing memory. By more precisely localizing the sources of seizures, Yale neurosurgeons became able to perform surgeries that interrupted seizures but preserved critical functions—especially language and vision—by removing only deeper portions of the brain's temporal lobe.

Examining the tissue removed during these operations in the mid-1980s, Nihal C. de Lanerolle, D.PHIL., D.SC., now professor of neurosurgery and neurobiology, found abnormalities in levels of the neurotransmitter glutamate, and Jung H. Kim, M.D., now professor emeritus of pathology, found that hippocampi from a majority of epileptic patients had fewer brain cells than those from unaffected people. When Anne Williamson, PH.D., associate professor of neurosurgery, performed electrophysiological measurements with slices of the removed tissue, she observed electrical changes that correlated with the chemical abnormalities de Lanerolle had observed.

Epilepsy, *page 6*

Out & about

December 11, 2008: Benefactors of the Yale Eye Center (YEC) joined faculty from the Department of Ophthalmology and Visual Science for a **PLAQUE UNVEILING IN THE YEC'S NEW LOCATION** at Temple Medical Center in New Haven. **1. Homer McK. Rees** and **Coverly R. Rees**. Last year, Homer Rees, member of the Yale College Class of 1951, established the Homer McK. Rees Research and Lectureship Fund. **2.** Yale Eye Center Advisory Board member **Peter Thorner** and **Jimmy K. Lee**, M.D., assistant professor of ophthalmology and visual science. A recent gift from Thorner established the Peter Thorner Research and Lectureship Fund. **3.** From left: **James C. Tsai**, M.D., M.B.A., chair and Robert R. Young Professor of Ophthalmology and Visual Science; **M. Bruce Shields**, M.D., chair emeritus and Marvin L. Sears Professor of Ophthalmology and Visual Science; **Rocky Cingari**, chair of the Yale Eye Center Advisory Board and member of the Lions Club of Darien, Conn.; and **Michael Del Re**, president of the Connecticut Lion's Eye Research Foundation (CLERF). After 50 years of partnership to prevent blindness, the cumulative total of CLERF grants to Yale tops $3 million, and the foundation has pledged to donate an additional $1 million to support research on macular degeneration and glaucoma, as well as pediatric eye care.



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January 10: A **RECEPTION FOR SCHOOL OF MEDICINE ALUMNI** was hosted by **Chip Skowron**, M.D. '98, PH.D. '00, and **Cheryl Skowron** in their Greenwich, Conn., home. From left: **Michael Tom**, M.D. '83; **Colleen Barnswell**; **Carlton Barnswell**, M.D., M.P.H. '88; **Henry Markley**, M.D. '43; Dean **Robert J. Alpern**, M.D.; Chip and Cheryl Skowron; **Russell Turk**, M.D.; and **Michele Turk**.

TOMMY WILLIAMS

MICHAEL MARSLAND

January 16: Connecticut Lieutenant Governor **Michael Fedele** joined New Haven Mayor **John DeStefano Jr.** and Yale University President **Richard Levin** at the ribbon-cutting for the **NEW WING OF THE CONNECTICUT MENTAL HEALTH CENTER**, a partnership of Yale and the Connecticut Department of Mental Health and Addiction Services. From left: State Representative **Toni Walker**; Levin; Fedele; State Representative **Patricia Dillon**; State Senator **Toni Harp**; State Representative **Gary A. Holder-Winfield**; and DeStefano. The center, which celebrated its 40th anniversary in 2006, provides inpatient and outpatient mental health services to 5,000 people each year, including New Haven's homeless mentally ill.

Neuromarketing *from page 1*

the drink in an fMRI scanner were accompanied by a visual presentation of the drink's brand.

The study "showed that branding alone can change the way people make decisions," Yudofsky says. This work inspired her to ponder the possibility of studying neural responses to marketing with an eye toward lessening the impact of public health problems such as smoking and obesity.

As a Yale freshman, Yudofsky was invited by the Yale Entrepreneurial Institute (YEI) to be one of 12 participants in the YEI's inaugural summer fellowship program.

Yudofksy found willing mentors at the medical school in Hilary Blumberg, M.D., associate professor of psychiatry and diagnostic radiology, and Rajita Sinha, PH.D., professor of psychiatry and IRCSSA director. Sinha helped Yudofsky to secure grant money to conduct fMRI research at the medical school's Anlyan Center for Medical Research and Education with the guidance of Marvin M. Chun, PH.D., professor of psychology and Yudofsky's advisor. In particular, she is studying brain activity associated with public-service ads aimed at preventing obesity.

While brain function is measured in the fMRI scanner, "subjects are asked to make a decision between two different objects or food items, and they're told to think about the consequences of their choices," Yudofsky explains. "Then they're shown obesity-prevention ads and another advertisement, and again asked to make decisions between two different items—some of the choices are healthful and some are unhealthful."

By applying imaging technologies to similar psychological tasks, Yudofsky, the subject of a recent *New York Times* profile, hopes "to assess validly in the brain the effectiveness of public service advertisements and other modes of communication on influencing healthful choices, decisions, and behaviors." Her ultimate goal, she says, is "to improve public health and diminish human suffering."

Galvani *from page 1*

she encountered a book during high school that would change the course of her life.

After reading *The Blind Watchmaker*, the bestselling account of modern evolutionary biology by University of Oxford biologist Richard Dawkins, D.PHIL., Galvani wrote a letter to Dawkins pointing out what she considered to be a minor inconsistency in his genetic mechanism of speciation. "He agreed and encouraged me to come to Oxford University" Galvani recalls.

After completing her undergraduate degree in biology at Oxford, concentrating on evolution and ecology, Galvani stayed on to earn her doctorate under the supervision of Lord Robert May, PH.D., in the university's very strong program in epidemiology, she says, "because I see epidemiology as the ecology of infectious disease, which I find fascinating."

In her current work at the Yale School of Public Health, she incorporates game theory and the psychology

Alison Galvani

of decision-making to create simulations that take crucial human factors—the likelihood of compliance with mandatory vaccination, the perception of risk, the role of social networks and more—into account, allowing her to easily compare the outcomes of various public health scenarios, a tool that government officials are finding increasingly valuable in designing public policy.

Funding received from Miriam and Charles Burnett has enabled Galvani to expand the scope of her studies and increase the range of collaborations nationally and internationally.

"Our research encompasses a wide variety of topics, including the intervention of influenza, tuberculosis, dengue fever and human papilloma virus," says Galvani. "I have observed increasing interest by policymakers in this tool."

Advances

Health and science news from Yale

Can we really 'catch' healthy behaviors?

Research suggesting that certain behaviors affecting health are "contagious"—that people who quit smoking are likely to influence friends to do the same, or that happiness spreads from one person to another—has generated a great deal of media buzz.

But the statistical techniques used to establish these so-called network effects are prone to "large biases that might produce effects where none exist," says Jason M. Fletcher, PH.D., M.S., assistant professor of public health.

Fletcher and a colleague studied headaches, acne and height, conditions for which network effects are implausible. In the December 4 issue of the *British Medical Journal*, the team reports "surprisingly high" network effects for these conditions that disappeared with statistical refinements.

"Our results suggest caution in attributing similarities of health outcomes between friends to a 'contagious' process," Fletcher explains.

A needless barrier to good patient care

According to the 2000 U.S. Census, more than 22 million Americans have limited proficiency in English, a 53 percent increase from 1990. Language barriers in health care settings can lead to poor understanding of instructions for medications, longer hospital stays and an increased risk of medical errors and misdiagnoses.

Despite these dangers, many physicians fail to use readily available interpreters with their non–English speaking patients, according to a study published in the February issue of the *Journal of General Internal Medicine*.

"It has become acceptable for a physician to rely on his or her own limited language skills, hand gestures or on the convenience of a patient's family member instead of calling a professional interpreter, even when one is available," says lead author Lisa C. Diamond, M.D., now of the Palo Alto Medical Foundation Research Institute, who initiated the study as a Robert Wood Johnson Clinical Scholar at the School of Medicine.

"The study shows that there will be no easy fix," says Elizabeth H. Bradley, PH.D., M.P.H., professor of public health, who co-authored the new report along with Research Scientist Leslie Curry, PH.D., M.P.H. "But clearly this is an important and widespread problem."

Not just weight loss: the new stomach surgery

Diabetes, apnea cures spark a reassessment of bariatric surgery's role

ROBERT A. LISAK

Surgeon Robert Bell (right) consults with a patient about bariatric surgery options. Once recommended strictly for weight loss, bariatric procedures have recently been found to have other benefits, including rapid and complete remission of type 2 diabetes, obstructive sleep apnea and other obesity-related disorders in a majority of patients, sometimes "before they leave the hospital," says Bell.

Bariatric surgery, long a popular operation for patients who want to lose weight, has gained some weight of its own in recent years. Once called "stomach stapling" and viewed simply as a technique to help the obese shed pounds, the surgery has recently been shown to cure or greatly improve such obesity-related conditions as type 2 diabetes and obstructive sleep apnea—often long before any significant weight is lost.

"There's been a huge change in the way we think about this surgery," says Robert Bell, M.D., assistant professor of surgery and director of the Yale Bariatric Surgery Program. "We used to think that if you helped a person lose weight, these weight-related problems would slowly get better as a function of the weight loss." What actually happens, according to Bell, is that metabolic changes brought on by the surgery cause immediate improvements in the weight-related disorders. Surprisingly, and for reasons that are not fully understood, these metabolic changes apparently don't occur if the patient loses weight naturally.

These findings prompted the American Society of Bariatric Surgery in June 2007 to change its name to the American Society of Metabolic and Bariatric Surgery, signifying "a shift in emphasis," Bell says. "It's not so much about weight loss; it's really more about getting patients healthier."

A study published in *JAMA: The Journal of the American Medical Association* in January 2008 found that 73 percent of patients resolved their type 2 diabetes after gastric banding surgery. Another *JAMA* study published in October 2004 found that after bariatric surgery, diabetes was eradicated in 76.8 percent of patients and eradicated or improved in 86 percent of patients.

"Unbeknownst to everybody doing this surgery was that there's a lot more going on than just that the patient filled up more easily," Bell said. "There's a variety of hormonal changes that occur that really were not described until this decade. It is these hormonal changes that confer the added medical benefits."

The first surgical procedure to aid in weight loss was introduced in the 1950s and was purely malabsorptive, meaning that after surgery, a patient could eat anything but only a small percentage would be absorbed. By the 1970s, gastric bypass surgery, a procedure in which the size of the stomach is surgically reduced, thereby restricting the amount of food a patient could eat, began catching on.

Bell said scientists are just beginning to understand the metabolic effects of this procedure. What is known is that favorable changes occur in levels of ghrelin, a hormone produced in the stomach, pancreas and brain that stimulates appetite, and in GLP-1 and GIP, two gastrointestinal hormones that increase the amount of insulin released after eating. How long after surgery it takes for weight-related disorders to improve depends on how long they've existed and how severe they are, says Bell. "In somebody who has only had type 2 diabetes for two years, it's going to be gone before they leave the hospital. If they've had type 2 diabetes for 15 years and have been on insulin for seven, it's going to get better but may not go away."

The implications of these findings are significant, says Bell, who predicts there will be a move toward earlier interventions, with surgeons operating on patients who are overweight but not yet obese, a transition that will most likely require the compilation of long-term efficacy data to convince insurance companies to change their coverage policies. "Right now you have to be a certain size and have a body mass index (BMI) of 40 or more to be covered," Bell said. A BMI of between 19 and 24 is considered normal; 25 to 30 is overweight, 30 to 35 is obese and 35 to 40 is morbidly obese. In November, the Centers for Medicare & Medicaid Services, a division of the Department of Health and Human Services, announced that bariatric surgery would not be covered by Medicare or Medicaid for beneficiaries with a BMI below 35.

Bell also anticipates the procedure being performed on younger patients. Bell, who performs about 100 gastric bypass surgeries a year, has done four on 17-year-olds. (Most insurers require the patient to be at least 18.) "It makes sense to help these patients when they're younger," he says, "because the years of obesity haven't added up, causing destruction to bones and joints that limit their exercise, which is key to the long-term success of this surgery."

Bell knows it will take time for patients, physicians and insurers to view gastric bypass surgery as more than just a weight-loss operation, but in his own practice, that's exactly what's happening. "Although we still talk about obesity and weight loss," Bell says, "we really focus on the fact that it's a cure for diabetes, hypertension, sleep apnea and high cholesterol." Medications, the usual course of treatment for these ailments, just manage the symptoms, Bell says. "Surgery eradicates the disease. It's gone."

Yale Netcast
"Is Bariatric Surgery for You?"

Feeling fuller faster

Bariatric surgery limits the amount of food the stomach can hold by reducing its capacity to a few ounces. Three procedures, all of which are offered by Yale surgeons, are covered by insurance carriers in the United States.

- In **gastric bypass**, the stomach is surgically shrunk from the size of a football to that of a golf ball. The smaller stomach pouch is then attached to the middle of the small intestine, bypassing the duodenum, the section of the small intestine that absorbs the most calories.
- Similar to gastric bypass, **biliopancreatic diversion with duodenal switch** involves the surgical construction of a sleeve-shaped stomach which is attached to the final section of the small intestine, bypassing the duodenum.
- In **laparoscopic adjustable gastric banding**, a silicone band filled with saline is wrapped around the upper part of the stomach to create a small pouch and cause restriction. The size of the restriction can be adjusted after surgery by adding or removing saline from the band.

None of these procedures is a substitute for exercise or healthy eating, cautions bariatric surgeon Robert Bell. "It's not like you have the surgery and—voila!—you lose all kinds of weight. You have to put a lot of effort into it. It's an adjunct, a tool to help you lose the weight."

Epilepsy *from page 3*

Positron emission tomography (PET) studies at Yale revealed lowered glucose metabolism in temporal lobe regions that caused seizures, and magnetic resonance imaging (MRI) showed that the hippocampi of patients with temporal lobe epilepsy were significantly smaller in volume than those in unaffected research subjects.

In the late 1980s the program's core shifted from the VA Hospital to the medical school campus; soon after, Yale neurologists and neurosurgeons built the epilepsy monitoring unit that Susan Spencer now oversees.

As reflected by the countless stacks of papers lining the shelves in Spencer's office, neurological research on epilepsy at Yale has been wide-ranging. One Yale-led study, conducted over a 10-year period ending in 2006, prospectively monitored 400 epilepsy patients at seven medical centers in the Northeast U.S. to identify the predictors of different clinical outcomes for temporal lobe epilepsy patients treated with surgery.

"We found that the most important aspect of outcome was control of seizures," Spencer says. "Even an 85 percent reduction in the number of seizures was not sufficient to improve quality of life. One had to cause complete cessation of seizures."

Prior to research conducted by Yale neurologists, scientists were unsure how to interpret the EEG recordings produced by the intracranial electrodes Dennis Spencer and others were using. "I've been able to study those signals and the way they appear in the context of how they predict surgical outcome, and the kind of tissue pathology that you'll discover when you do the surgery," says Susan Spencer.

Much of Susan Spencer's research focuses on the "network" phenomenon of epilepsy, or the notion that seizure activity in the brain often involves multiple regions, and that understanding how seizures form networks in individual cases has significant implications for treatment—surgical or otherwise.

"'Network' is now becoming a buzzword, whereas for awhile it was kind of an unknown," says Spencer.

Further advances spurred at Yale include the development of a navigation system that precisely directs electrodes to specific areas of the brain; the design of a membrane that can accompany depth electrodes to gather minute samples of the brain's neurochemical milieu.

Magnetic resonance physicist R. Todd Constable, PH.D., uses functional MRI (fMRI), a noninvasive neuroimaging technique that measures neural activity during cognitive or visual tasks, to provide Yale neurosurgeons with similarly important information about the relationship between sites where seizures originate and those areas of the brain that govern functions such as vision and verbal memory. Husband-and-wife team Hoby P. Hetherington, PH.D., and Jullie W. Pan, M.D., PH.D., joined the Department of Neurosurgery in 2006, just before the 2007 arrival at Yale of a powerful 7 Tesla (7T) MRI system, one of only about a dozen worldwide.

Hetherington and Pan brought to Yale a wealth of expertise in magnetic resonance spectroscopy (MRS), a technology that can noninvasively create precise chemical profiles of brain tissue. Yale's 7T system can analyze brain areas as small as three cubic centimeters; in addition to providing valuable information for the treatment of epilepsy, MRS can detect neurochemical changes that may signal the onset of neurodegenerative diseases like Alzheimer's and multiple sclerosis.

Hal Blumenfeld, M.D., PH.D., uses studies how epilepsy interferes with people's consciousness and ability to think. With fMRI, he can precisely locate brain activity during absence seizures, in which children stare and remain still (see photo, p. 3). But fMRI is prone to artifacts from the body movements that occur during larger seizures, so he complements his fMRI work with single photon emission computed tomography (SPECT). In SPECT, patients are injected with a radioactive tracer just as a seizure begins, allowing imaging to be performed later, when they are no longer moving. The resulting images provide a snapshot of brain activity occurring just after the injection.

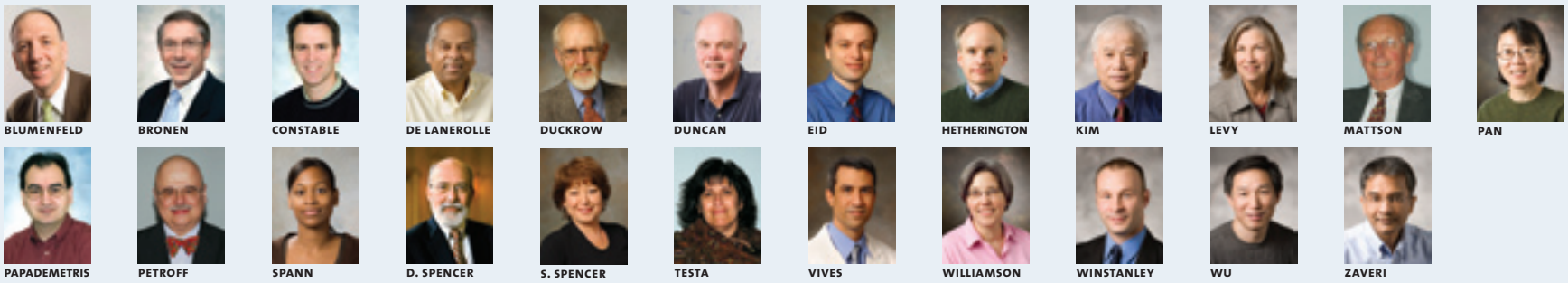
In another line of research, Blumenfeld and colleagues reported in 2008 in the journal *Epilepsia* that an anticonvulsant given early in life can prevent the development of seizures in a mouse model of epilepsy, "the first time it was shown that treatment during development can change the outcome in epilepsy," he says.

"There are maybe half a dozen other places in the world with the kind of experience we have," says Susan Spencer, who adds that many cases are referred to the Yale team because they've been untreatable elsewhere. "We have highly developed technology to localize those regions generating seizures, and a team of knowledgeable people who continue to do research to advance the field in multiple ways."

Yale Netcast
"Doctors Develop Surgical Cure for Epilepsy by Watching the Brain at Work"

Covering all the bases: the Yale Epilepsy Program

A team with deep expertise in the understanding and treatment of seizures



Hal Blumenfeld, M.D., PH.D.
Associate professor of neurology, neurobiology and neurosurgery
"I'm interested in understanding epilepsy in order to try to improve patient quality of life."

Richard A. Bronen, M.D.
Professor of diagnostic radiology and neurosurgery
"My research interests include imaging of epilepsy, cortical dysplasias, temporal lobe anatomy, and anatomic variants."

R. Todd Constable, PH.D.
Professor of diagnostic radiology, neurosurgery and biomedical engineering
"My interests focus not only on the development of MRI techniques to provide high quality pictures of anatomy but on the development of such techniques for providing information on function."

Nihal C. de Lanerolle, D.PHIL., D.SC.
Professor of neurosurgery and neurobiology
"The focus of our research is the anatomical and molecular characterization of seizure foci, in particular the hippocampal seizure focus in patients with temporal lobe epilepsy."

Robert B. Duckrow, M.D.
Associate professor of epidemiology
"I look for markers of seizure susceptibility in the electrical activity of the brain recorded during intracranial monitoring or with chronically implanted neurostimulators used to treat epilepsy."

James S. Duncan, PH.D.
Professor of diagnostic radiology and biomedical engineering
"My efforts within the neurosurgery program have been to perform image analysis research to better integrate the multimodal information necessary for both diagnosis and to perform image-guided epilepsy surgery."

Tore Eid, M.D.
Associate research scientist in neurosurgery and laboratory medicine
"Using chemical profiling by mass spectrometry, my laboratory's research focuses on the discovery of novel diagnostics and therapeutics of epilepsy."

Hoby P. Hetherington, PH.D.
Professor of neurosurgery and diagnostic radiology
"The overall goal of our work is to develop and utilize magnetic resonance spectroscopic imaging methods to characterize the metabolic and bioenergetic changes associated with epilepsy."

Jung H. Kim, M.D.
Professor emeritus and senior research scientist in pathology
"In addition to neuropathological evaluation of surgically resected brain tissue, we quantitatively evaluate neurons and glial cells, making correlations with clinical parameters and electrophysiological, biochemical and imaging findings."

Susan R. Levy, M.D.
Clinical professor of pediatrics and neurology
"Our clinical interests include pediatric epilepsy and clinical neurophysiology. Our research interests involve the risks and predictors of intractability and morbidity in childhood epilepsy."

Richard H. Mattson, M.D.
Professor emeritus and senior research scientist in neurology
"I continue to look for new and different antiepileptic drugs that bring possibilities for control and unique compounds that prevent epilepsy."

Jullie W. Pan, M.D., PH.D.
Associate professor of neurosurgery, diagnostic radiology and neurology
"The data we gather via imaging techniques is used to identify the brain regions giving rise to seizures to aid in surgical planning and to develop new therapeutic approaches to treating epilepsy."

Xenophon Papademetris, PH.D.
Assistant professor of diagnostic radiology and biomedical engineering
"Medical image analysis can be broadly defined as the extraction of quantitative information from medical images. One aspect of this work that relates to epilepsy is the registration of images from different modalities into a common coordinate space."

Ognen A.C. Petroff, M.D.
Associate professor of neurology
"We use a variety of tools to better understand the alterations of cerebral metabolism that promote epileptic seizures, and to develop therapies, which lead to a more normal state of GABAergic inhibition and glutamatergic excitation."

Marisa N. Spann, M.A.
Associate research scientist in neurology
"My current research aims to better understand and delineate the neuroanatomical pathways involved in childhood absence epilepsy, in particular those involved in attention and learning."

Dennis D. Spencer, M.D.
Chair and Harvey and Kate Cushing Professor of Neurosurgery
"Epilepsy research at Yale has a unique emphasis on the continuum of human investigation, from clinical research, which applies cutting edge tools of imaging, electrophysiology, neurochemistry, genetics and epidemiology in order to clearly define the human pathophysiology, to basic laboratory analysis of surgically resected human tissue substrates and the use of that tissue in developing animal models for new therapies."

Susan S. Spencer, M.D.
Director, Yale Epilepsy Program
Professor of neurology and neurosurgery
"There is increasing evidence that many forms of epilepsy are generated in networks of abnormally functioning, connected regions of the brain, rather than in single abnormal areas."

Francine M. Testa, M.D.
Clinical professor of pediatrics and neurology
"We have been involved, along with Dr. Anne Berg, in a longitudinal study that continues to provide unique information about the outcomes of epilepsy in children over the course of more than a decade after initial diagnosis."

Kenneth P. Vives, M.D.
Associate professor of neurosurgery
"We are participating in a clinical trial of an implantable device designed to detect focal seizure activity and treat this activity through the use of electrical stimulation."

Anne Williamson, PH.D.
Associate professor of neurosurgery
"I work primarily on the physiological and metabolic changes associated with epileptic tissue from patients as well as in animal models."

F. Scott Winstanley, PH.D.
Assistant professor of neurosurgery
"My interests include the neuroanatomical representation of language, electrical cortical stimulation mapping, intracarotid amobarbital procedure, fMRI of language and memory, and deep brain stimulation."

Kun Wu, M.D., PH.D.
Associate research scientist in neurosurgery
"I co-register functional images, electrophysiological data with structural MRI or CT images, into the navigational system that allows the neurosurgeon to guide therapeutic intervention without harming normal brain function."

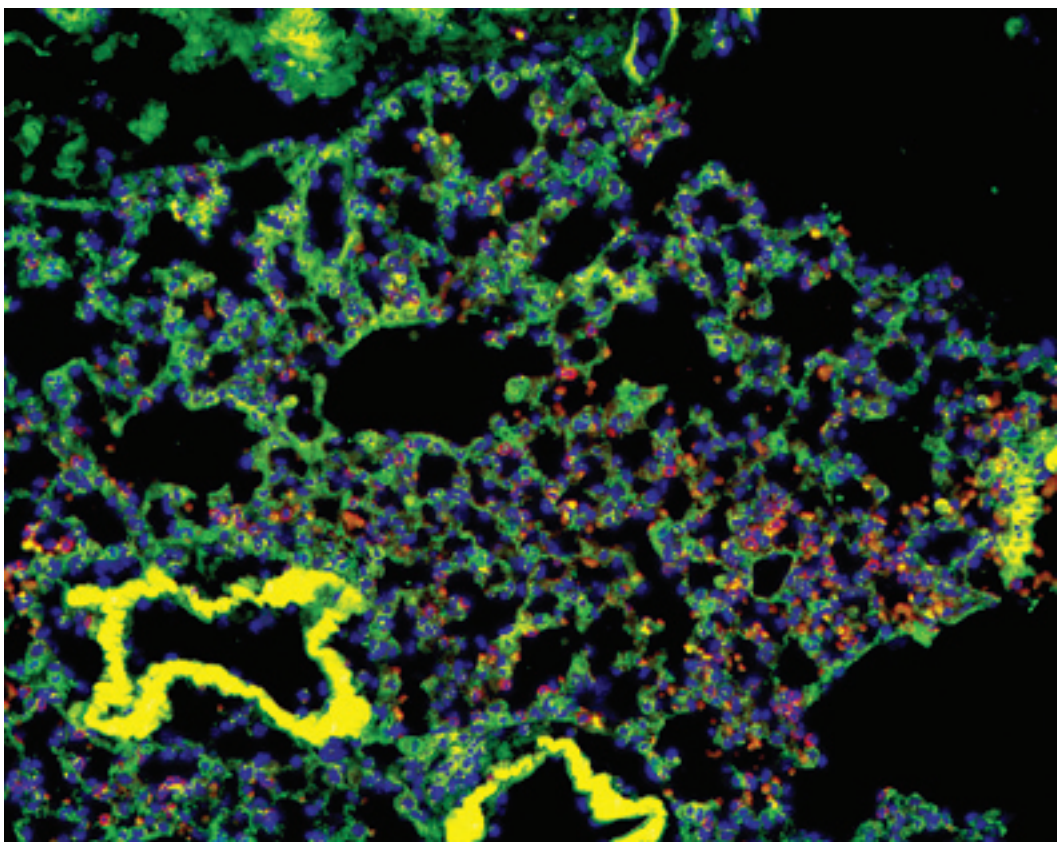
Hitten P. Zaveri, PH.D.
Associate research scientist in neurology
"My lab seeks to understand how seizures are generated and predict seizures with advanced computational methods and abort them once they have been detected."

Grants and contracts awarded to Yale School of Medicine

May/June 2008

Federal

Serap Aksoy, NIH, *Tsetse–Trypanosome Interaction*, 2 years, $454,221 • **Jeffrey Bender**, NIH, *Molecular Models of Immune-Mediated Vascular Injury*, 5 years, $2,068,645 • **Alfred Bothwell,** NIH, *PPAR—Mediated Inhibition of Vascular Remodeling*, 4 years, $1,654,688 • **Arthur Broadus**, NIH, *Parathyroid Hormone-Related Peptide*, 4 years, $2,035,479 • **William Cafferty**, NIH, *Plasticity of Intact Circuits Restores Function after Spinal Cord Injury*, 2 years, $179,820 **Tara Chaplin**, NIH, *Gender, Emotional Arousal, and Risk for Adolescent Substance Abuse*, 5 years, $774,714 • **Lynn Cooley**, NIH, *Oocyte Development in* Drosophila, 4 years, $2,363,907 • **Jonathan Cornett**, NIH, *Transposon Mutagenesis Screen for Mammalian Cancer Gene Discovery*, 3 years, $147,750 • **Erol Fikrig**, NIH, Borrelia burgdorferi *Interactions with* Ixodes scapularis, 5 years, $2,001,804 • **Jorge Galán**, NIH, *Virulence Factors of* Salmonella typhi, 5 years, $2,068,646; NIH, *Host Cell Signaling Pathways Induced by* Salmonella, 5 years, $2,995,445 • **Carlos Grilo**, NIH, *Treatment of Obesity and Binge Eating: Stepped-Care Versus Standard Behavioral Weight Loss*, 5 years, $3,027,963 • **Sohail Husain**, NIH, *Calcineurin in Pathologic Zymogen Activation*, 2 years, $165,460 • **Manisha Juthani-Mehta**, NIH, *UTI in Nursing Home Residents: Research Training and Clinical Investigation*, 5 years, $798,525 **Anthony Koleske**, NIH, *Regulation of Dendritic Spine Shape and Synapse and Dendrite Stability by Arg*, 5 years, $1,809,973 • **Diane Krause**, NIH, *Type II Pneumocyte Engraftment of Bone Marrow Stem Cells*, 5 years, $2,068,645 • **Jack Kronengold**, NIH, *Slick and Slack Heteromers in Neuronal Excitability*, 3 years, $113,316 **Rachel Lampert**, NIH, *T-Wave Alternans and Emotion in Daily Life*, 5 years, $1,747,627 **Patty Lee**, NIH, *Heme Oxygenase-1 in Lung Ischemia-Reperfusion Injury*, 5 years, $2,068,542 **Chiang-Shan Li**, NIH, *Cognitive Control and Cocaine Dependence*, 5 years, $1,591,444 **Richard Lifton**, NIH, *Genetics and Genomics of Human Disease*, 5 years, $1,522,800 • **Jinyu Lu**, NIH, *Decipher the Genetic Basis of Tumor Metastasis in* Drosophila, 3 years, $159,018 **Laura Manuelidis**, NIH, *New Animal and Culture Models to Rapidly Evaluate Infectivity of the vCJD Agent*, 2 years, $455,063 • **Andrew Miranker**, NIH, *Conformations and Dynamics of Amyloid-Induced Membrane Disruption*, 2 years, $416,950 • **Elijah Paintsil**, NIH, *HIV Nucleoside Analogs Translational Studies; Resistance and Metabolism*, 5 years, $629,100 **Christopher Pittenger**, NIH, *CREB and the Molecular Underpinnings of Habit Learning*, 5 years, $904,230 **John Rose**, NIH, *Immune Responses to VSV/HIV/SIV Hybrids in Macaques*, 3 years, $1,969,162 • **Ruth Sharf**, NIH, *Role of Orexin in Morphine Dependence and Withdrawal*, 2 years, $96,472 • **Jody Sindelar**, NIH, *Equity and Efficacy in Health and Healthcare? 2nd Biennial ASHE Conference*, 1 year, $25,000 • **Julie Staley-Gottschalk**, NIH, *Nicotine Vaccine and Nicotine Occupancy of Brain Nicotinic Receptors*, 2 years, $353,523 **Ning Sun**, NIH, *Statistical Methods to Study Dynamic Transcriptional Regulatory Networks*, 2 years, $455,020 **Jane Taylor**, Dept of Defense (U.S.), *Stimulant Therapy and Memory Strength: Implications for the Emergence and Treatment of PTSD*, 18 months, $213,410 • **Christian Tschudi**, NIH, *RNA Capping in Trypanosomes*, 5 years, $2,068,541



COURTESY OF DIANE KRAUSE

With support from the National Institutes of Health and the Connecticut Stem Cell Research Program, Diane S. Krause, M.D., PH.D., professor of laboratory medicine and pathology and associate director of the Yale Stem Cell Program, is studying bone-marrow cells that differentiate into cartilage, bone, muscle, lung and liver tissue. Here, lung tissue from a male mouse is stained for the Y chromosome (yellow dots), CD45+ blood cells (red), and cytokeratin-positive epithelial cells (green).

Non-Federal

Amy Arnsten, Nat'l Alliance for Research on Schizophrenia and Depression, *The Role of DISC1 in Primate Prefrontal Cortical Networks*, 1 year, $99,900 • **Elizabeth Bradley**, South Essex Partnership NHS Foundation Trust, *Leadership Workshop*, 1 year, $120,000 • **Leo Cooney**, Association of Directors of Geriatric Academic Programs, *Chief Resident Immersion Training in the Care of Older Adults*, 2 years, $114,000 **Mark Gerstein**, European Bioinformatics Institute, *EDAC: Encode Data Analysis Center*, 4 years, $587,948 • **Elena Grigorenko**, Columbia University–Teachers College, *Maternal Drug Use, Psychopathology and Child Adaptation*, 1 year, $211,626 • **Robert Heimer**, U.S. Civilian Research and Defense Foundation, *Russian Research and Methodological Center for HIV/AIDS Prevention*, 2 years, $79,098 • **Kevan Herold**, Juvenile Diabetes Research Foundation Int'l, *The Role of the Pancreas in Beta Cell Regeneration*, 2 years, $451,111; The Children's Hospital of Philadelphia, *Progenitors of Beta Cell Mass Expansion in Arrested Autoimmune Diabetes*, 1 year, $30,760 • **Roger Jou**, American Psychiatric Institute for Research and Education, *Characterization of Abnormal Neural Connectivity in Autism Spectrum Disorders using Combinatory Magnetic Resonance Imaging Techniques*, 1 year, $46,992 • **Patricia Keenan**, The Pennsylvania State University, *Regional Quality Strategy Evaluation Aligning Forces for Quality II*, 18 months, $79,763 • **Trace Kershaw**, Duke University, *Project Parivartan*, 6 months, $49,747 • **Paul Lombroso**, FRAXA Research Foundation, *The Role of STEP in Fragile X Syndrome*, 1 year, $84,450 • **Stephanie Massaro**, Amgen, Inc., *Regulation of Megakaryocytic Differentiation in Human Embryonic Stem Cells*, 1 year, $40,000 • **Linda Mayes**, Columbia University–Teachers College, *Family Research Consortium V: Transdisciplinary Consortium on Mental Health*, 3 years, $228,177; University of California–Irvine, *Parent/Health-Care Provider Behaviors and Child's Anxiety*, 1 year, $63,527 • **Pasko Rakic**, March of Dimes, *Origin, Morphogenetic Characteristic and Fate of Cannabinoid Type 1 Receptor (CB1R) Containing Interneurons in Developing Mammalian Cerebrum*, 3 years, $298,662 • **Albert Sinusas**, Medical University of South Carolina, *Collagenase Inhibition in Heart Failure*, 2 years, $198,394 • **Hugh Taylor**, Wyeth Pharmaceuticals Inc., *Mechanism of Tissue-Specific Estrogen Complex (TSEC) Action in the Endometrium*, 1 year, $224,000

Dyslexia *from page 1*

about our work and hope that I can provide some sage advice to help the third grader who comes home crying in frustration or the bright high school student whose standardized test scores make college seem out of reach," says Gruen. "These families could be helped through the creation of a simple, inexpensive dyslexia screening test that would apply to the general American population, including groups who have been excluded from dyslexia research up to now. We have the knowledge and the capability to develop such a test."

Over the past decade, scientists have identified four genes in the "human lexinome" a term Gruen coined for the suite of genes that underlies our species' unique ability to transmit and extract meaning via speech, writing and reading in which mutations appear to play a significant role in dyslexia, including *DCDC2*, the gene discovered in Gruen's lab in 2005.

According to Gruen, there is good reason to believe that these four genes tell much of the genetic story of reading disorders, which affect between 7.5 and 20 percent of the population. "Studies have shown that the number of loci—areas in chromosomes where there is an effect—is very limited," Gruen says. "So we're not talking about hypertension, cancer or schizophrenia where there may be 100 genes at work. We're talking about, maybe, 10. I think it's likely that these four genes, or even two of the four, will be found to have very large effects."

Accordingly, with a grant from the National Institute of Neurological Disorders and Stroke, Gruen has launched a study of these four genes using DNA taken from 10,000 English children whose educational performance has been tracked from birth through high school.

By documenting the range of mutations in the four "dyslexia genes" in these children and correlating these variants with reading ability and academic accomplishment, Gruen says, we can begin to assign the relative risk each gene and variant contribute to the development of dyslexia, a necessary component for any future genetic test to be of value.

In another effort to establish how gene variants change the way in which the brain decodes and interprets written language, Gruen has begun a series of "imaging-genetics" studies. Using functional magnetic resonance imaging (fMRI) to record activation in specific reading centers of the brain in awake, alert subjects, his group is linking individual differences in brain activity during specific reading tasks to particular genetic variations.

Unlike the study of the English children, which specifically targets four genes, the project underwritten by the new Manton Foundation grant will be a genome-wide association study, or GWAS ("gee-wahs"), exploring the entire genomes of the 2,000 study subjects at a fine level of detail.

In addition to finding new variants in the four previously discovered genes, some of which may not yet have been uncovered in European-American populations, Gruen says that the wide net cast by the GWAS method may unveil entirely new genes that confer a risk of developing reading disabilities.

The new grant will also fund fMRI research on a subgroup of 200 subjects, which Gruen says will be the largest imaging-genetics study of dyslexia to date.

While juggling these multiple scientific endeavors, Gruen keeps his eye on the prize of an eventual genetic test for dyslexia. "Unfortunately a lot of kids, possibly as many as a third, are missed—either misdiagnosed or not diagnosed at all. Now you've got a kid who hits fourth or fifth grade and they're struggling; their self-esteem begins to diminish, and it almost becomes a self-fulfilling prophecy," Gruen says. "If you can identify these kids early, by third grade, and get them into an intervention program, you can frequently get them reading up to grade-level, and that effect is long-lasting. That's a wonderful thing."

Gruen says that the School of Medicine, which combines scientific prowess with an interdisciplinary, collegial spirit, has been an ideal incubator for his ideas. "It's all here," he says. "It's a unique confluence of strength in genetics, dyslexia, imaging and neurobiology. I don't think there's another place where I could have been where this work would have come together like it has."

Innovative teacher, RNA expert is new Ford Professor

Scott A. Strobel, PH.D., chair of Yale's Department of Molecular Biophysics and Biochemistry and professor of chemistry, has been named Henry Ford II Professor of Molecular Biophysics and Biochemistry.

An expert on the function of RNA, Strobel employs such technologies as organic synthesis and X-ray crystallography to study reactions catalyzed by RNA. Using a multidisciplinary approach, he studies three systems: RNA splicing, ribosome catalyzed peptide bond formation and RNA riboswitches. He is considered a leader at the interface between chemical and structural biology, and many scientists now use techniques that he developed to study RNA activity.


Scott Strobel

In 2006, Strobel was named a Howard Hughes Medical Institute (HHMI) Professor, receiving a $1 million grant from HHMI to implement an undergraduate course that features an annual "bio-prospecting" expedition to one of the world's rainforests. Students in the course design their own research projects and conduct experiments on the plant samples they collect in the field.

For his scientific contributions, Strobel was honored in 2008 with the Schering Plough Research Institute Award by the American Society of Biochemistry and Molecular Biology. His other honors include Yale's Dylan Hixon Prize for Teaching Excellence in the Natural Sciences, a Yale Graduate Mentoring Award in the Sciences, a Searle Scholar Award and a Beckman Young Investigator Award. He serves on the editorial board of the journal *RNA* and has been a member of numerous National Institutes of Health study sections.

Yale Netcast
"Teaching Science: Lighting a Fire"

New Duberg Professor explores the brain's intricate networks

David A. McCormick, PH.D., an expert on the cellular networks of the brain's cerebral cortex and thalamus, has been named Dorys McConnell Duberg Professor of Neurobiology.

Recently, McCormick and colleagues discovered that synaptic communication within the cortex operates in both an analog and digital mode, and his lab is currently investigating how axons and synapses may operate in this regime. He is also studying rapid forms of plasticity of the visual cortex, the mechanisms by which the cortex generates changes in vision that allow for the perceptual "filling-in" of regions of visual space and help the visual system adapt to prolonged light stimulation. McCormick also conducts studies of the thalamus, a brain region involved in information flow to and from the cortex, and in sleep and consciousness.


David McCormick

A graduate of Purdue University, McCormick received his PH.D. in neuroscience from Stanford University. He was a postdoctoral fellow at Stanford before coming to Yale in 1987 as an assistant professor in the Department of Neurobiology. He was named a full professor in 1994 and served as director of graduate studies in neurobiology from 1994 to 1999.

McCormick has earned numerous honors for his research, including the John R. Whittier Award from the Committee to Combat Huntington's Disease, the Donald B. Lindsley Award for Outstanding Dissertation in Behavioral Neuroscience, the Jane and Peter Pattison Award, a Sloan Foundation Award, the Esther and Joseph Klingenstein Fund Senior Investigator Award, a McKnight Foundation Investigator Award, the Yngve Zotterman Prize from the Swedish Physiological Society and a Jacob Javits Investigator Award from the National Institutes of Health.

McCormick is the associate editor of the journal *Cerebral Cortex*, among others, and a reviewing editor for *Thalamus and Related Systems*. He serves on the editorial board of *Visual Neuroscience*. He is a member of the Society for Neuroscience, the American Physiological Society and the International Brain Research Organization.

In addition, McCormick is an avid cyclist who rides with and serves as faculty sponsor to the Yale cycling team, winners of the Ivy League championship for the last three seasons.

Dorys McConnell Duberg was the daughter of David Hall McConnell, founder of the Avon Corporation. After her death, her husband, H.P. John Duberg, established the Dorys McConnell Duberg Charitable Trust—which has endowed several other professorships and fellowships, particularly at Johns Hopkins University—in her memory in 1981. H.P. John Duberg died in 1990.

Protein sorting, kidney disease are interests of Long Professor

Michael J. Caplan, M.D., PH.D., professor of cellular and molecular physiology and of cell biology, has been named the C.N.H. Long Professor of Physiology.

Caplan is renowned for his research on the sorting and trafficking of ion transport proteins in epithelial cells, "polarized" cells in which the positioning of various transport proteins in different regions of the membrane is crucial to their proper function. His laboratory team focuses on identifying the proteins that interact with ion transporters to determine their localization and trafficking properties. His research group also studies two genes that are mutated in polycystic kidney disease and the unique trafficking processes that govern the distributions of polycystin-1 and -2, the proteins encoded by these genes.

Currently the interim chair of the Department of Cellular and Molecular Physiology, Caplan has been honored with numerous awards for his scientific contributions, including the School of Medicine's Charles W. Bohmfalk Teaching Prize, the Bowditch Young Investigator Award Lectureship of the American Physiological Society, the Young Investigator Award from the American Society of Nephrology, a fellowship from the David and Lucille Packard Foundation and a National Science Foundation National Young Investigator Award, among others.

An associate editor of the journal *Physiology*, Caplan is also on the editorial boards of many other scientific journals, including the *American Journal of Physiology: Renal Physiology*, the *Journal of the American Society of Nephrology*, and *The Journal of General Physiology*. He serves on the scientific advisory board of Telethon Italia.

Caplan is a member of the American Society for Cell Biology, the American Association for the Advancement of Science, the American Society of Nephrology and the American Physiological Society.


Michael Caplan

The C.N.H. Long Professorship is named in honor of Cyril Norman Hugh Long, M.D., a distinguished educator, administrator and scientist who was a member of the School of Medicine's faculty for 33 years. Internationally known for his research on the role of pituitary and adrenal hormones in metabolism, in 1937 Long and Abraham White, PH.D., isolated bovine prolactin, the first of the pituitary protein hormones to be obtained in pure crystalline form. Long served as dean of the medical school from 1947 to 1952, and died in 1970. The professorship was established in 1966 with an anonymous gift to support a faculty member working in endocrinology and metabolic disease, an unusual tribute because Long became the first person at Yale to have a chair named after him while he was still an active member of the faculty. In later years the endowment was expanded to support several professors.

Protein basic to life is research focus of new Higgins Professor

Mark Hochstrasser, PH.D., the newly named Eugene Higgins Professor of Molecular Biophysics and Biochemistry, is engaged in research at the crossroads of biochemistry and genetics aimed at understanding how specific proteins are rapidly degraded within cells while most others are spared.

Using baker's yeast as a model system, Hochstrasser and his laboratory team focus on ubiquitin, a fundamental regulatory protein found, as its name implies, throughout all eukaryotic cells. Among many other functions, ubiquitin tags proteins for destruction. Defects in the ubiquitin pathway have been linked to cancer, developmental abnormalities, Parkinson's disease, Alzheimer's disease and certain forms of mental retardation.

In related research, Hochstrasser is analyzing the function and dynamics of protein modification by other, ubiquitin-related proteins. One such protein he is studying, called SUMO, attaches to many other proteins and is crucial for progression of the cell cycle.

Hochstrasser holds two patents related to this work, which has been published in numerous scientific and medical journals, including *Nature*, the *Journal of Cell Biology*, *Cell*, the *Proceedings of the National Academy of Sciences*, *Genetics* and *Nature Cell Biology*.


Mark Hochstrasser

Part of the Yale faculty since 2000, Hochstrasser holds appointments in the Department of Molecular Biophysics and Biochemistry, the Department of Molecular, Cellular and Developmental Biology and the School of Medicine's Biological and Biomedical Sciences Program. He earned his B.A. at Rutgers University and his PH.D. at the University of California, San Francisco, and conducted postdoctoral research at the Massachusetts Institute of Technology.

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