Vanderbilt Medicine

WINTER 2011

A New Prescription for Drug Discovery

Bridging the gap between research and remedy

Snow Angel

January brought several inches of snow to Nashville, blanketing the Medical Center and the sculpture "Guardian Spirit" by musician Herb Alpert, who has been creating abstract expressionistic style paintings and figurative bronze sculptures for more than 20 years.

ANNE RAYNER

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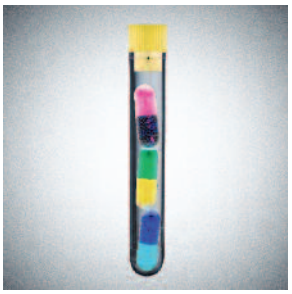
VanderbiltMedicine
WINTER 2011

:: on the cover

Drug discovery, previously the domain of biotech and pharmaceutical companies, is changing as university scientists become more engaged in identifying new compounds that will lead to cures.


CAVE MAN 18


PRISON OF BONE 20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Look for these stories and multimedia features online at www.mc.vanderbilt.edu/vanderbiltmedicine.

VIDEO: Psychiatrist Beth Baxter, M.D., talks about being both a provider and consumer of mental health.

VIDEO: Go underground with chemist Brian Bachmann as he searches for cures in caves.

ARTICLE: A history of drug development at Vanderbilt dates back to Canby Robinson's vision to bring the scientific enterprise under one roof.

JOE HOWELL

BY JEFF BALSER, M.D., PH.D.
Vice Chancellor for Health Affairs

We know that genetic differences in humans at the molecular level not only contribute to the disease process, but also significantly impact an individual's ability to respond optimally to drug therapy. We are rapidly expanding our ability to precisely identify genetic differences between patients, and make rational treatment decisions at the bedside. Through a unique and cohesive set of advances that combine innovations in health care informatics, genomics and drug discovery, we are beginning to 'deliver' on the promise of highly personalized therapy for our patients.

This edition of *Vanderbilt Medicine* is devoted to exploring drug discovery, and how it is changing as university scientists, here and at other leading medical centers, are engaging not only in the elucidation of the key molecular causes of disease, but in the identification and optimization of the new compounds that will be used to treat patients. Universities are now engaged in – and are innovatively changing – the process of drug discovery, previously the domain of biotechnology and pharmaceutical companies.

Vanderbilt has a leading role to play in this historic time. Our unique culture of cooperation amplifies extraordinary capabilities that have developed over a decade, and are concurrently changing the patient experience and redefining discovery science in academic medicine. We are beginning to take the first steps in moving personalized medicine from vision to reality.

In this issue, you will read about scientists and clinicians on the brink of therapeutic discovery across a broad array of disease arenas, including:

• Doug Sawyer, M.D., Ph.D., Lisa M. Jacobson Associate Professor of Medicine (Cardiology), describes his work on GGF2, a protein which protects heart cells from damage due to stress, enhances survival in animal models, and is poised for trials in humans.

• James Crowe Jr., M.D., professor of Pediatrics, Microbiology and Immunology, Ingram Professor of Cancer Research, talks about his work on vaccine development and its importance for the treatment of children, here and across the globe.

• Jeff Conn, Ph.D., professor of Pharmacology, Lee E. Limbird Chair in Pharmacology, who oversees research on brain diseases, including schizophrenia and Parkinson's disease, discusses his journey to forge a new paradigm for drug discovery in academic medical centers involving innovative partnerships with industry and government.

The notion of the blockbuster drug that everybody takes is going to change. We will be able to prescribe medications tailored not only to the genetic makeup of the individual, but also to our social, cultural and economic circumstances. Vanderbilt is working aggressively in broad areas essential to personalizing health care.

Innovation in drug discovery is a linchpin for meaningful progress. This issue of *Vanderbilt Medicine* provides a window into that future. VM

Gene variation could increase risk for late-onset Alzheimer's

Researchers have identified a genetic variation that appears to nearly double the risk of developing late-onset Alzheimer's disease, according to a genome-wide association study released in the Sept. 23 issue of the journal *PLoS Genetics*.

Small differences in the genetic sequences of MTHFD1L, a gene on chromosome six, were identified in 2,269 participants with late-onset Alzheimer's disease and 3,107 without Alzheimer's disease.

Individuals with the genetic variation were almost twice as likely to develop Alzheimer's disease, according to co-author Jonathan Haines, Ph.D., director of Vanderbilt's Center for Human Genetics Research.

"By applying the new tools of genomics we are now making rapid progress in finding out what genetic changes are involved in Alzheimer's disease," Haines said.

"These findings will lead to a better understanding of what's happening in Alzheimer's disease, and how we can improve treatments."

The World Health Organization estimates there are currently 18 million people worldwide with Alzheimer's disease, which is projected to nearly double to 34 million by 2025.

"This finding gives us unique insight into possible interactions between genetic and environmental risk factors that contribute to Alzheimer's disease," said Joseph Buxbaum, Ph.D., Department of Psychiatry, Mount Sinai School of Medicine. "We know of environmental and lifestyle factors that can impact homocysteine levels and it will be important to understand whether variations of the MTHFD1L gene can modulate these effects."

In addition to Haines, the collaborative team of researchers was led by Margaret Pericak-Vance, Ph.D., director of the John P. Hussman Institute for Human Genomics at the University of Miami Miller School of Medicine. VM

– CRAIG BOERNER

ANNE RAYNER

Rascal Flatts honored for tireless support

Award-winning music group Rascal Flatts is being honored at the Monroe Carell Jr. Children's Hospital at Vanderbilt for their unwavering devotion to the care of children.

Rascal Flatts has raised nearly $3 million over the past several years through concerts and other events, and they also have spent generous amounts of time with children and families. Money from their fundraisers will be used to build a new specialized radiology suite.

As a tribute to their continued dedication, Children's Hospital administration unveiled the naming of the pediatric surgical suite as the "Rascal Flatts Surgery Center."

"In honor of the extraordinary philanthropic commitment of Rascal Flatts to our patients and families at the Monroe Carell Jr. Children's Hospital, we are truly delighted to announce the naming of the new Rascal Flatts Surgery Center," said Jonathan Gitlin, M.D., James C. Overall Professor and chair of the Department of Pediatrics.

Rascal Flatts members, whose photos and albums decorate walls in Children's Hospital, said they are humbled by the generous display of appreciation.

"We became involved with the work at Children's Hospital so that children will continue to have a wonderful place to get better and to help their families move on with their lives," said lead vocalist Gary LeVox. "We have built some long-lasting relationships, not only with the staff, but with some of the kids and their parents as well."

Rascal Flatts' contributions will allow Children's Hospital's surgery center to develop a new interventional radiology suite to expand services offered to families.

More than 12,700 pediatric surgeries are performed each year at Children's Hospital. VM

– CHRISTINA E. SANCHEZ

Female sterilization procedures now available in clinic

Vanderbilt's Center for Women's Health is offering women two faster, safer and highly effective methods of permanent sterilization, both performed by physicians in the office at the Vanderbilt Health One Hundred Oaks and Cool Springs locations.

Unlike traditional laparoscopic tubal ligation procedures, which require abdominal incisions to block or remove portions of the fallopian tubes, the two non-reversible procedures – Essure and Adiana – rely on a small scope passed through the cervix and into the uterus to block the tubes. The procedure can be performed as early as six weeks postpartum.

In the Essure procedure, approved by the Food and Drug Administration in 2002, a soft, flexible coil is placed partially into the fallopian tubes.

The Adiana technique, approved by the FDA last year, uses radiofrequency and a tiny silicone plug, about the size of a grain of rice. Vanderbilt's Ted Anderson, M.D., Ph.D., associate professor of Obstetrics and Gynecology, was involved in Adiana's clinical trials.

Both can be performed in clinic procedure rooms instead of operating rooms and usually take less than 12 minutes.

Women who undergo the office sterilization must use another form of birth control during the three months following the procedure. Three months after, an X-ray using dye is done to make sure the fallopian tubes are blocked.

Tamara Callahan, M.D., M.P.P., assistant professor of Ob/Gyn, said that although no birth control method is 100 percent effective, Essure is believed to be 99.74 percent effective and Adiana, 98.4 percent effective in preventing pregnancy.

Ob/Gyn residents who are trained at Vanderbilt will leave their residency knowing how to do both procedures. **VM**

– **NANCY HUMPHREY**

Hearing loss spikes among U.S. adolescents

Hearing loss is now affecting nearly 20 percent of U.S. adolescents age 12-19, a rise of 5 percent over the last 15 years, according to a *Journal of the American Medical Association* (JAMA) study co-led by Ron Eavey, M.D., director of the Vanderbilt Bill Wilkerson Center and the Guy M. Maness Professor in Otolaryngology.

Eavey, who conducted the study with former Harvard colleagues Josef Shargorodsky, M.D., Sharon Curhan, M.D., and Gary Curhan, M.D., said the results are troubling because hearing loss in adolescents is on the rise and researchers don't have any hard evidence to explain why.

The study compared hearing tests conducted as part of the Third National Health and Nutrition Examination Survey (NHANES III), 1988-1994, and NHANES, 2005-2006.

The earlier study examined 2,928 participants and the 2005-2006 study examined 1,771 participants, ages 12-19.

The prevalence of any hearing loss increased from 14.9 percent in 1988-1994 to 19.5 percent in 2005-2006.

"One could have hypothesized the opposite," Eavey said. "There are vaccines out now that can stop bacterial meningitis and they also help get rid of some cases of ear infections, so that incidence is down.

"The knee-jerk answer that one might conclude, although supporting data is not clear, is that the increase is caused by loud volume."

Hearing loss in young persons can compromise social development, communication skills and educational achievement, according to the authors.

"We are looking at the front wall of an epidemic and we can help to prevent the loss to allow the kids to enjoy their ears and their great music a lot longer," Eavey said. **VM**

– **CRAIG BOERNER**

JOE HOWELL

JOE HOWELL

Chelsa Everley, R.N., gives a flu shot to Jerry Michael Howard. The Shade Tree Clinic received a grant to purchase flu vaccine which was delivered to the homeless under a bridge in downtown Nashville.

Students provide flu vaccine to the homeless

Vanderbilt University School of Medicine and School of Nursing students took the flu vaccine to Nashville's homeless where they all too often eat, sleep and live – under the Jefferson Street bridge.

Jerry Michael Howard, who said he has been living in Nashville since being displaced from New Orleans by Hurricane Katrina, stepped up to be the first vaccine recipient of the night when the program was implemented in October.

"It's a great idea for people who are living on the street. We don't have a choice and this environment can be tough on your health," Howard said.

Chelsa Everley, R.N., a student in the Psych/Mental Health Nurse Practitioner program, gave Howard his first immunization, while first-year medical student Anupam Kumar filled out the required health information forms. Kumar said the experience is exactly what Vanderbilt students are looking for.

"It's hard to process the environment that many people live in, so coming out to a common gathering spot under a bridge reminds us about the population we want to serve, and reminds us why we are here," Kumar said.

Nani Kalama, another vaccine recipient, said this helps people who are homeless see that they are not forgotten.

"My life might be on the street, but I care about my health. There are so many things we are exposed to out here, this is great. Coming out here helps keep homeless people healthier," Kalama said.

The students ran the clinic under the bridge and at other locations until their supply of flu shots — 1,400 vials — ran out. **VM**

– CAROLE BARTOO

Melanoma drug shows promise in shrinking tumors

A new drug used to treat metastatic melanoma patients who have the genetic mutation known as BRAFV600E demonstrated significant tumor shrinkage in the majority of patients during a clinical trial.

Data from the Phase I trial of the drug PLX4032, developed by Plexxikon Inc. and Roche Pharmaceuticals, showed that nearly all patients with the mutation who were treated with the drug showed some response, and 81 percent of patients had tumor shrinkage of at least 30 percent. The data were published in the *New England Journal of Medicine.*

Melanoma, a form of skin cancer, is curable when caught in its early stages but it can be lethal when it metastasizes to other areas of the body. Fewer than 10 percent of patients with metastatic melanoma are still alive five years after diagnosis, according to the National Cancer Institute.

"In the more than 20 years that I have been taking care of melanoma patients, I have not seen this kind of patient response to a therapy," said Jeffrey Sosman, M.D., director of the Melanoma Program at Vanderbilt-Ingram Cancer Center.

"We finally have a way to identify patients with a specific genetic mutation who are most likely to benefit from a treatment, and a drug that targets that mutation. This is the promise of personalized medicine and Vanderbilt's patients are benefiting from this approach to cancer treatment."

The PLX4032 drug, which is administered as a pill, is currently in parallel and ongoing Phase II and Phase III trials. The drug is a small molecule that is selective for a key oncogenic driver in melanoma and other cancers. Sosman is leading the Phase II trial. **VM**

– DAGNY STUART

Patient genotypes guide drug therapy in new VU program

All patients undergoing cardiac catheterization at Vanderbilt University Medical Center are being tested for a genetic variation that can affect their response to a blood-thinner many of them will end up taking.

The new program, which launched Sept. 15, 2010, is called PREDICT, for Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment.

The genetic information will be placed in their electronic medical records to help their physicians choose the drug and dose that is best for them. Having the information there means it's immediately available to doctors when the drug is prescribed, not hours or days later.

The goal is to reduce the risk of future complications, including strokes, heart attacks and sudden cardiac death.

Vanderbilt is the first academic medical center in the country to deliver this form of "decision-supported, personalized" drug therapy. It was developed by a team of experts led by Dan Roden, M.D., assistant vice chancellor for Personalized Medicine; Dan Masys, M.D., chair of Biomedical Informatics; Jim Jirjis, M.D., MBA, chief medical information officer; and Jill Pulley, MBA, assistant professor of Medical Education and Administration.

Every year, 4,000 patients at Vanderbilt undergo cardiac catheterization because of suspected heart disease. The X-ray test can detect "narrowings" in the coronary arteries that threaten to cut off the heart's blood supply.

In about 1,700 patients, tiny tubes called stents will be placed in narrowed arteries to keep them open, and the patients will be given the anti-coagulant drug Plavix to prevent clots from forming around the stent.

The problem is, about 1,000 of the patients will carry a genetic variation that prevents Plavix from being efficiently converted in the liver into its active form. VM

– BILL SNYDER

Surgery helps seal African child's abdomen, future

Grace Dobor, the sixth child of CeCelia and David Dobor, a traveling minister, was born in a small village in Liberia with her intestines and part of her liver outside her body at delivery. Village officials, feeling superstitious about the defect, advised the parents to let her die, but her parents steadfastly went in search of answers for their daughter.

When Grace was 5 weeks old, a Chinese doctor who had come to Monrovia, the capital of Liberia, to offer volunteer medical care, agreed to operate and closed the baby's skin over her intestines to prevent infection. But more surgery would be needed to prevent the risk of loops of bowel becoming entangled and cutting off circulation, a potentially fatal side effect.

Fate intervened. Ginger Moore, a Goodlettsville, Tenn., resident and member of a Christian women's ministry, traveled to Liberia in June for a speaking engagement. CeCelia stayed after hearing her speak to tell her about her youngest daughter's plight. Moore was amazed by Grace's story and determined she would find a way to get the baby's surgery donated in the United States.

Within a few weeks, the Monroe Carell Jr. Children's Hospital at Vanderbilt had agreed to donate Grace's care, and surgeon Wallace "Skip" Neblett, M.D., agreed to perform the procedure.

The surgery took place Oct. 21, 2010, and was a success. Neblett and senior Pediatric Surgery Fellow, Tom Rauth, M.D., neatly tucked her intestines and liver into her abdominal cavity and closed everything up. VM

– CAROLE BARTOO

Grace Dobor from Liberia was born with a large omphalocele – her stomach muscles never fully developed so her intestines bulged under the skin. She came to Vanderbilt for surgery. Shown with her is her mother, CeCelia Dobor.

MARY DONALDSON

NOT A DRY EYE

BY JESSICA PASLEY

ISTOCKPHOTO.COM

John Miller, 71, doesn't want to look back on the days prior to his entering the Vanderbilt Eye Institute, seeking relief for his dry eyes.

A cancer survivor and bone marrow transplant recipient, he developed a common side effect of allogeneic stem cell procedure called graft versus host disease that affects his eyes.

Miller, who recently moved to Nashville from Santa Fe, N.M., said he noticed his condition worsening in the often dry climates of the Southwest. He had hoped the humidity of Nashville would be of some help.

He found more than a hospitable climate — he rediscovered his life.

Itchy, red, burning and painful eyes are the most common complaints of the patients seeking solace in the new Scleral Lens Clinic at the Vanderbilt Eye Institute.

The clinic is one of a few specialized sites in the country dedicated to chronic dry eye and irregular corneal surface ailments. Vanderbilt's program is the only sclera lens clinic of its kind in the state.

"These patients walk into our clinic with just the smallest sliver of their eyes open," said Jeffrey Sonsino, O.D., F.A.A.O., assistant professor of Ophthalmology. "They are feeling so miserable and they have tried most everything to relieve their symptoms. Once they get to us, they are often in a very severe stage of dry eyes syndrome."

Sonsino and his colleagues are able to assist patients with dry eyes from various ailments including Sjorgen syndrome (an autoimmune disorder), corneal irregularities following surgery and transplants, keratoconus (a genetic condition of the cornea), post traumatic injuries and Stevens-Johnson syndrome.

Patients range in age from 6 to 80 and are referred to the clinic by various specialists including cornea specialists, ophthalmologists, optometrists and authorities on autoimmune disorders. VEI staff spend hours working with each patient to ensure the measurements for the specialized contact lenses used for treatment are correct.

Scleral lenses are large, rigid gas-permeable contact lens that cover the entire cornea. They create a moisture chamber of tears by vaulting over the cornea and resting on the white part of the eye (sclera) They tend to be comfortable because they do not move as much as a traditional gas-permeable lens. This moisture chamber can be used to provide tears to dry eye patients or optical correction for severely irregular corneas.

"I have never seen such a change in a patient's quality of life," said Sonsino. "In all of my time in practice, this is the most fulfilling clinic I have had a chance to participate in. Our patients are just so thankful and the relief they experience is life altering."

Miller, who has had several pairs of lenses, has been able to enjoy activities that for a while he had to put aside, like reading and painting.

"I could not have painted without Dr. Sonsino's help," said Miller. "I was given my life back. Frankly, I am thrilled with Vanderbilt." VM

Turn of the Tide

"The lowest ebb is the turn of the tide."
– Henry Wadsworth Longfellow

WRITTEN BY **KATHY WHITNEY**
PHOTOGRAPH BY **SUSAN URMY**

The office of psychiatrist Beth Baxter, M.D., MD '90, is homey. Located on the first floor of a nondescript building on 21st Avenue in Nashville, it doesn't sport a sleek leather couch on which patients might recline. Instead, they can plop down on an overstuffed loveseat, whose cushions are slightly catawampus. Knickknacks occupy real estate on tables, shelves and walls, and one quickly takes note of the numerous turtles among them.

Why so many turtles?

"I use turtles as a metaphor for the gradual decline into mental illness, and the slow, steep climb out of it," Baxter explained.

Baxter is referring not only to her patients' struggle to escape the quagmire that is mental illness, but to her own.

While a student at Vanderbilt University School of Medicine, and for the 20 years since graduating, Baxter has suffered from mental illness, which has taken her to the depths of despair and back. She shares her story of perseverance with advocacy groups, mental health associations and even her patients, offering hope and reminding them that the "lowest ebb is the turn of the tide."

Poised for Success

Baxter grew up in Nashville and attended Hillsboro High School, where she excelled academically and graduated fourth in her class of 300 in 1981.

"No real problems," she recalled of those years. "I had a lot of friends, did a lot of things, studied a lot and worked at the Green Hills public library."

After graduation, she went to Rhodes College in Memphis.

"That is where my story starts," she said.

She was majoring in chemistry and became involved in a lot of extracurricular activities. She was a resident assistant, and a leader in several organizations, eventually becoming president of the student government association. She began to experience clinical depression her freshman year, but didn't know what was happening to her.

"I knew there was something wrong with my brain," Baxter said. "I had to study very long periods of time to do what I needed to do because it was so hard to concentrate."

Even though she was active, she began to withdraw socially, avoiding personal interaction when possible. The school cafeteria opened at 4:45 a.m. and she would hurry in, make a peanut butter sandwich and go across the street to the chemistry building where she would study for hours in the basement. Before the cafeteria closed again, she'd go back and make herself another sandwich, and that would be her dinner.

She started to experience symptoms of psychosis while in college, what she calls "ideas of reference." She believed she was receiving messages from inanimate objects in her environment. A magazine opened to a certain page, the noise of an airplane overhead and people on television were telling her what to do.

"I was the only one who knew what the messages were supposed to mean," she said. "I was getting messages from everything. I was always looking for messages and it was hard to do other things in addition to that."

She sought the help of a guidance counselor once, but embarrassed by her problem, she never went back. She graduated in four years, applied to medical school, and was accepted to Vanderbilt.

Managing Medical School

She entered VUSM in 1985 and was elected president of the first-year class. She had difficulty assimilating new information, but managed to pass her courses, despite her illness becoming more pervasive and debilitating.

During her second year, she experienced more severe psychotic symptoms.

She recalled sitting in a classroom, staring at an exam paper for four hours. After she left the lecture hall, she called a Psychiatry professor who asked a resident to examine her in the hospital.

"They recommended me to get care, and of course, I didn't. I was not very open to it at the time," she said.

She failed all of her mid-term exams. She took a leave of absence and went to her grandparents' farm in Texas thinking she could recover in the serene surroundings of the wide open space. One day, in a delusional state, she packed her car and drove away. She was found along a Texas highway after her grandparents issued a missing persons report. She was admitted to the hospital for the first time and was diagnosed with bipolar disorder.

"It was hard to believe that a future doctor was psychotic. It's unusual," she said about the original diagnosis. She would eventually be diagnosed with schizoaffective disorder, a condition in which a person experiences a combination of schizophrenia symptoms – such as hallucinations or delusions – and of mood disorder symptoms, such as mania or depression.

She returned to VUSM and repeated her second year with the help of a tutor for each of her classes. Together, they talked through all the notes she had to learn. Despite having some recurring episodes of depression and psychosis during the third and fourth year, she graduated in 1990.

"I had a lot of teachers who really stuck by me and were loyal to helping me out," Baxter said.

Jeanette Norden, Ph.D., professor of Cell and Developmental Biology and Neuroscience, was one of the faculty members who advocated for Baxter.

"When I see a student who is struggling with something – whether that is depression or any other mental illness or personal issues – I always feel that every effort should be made to help the student. The only time which I would not do that would be if it's a student I felt clearly didn't care about being a doctor. What I remember about Beth is that she really wanted to be a doctor; she really wanted to care for others," said Norden, who was asked by the Dean's Office a few years ago to formally serve as the second-year academic and personal adviser.

"Different students have different challenges. You've got to be a strong person to make it through even if there's nothing else wrong. Part of what I look for in knowing how to help someone is how strong they are as a person. Beth was very strong. She had a couple of setbacks while in medical school, but I think having people believe in you, and believe that you have what it takes, I think it makes a difference."

Both Doctor and Patient

While interviewing for a residency slot, Baxter was forthcoming with her potential employers about her mental illness. As a result, she fell through the residency match program, but eventually secured and completed an Internal Medicine internship at the University of Tennessee in Memphis. Working in the public hospitals of Memphis is what she called "an incredible experience."

Left: Baxter, right, at her medical school graduation, received the Dean's Award from Dean John Chapman, M.D., in 1990 while Deborah German, M.D., left, looked on.

Right: Baxter, who speaks openly about her mental illness, was a panelist at the 7th annual Fountain House Symposium and Luncheon, which took place in New York in May 2010.

LESLIE BARBARO

"It was very difficult, but probably one of the best things I ever did because it gave me a lot of confidence about myself as a doctor."

Because of her own illness and a strong desire to help others, she decided to specialize in Psychiatry. She went to the University of Rochester in Rochester, N.Y., for her residency. While learning to treat others with mental illness, she was under the care of a psychiatrist and a therapist, neither of whom could "make a dent in the problem."

"I had learned to hide it pretty well, even though my illness became severe," Baxter said.

She functioned by compartmentalizing her internal psychotic world from her external professional world. In November 1994, after her fourth year of residency, however, "the messages had won." She attempted suicide by smashing a glass tumbler and using it to try to sever her carotid artery. She referred to this time as the "lowest ebb."

The Tide Turns

After an extended hospital stay, she returned to Nashville to live with her parents, and her doctors told them she would never recover. The best she could hope to do, they said, would be to work on an assembly line, putting objects into boxes.

"My functioning had finally caught up with my symptoms," she said.

Baxter found a psychiatrist whom she credits with helping her escape the riptide of her disease.

"He believed in me and saw, despite my illness, I was highly functional in college. He thought I could get back to that. He was very, very hopeful."

Not everyone was as optimistic.

"I remember when my doctor was on vacation, he had a colleague check on me while I was in the hospital. He sat me down and told me I would never be a psychiatrist. That lit a fire under me. I've had a big fire under me from all of the people who didn't think I could make it," she said. "I did [make it], but it was a long road up."

Baxter began treatment with clozapine, a heavy duty anti-psychotic reserved for patients in whom all other medications have failed. Day by day she slowly felt better.

Practicing Psychiatry

In 1995 she started to work for TennCare's Merit Behavioral Care Corporation as a consumer advocate, serving as an adviser on policies and programs for people with mental illness. She traveled around the country telling her story. The message she delivered was one of hope.

"My story has been received very, very well. It gives people hope that they or their family members can recover."

In 1998, she returned to her first love, the practice of Psychiatry. She became a clinician with the Mental Health Cooperative, and later with Park Center, a non-profit agency for adults in Middle Tennessee diagnosed with a severe and persistent mental illness. She began part-time private practice in 2003, moving to full time in 2006. Aside from her Hillsboro Psychiatry practice, she sees patients at the Babb Center in Hendersonville, Tenn., on Wednesdays and works at an eating disorder clinic two mornings a week.

She said most of her patients know about her mental health history before they come to see her.

"I have years and years of experience of being able to set the boundary between myself and my patients," Baxter said. "Despite the fact that I go around and talk about my illness in public, I really don't do that with my patients a whole lot. I do it at specific times when I think it can be helpful, but I try to really focus on my patients.

"My story makes me more interesting to them. If I can do it, they can do it. It's really exciting to see them make that turn. It's very rewarding."

David Walley, director of the Babb Center and a therapist, has worked with Baxter for three years, and said he believes her personal experience with mental illness is a benefit to both her patients and her colleagues in the profession.

"Beth is one of the most caring psychiatrists I have ever met. Her experience with mental illness and the depths it has taken her to have taught her a lot about what people go through and how important it is to be able to come alongside that in a caring way. She is very good at that," Walley said.

"Our therapists consult with her regularly. She is giving of her time and her knowledge. She is full of knowledge that comes not only from her education, but her experience. At our clinic, she is deeply respected, and I think people value what she offers."

Baxter received the Mental Health Association of Nashville's Clifford Beers Award in 1997, National Alliance on Mental Illness (NAMI) Nashville's Consumer Advocate of the Year Award in 1998, national NAMI's Exemplary Psychiatrist Award in 2000, and Eli Lilly's Honorary Public Eye Reintegration Award in 2001. She was named a fellow in the American Psychiatric Association in May 2010.

A clinical instructor of Psychiatry at Vanderbilt, she has led grand rounds and has spoken to second-year medical students about her struggles. She is active in her church and continues to educate people about mental illness and to dispel myths and negative social stigma.

"I am doing very well. I still have episodes of illness from time to time, but I see my therapist and my psychiatrist regularly. I keep my system of checks and balances," Baxter said. "I want to keep doing what I am doing. It brings a lot of satisfaction when a patient comes in and says, 'I am feeling better.' To me, that is just wonderful." VM

WEB LINK
To watch a video of Beth Baxter telling her story in her own words, please visit www.mc.vanderbilt.edu/vanderbiltmedicine.


A New Prescription
for Drug Discovery
coming to a medicine cabinet near you

WRITTEN BY **BILL SNYDER**
ILLUSTRATION BY **DAVID REINBOLD**

RESEARCHERS AT VANDERBILT UNIVERSITY ARE BUSY BUILDING THE PHARMACY OF THE FUTURE. ON ITS SHELVES MAY BE:

- New medications for schizophrenia and Parkinson's disease, and the first drug treatment for Fragile X syndrome;
- A drug that can stop a particularly vicious form of breast cancer in its tracks;
- A replacement for acetaminophen that can be given in higher, more effective doses without causing liver damage; and
- A new way to treat obesity and diabetes by "tickling" a receptor in the brain.

These bold ideas are being pursued today at Vanderbilt, thanks to a unique recipe for drug discovery that blends bench science with clinical medicine and academia with industry.

While there's no guarantee that any of these potential drugs will survive the tortuous road to market, Vanderbilt scientists and their physician colleagues believe they are on the threshold of a new era of innovation.

"I think we're right on the cusp of real breakthroughs because our scientific understanding has increased dramatically," said Jeffrey Conn, Ph.D., director of the Vanderbilt Program in Drug Discovery (VPDD), which explores new treatments for neurological and psychiatric diseases.

"If we are able to overcome the technical hurdles and if we can find small molecules that inhibit these targets that we're pursuing," added Stephen Fesik, Ph.D., a leader of Vanderbilt's cancer drug discovery effort, "we could have a dramatic effect on cancer therapy, effects that won't just give you a slight increase in lifespan … but would actually lead to cures."

"One thing that's unique about Vanderbilt now is we've built the infrastructure to look just like a pharmaceutical company,"

said Craig Lindsley, Ph.D., director of Medicinal Chemistry in the VPDD who, like Conn, came to Vanderbilt from Merck. "We have all of the instrumentation and technology that you'd find at a Merck or a Pfizer or a GlaxoSmithKline."

Vanderbilt, of course, is not capable of bringing products to market, and later-stage clinical trials of drugs discovered here probably will be conducted elsewhere.

But drug companies have struggled lately to fill the "pipeline" with new compounds that potentially can solve important problems in human health. At the same time, many firms are downsizing their research operations, laying off scientists and tightening their belts, as patent protection ends for some of their best-selling brand name products.

"Changes in reimbursement for drugs will have a huge impact on the availability of new drugs," noted Nancy Brown, M.D., who chairs the Department of Medicine and is acting director of Clinical Pharmacology at Vanderbilt.

It can cost over a billion dollars to bring a drug to market. If it becomes more difficult to recoup that investment, Brown said, companies "either have to become more efficient in developing drugs and predicting which drugs will make it, or new drug development will decline – and has."

This is where Vanderbilt researchers can help.

"Ultimately it takes the pharmaceutical industry to fully develop and market a drug," said Conn, the Lee E. Limbird Professor of Pharmacology. "Anything we can do to increase the probability of success … in taking those drugs to market (will) have an impact on patients and the economy."

The National Institutes of Health, which funds the major portion of biomedical research in the United States, "is really pushing on us now to do drug discovery in the academic environment," added Lindsley, professor of Pharmacology and Chemistry. "It's a whole new paradigm of NIH-sponsored research, and Vanderbilt, I think, is uniquely positioned to capitalize on this whole next wave."

Consider these examples:

Dimmer switches in the brain

Conn, Lindsley and their colleagues have pioneered a novel approach to treating neurological and psychiatric disorders using compounds called "allosteric modulators."

Rather than turning a receptor "on" or "off" (which is what traditional drugs usually do), allosteric modulators "tune" the receptor function up or down, like a dimmer switch in an electrical circuit.

The researchers have discovered promising candidates for treating a wide range of disorders including Parkinson's disease, schizophrenia and Fragile X syndrome.

An estimated 1.5 million Americans have Parkinson's disease, a progressive brain disorder characterized by uncontrollable muscle tremors and rigidity. It is caused by the death of nerve cells in a specific brain region that produce the neurotransmitter dopamine.

Dopamine replacement therapy can relieve symptoms, but it also causes side effects and eventually becomes less effective as the disease progresses.

With support from the NIH and the Michael J. Fox Foundation for Parkinson's Research, the Vanderbilt researchers have identified two drug-like molecules that may avoid the limitations of current therapy by acting on a brain receptor that binds a different neurotransmitter, glutamate.

Schizophrenia affects more than 2 million Americans. Current therapy can reduce hallucinations and delusions but is less effective in relieving cognitive symptoms and social withdrawal.

With funding from the NIH and Janssen Pharmaceutica, a Johnson & Johnson company, Conn's team is testing ways to "tune" a specific glutamate receptor in order to alleviate all symptoms of schizophrenia.

Fragile X syndrome is the most common inherited form of intellectual and developmental disabilities, and the most common genetic cause of autism.

In collaboration with Seaside Therapeutics in Cambridge, Mass., the researchers are trying to "tune down" signaling through two different brain receptors – one involved in learning and memory, and the other associated with autistic and other behavioral symptoms of Fragile X syndrome.

So far, the researchers have shown that the compounds penetrate the blood-brain barrier and have the desired effects in animal models of each of these diseases. If they pass further animal testing and toxicity studies, Lindsley and Conn predicted they may be ready for testing in humans by early 2012.

"The unique thing about these academic drug discovery efforts at Vanderbilt is that novel mechanisms are being

explored, and the drugs that result have the promise of fundamentally changing how diseases such as schizophrenia, Alzheimer's, Parkinson's and autism are treated," said Heidi Hamm, Ph.D., the Earl W. Sutherland Jr. Professor of Pharmacology and chair of the Department.

"Early studies are hinting that the compounds may not only treat the symptoms of these diseases, but actually alter the course of the pathology."

'Hit molecules' for cancer

Fesik, the Orrin H. Ingram II Chair in Cancer Research, is developing new approaches to target proteins that currently are considered to be "undruggable."

Protein-protein interactions play a central role in nearly all signaling processes in cells, including cancer cells, but targeting these proteins will require a new set of tools beyond those used in traditional drug discovery.

Fesik, who came to Vanderbilt in 2009 from Abbott Laboratories, is using fragment-based methods – screening small chemical fragments for their ability to bind to small pockets on a protein target.

He and his colleagues then obtain and examine crystal structures of the "hit molecules" bound to their targets. This information can show them how to link the fragments into drug-like compounds with the "right pharmaceutical properties to move forward," he said.

In August 2010, Fesik became the first Vanderbilt scientist to receive a prestigious NIH Director's Pioneer Award, which will provide $2.5 million in direct costs over the next five years to support his work.

Fesik also is part of Vanderbilt's cancer drug discovery program, established in 2009 by a two-year $4.7 million NIH "Grand Opportunities" grant funded by the federal Recovery Act.

The Vanderbilt Molecular Target Discovery and Development Center, a joint effort of the Vanderbilt Institute of Chemical Biology (VICB) and the Vanderbilt-Ingram Cancer Center, initial-

Discovery Discussion

Photos by Joe Howell

Vanderbilt's team approach to discovery science includes heavy hitters (clockwise from top left) Stephen Fesik, Ph.D., Gary Sulikowski, Ph.D., Craig Lindsley, Ph.D., and Jeffrey Conn, Ph.D. The four recently participated in a round table discussion of the current state of biomedical research in the United States and Vanderbilt's role in moving it forward.

ly will hone in on "triple-negative" breast cancer, a particularly deadly form of the disease.

The most successful treatments for breast cancer target tumors that "express" receptors for the hormones estrogen and progesterone and for the human epidermal growth factor receptor 2 (HER2). Because "triple-negative" breast cancers don't express any of these receptors, they are difficult to treat, and account for 25 percent of all breast cancer deaths.

Researchers are searching for genes – and the proteins they encode – that "drive" different subtypes of the cancer. Then they will try to fashion compounds that can block the proteins and kill the cancer cells.

"This is really personalized drug discovery," said VICB director Lawrence Marnett, Ph.D., Mary Geddes Stahlman Professor of Cancer Research and principal investigator of the Grand Opportunities grant. "We think (it) represents the model for the future."

> "This is really personalized drug discovery," said Lawrence Marnett, Ph.D. "We think (it) represents the model for the future."

Gary Sulikowski, Ph.D., Stevenson Professor of Chemistry and associate director of the VICB Chemical Synthesis Core, is leading another cancer drug discovery effort. His group has synthesized several anti-tumor antibiotics isolated from various soil microorganisms.

Sulikowski also is co-principal investigator with Alex Waterson, Ph.D., research assistant professor of Pharmacology, of the Vanderbilt Chemical Diversity Center, part of a National Cancer Institute effort to spur the discovery and development of new cancer drugs.

The partnership between the School of Medicine and Department of Chemistry "really opens up new approaches," Sulikowski said.

Breaking the dose 'ceiling'

Acetaminophen, the ingredient in Tylenol and similar drugs, is the most commonly used fever and pain reliever in the world. In high doses, however, it is toxic to the liver.

Every year in the United States, acetaminophen overdose causes more than 50,000 cases of liver toxicity – and more than 400 deaths, said John Oates, M.D., the Thomas F. Frist Sr. Professor of Medicine and professor of Pharmacology.

Were it not for the 4-gram-a-day dose 'ceiling' imposed by toxicity, acetaminophen could do more than ease pain and lower fever.

Recent animal studies conducted by Oates and his colleagues suggest that in higher doses the drug could prevent kidney failure following traumatic injuries, and neurological damage following bleeding in the brain.

Myoglobin is a protein that transports oxygen to the muscle, just as hemoglobin does in the blood. When muscle is crushed, it releases myoglobin, which travels to the kidneys and, through a reaction called lipid peroxidation, generates free radicals and other kidney-killing products.

"In a situation like (last year's) earthquake in Haiti … they had to go to the medieval extreme of amputating limbs that were crushed in order to prevent kidney failure," Oates noted. Similarly, bleeding in the brain can, via lipid peroxidation, cause stroke-like damage.

Oates, who founded Vanderbilt's Division of Clinical Pharmacology, and longtime colleague L. Jackson Roberts II, M.D., the T. Edwin Rogers Professor of Pharmacology, wondered if they could design a replacement for acetaminophen – a drug that blocks lipid peroxidation without damaging the liver.

They joined forces with Stevenson Professor of Chemistry Ned Porter, Ph.D., to do just that.

"I have a high level of confidence … that we will have some successful compounds because we're working on a mechanism we understand for both the effectiveness and the toxicity," said Oates, who has applied for NIH funding to continue the work. "We know enough about those to know that we can pull them apart."

Oates credited an $180,000 Vanderbilt pilot grant awarded in 2007 with accelerating the research and moving it to a more advanced drug development stage. "If we'd not had that, we would be proceeding at a molasses pace," he chuckled.

Tickling the appetite receptor

Drugs prescribed for the twin epidemics of modern life, obesity and type 2 diabetes, are among the biggest sellers in the pharmaceutical industry. According to some estimates, they will exceed $50 billion in annual worldwide sales by 2015.

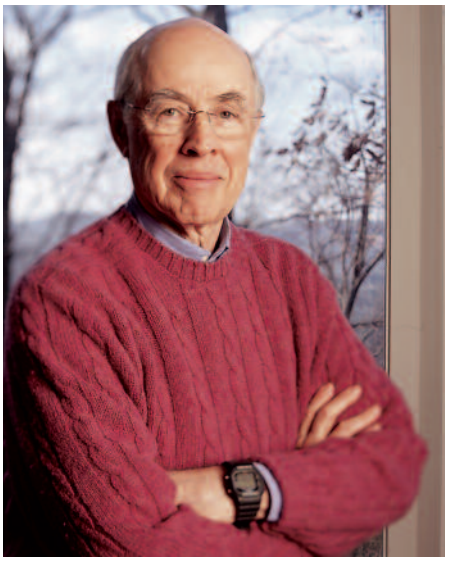
A class of diabetes drugs called GLP-1 analogs has been particularly successful in controlling blood glucose while helping patients maintain, or even lose weight.

GLP-1 (for glucagon-like peptide 1) is a hormone that stimulates insulin secretion in response to elevated blood glucose levels, while decreasing secretion of glucagon, which opposes insulin action. Once glucose levels are normal, the GLP-1 effect shuts off.

The peptide also slows gastric emptying in the stomach and reduces appetite by acting on the satiety centers in the brain, thereby helping to control weight. "Analog" drugs, like Byetta, that bind to and activate the GLP-1 receptor can amplify the natural hormone. But they are not without side effects, including nausea and vomiting.

(from left) John Oates, M.D., who founded the Division of Clinical Pharmacology, Heidi Hamm, Ph.D., chair of the Department of Pharmacology, and Gordon Bernard, M.D., director of the Vanderbilt Institute of Clinical and Translational Research, exemplify the breadth of Vanderbilt's commitment to drug discovery.

DEAN DIXON



DEAN DIXON

STEVE GREEN

Kevin Niswender, M.D., Ph.D., and David Weaver, Ph.D., director of Vanderbilt's high-throughput screening facility, wondered if they could develop an allosteric modulator to "tickle" the receptor in a way that preserves or even enhances the benefits of GLP-1 analogs while limiting their side effects.

They have begun to search for small molecules that bind to and activate the receptor in unique ways. The compounds will be tested in isolated pancreatic islets to see whether they affect insulin secretion.

In the end, "tickling" the receptor may be no better than simply switching it on. But the researchers hope their study will reveal more of what GLP-1 is doing in the brain and how the GLP-1 receptor works.

Could drugs that improve insulin and GLP-1 signaling in the brain strengthen one's preference for low-fat, low-carbohydrate foods over less healthy choices?

Obesity is not "a defect in the push-away-from-the-table muscle," said Niswender, assistant professor of Medicine and of Molecular Physiology & Biophysics."It's a very potent neural circuitry. It's not just the appetite circuits, but it's the mood circuits, it's the cognition circuits, it's the impulsivity circuits that are all colluding against somebody's efforts to make good decisions and ultimately lose weight."

'Valley of death'

In today's economically strained environment, companies are reluctant to invest in high-risk drug discovery projects – because most won't pan out.

Of the thousands of "drug-like" compounds identified each year, only a few hundred will show sufficient activity to enter pre-clinical testing in cell cultures and animals.

Only a handful of these will meet the criteria for testing in humans. They must be absorbed by the body and reach their target tissue at a high-enough concentration to do the job, and they must be effectively eliminated by the body so they don't reach toxic levels.

A final challenge is to cross what is called the "valley of death."

That's "where the drug has to undergo a number of studies to prove that it's reasonably safe to give to human beings," said Gordon Bernard, M.D., associate vice chancellor for Research and director of the Vanderbilt Institute for Clinical and Translational Research.

Increasingly these studies are being outsourced to academia. However, they're costly and scientifically uninteresting, and this is where many drug candidates fall by the wayside. "Unless we can come up with a clever strategy to fund these requisite studies, I fear a lot of these opportunities will be lost," warned Marnett.

Protecting the intellectual property (IP) rights of a discovery is equally important. "If there is no IP, no matter who develops an idea … nobody will make the $300 million investment to get it to people," Niswender explained.

Vanderbilt's drug discovery program is flourishing in part because the university's attorneys and technology transfer officials have been willing to "think out of the box," to move outside of the "comfort zone" of the traditional academic setting, Conn added.

"It's … the willingness to take risks … to move into new areas in terms of IP and negotiating agreements with companies, and not allowing the complexity of legal issues that are uncharted territory for most universities to stop you," he said.

"That's what really has to continue at Vanderbilt." VM

WEB LINK
Drug discovery at Vanderbilt dates back to 1925. Visit www.mc.vanderbilt.edu/vanderbiltmedicine for a retrospective.

Cave Man

CHEMIST BRIAN BACHMANN DISCOVERS RESEARCH IS MORE FUN UNDERGROUND

WRITTEN BY **DAVID F. SALISBURY**
PHOTOGRAPH BY **JOHN RUSSELL**

Every few months, chemist Brian Bachmann sheds his white lab coat, collects his flashlight, helmet, surgical gloves and knotted rope, puts on old clothes and hiking boots and heads to a nearby cave.

Bachmann, an assistant professor of Chemistry at Vanderbilt, has combined his industrial experience in natural products drug discovery with his undergraduate hobby of caving to set up the first systematic program to search for novel drugs produced by cave-dwelling microorganisms.

To most people, caves may be dark, spooky and claustrophobic, but to Bachmann they are a treasure trove – "an untapped source of potential therapeutics," he said.

The hope is that treatments – perhaps even cures – for cancer and other ailments are lurking in caves just waiting to be discovered.

Each cave is a unique ecosystem that has existed for millions of years, Bachmann explained. During this time, microscopic cave dwellers have been engaged in a microbial arms race, competing fiercely for the limited amounts of food that are available. In the process, these microorganisms should have produced a variety of novel chemicals to attack competitors, defend themselves and communicate with each other. These are exactly the types of natural compounds that tend to make effective drugs.

Conducting research in caves is a relatively new passion for Bachmann. In 2003, when he joined the Vanderbilt chemistry department, he had no intention of starting such a program.

"Although many important drugs, like penicillin, erythromycin and taxol, come from natural sources, natural products discovery had fallen out of fashion at the major drug companies," Bachmann said. High throughput techniques were developed that could test thousands of synthetic compounds for interesting biological activity per month. That compares to the "grind and find" natural products approach that produces one or two candidate compounds in a month, starting with extracts from 10,000 organisms.

"The accountants preferred thousands of leads to one," he said. "That is one of the reasons the drug companies gradually dismantled their natural products discovery programs."

The success of the Vanderbilt Institute of Chemical Biology's Program in Drug Discovery – established by Jeff Conn, Ph.D., and Craig Lindsley, Ph.D., who came to Vanderbilt from the drug company Merck & Co., Inc. – convinced Bachmann that what had previously been industrial paradigms could be applied with great success within academia. As a result, there was a real opportunity for a university program in natural products drug discovery to succeed.

To be successful, such a program also needed a way to distinguish itself, Bachmann realized. One way to stand out in natural products discovery is to have a unique biological

Opposite page: Assistant Professor of Chemistry Brian Bachmann collects sediment inside Snail Shell Cave near Murfreesboro, Tenn.

Below: Bachmann in the lab.

source to explore. That led him to think about cave organisms. Although a few drugs have been developed from cave organisms, their origins were accidental, Bachmann determined. No one had ever searched underworld microbes for this purpose.

"When I was an undergraduate at Virginia Tech, I joined the VPI Cave Club and went caving almost every weekend," he said. "I guess you could say it was an obsession."

Bachmann dropped his caving hobby when he went to graduate school. After his postdoctoral fellowship, he took a job at Ecopia BioSciences, a small company in Quebec that specializes in developing drugs based on natural products. Bachmann eventually began looking for an academic position that would allow him to pursue scientific ideas which required longer lead times than allowed by the industry's emphasis on quarterly results. That led him to Vanderbilt.

"It turns out that Vanderbilt is the perfect place for a drugs-from-caves program," Bachmann said. "There are more than 9,000 caves in the state of Tennessee alone."

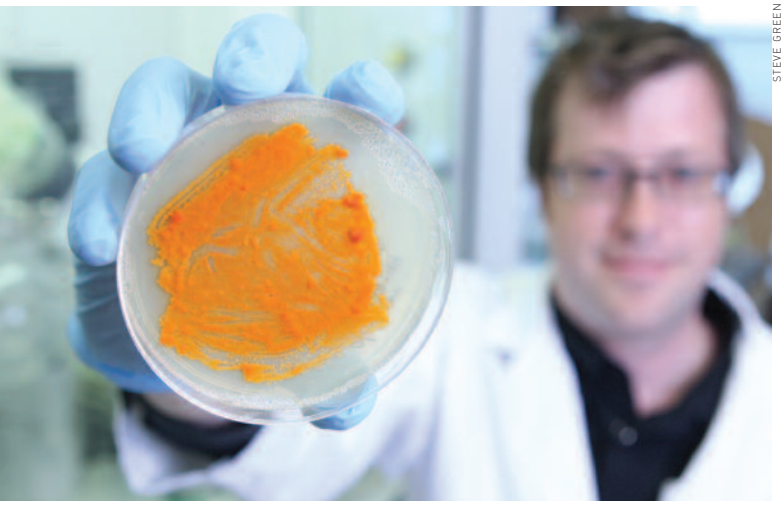
Bachmann assembled his team for their first cave collection expedition in 2007. It proved to be everything he had hoped.

"It's fascinating science with a touch of 'Journey to the Center of the Earth' adventure," he said.

"Cave walls are giant biofilms," Bachmann said. "In some places they sparkle gold and silver from a distance, but up close you find out these sparkles are gold and grayish-white single colonies or consortia of microbes. Colonies like this are something you don't usually see outside of a Petri dish in the lab."

The scientists only need small amounts of cave sediment to isolate organisms capable of producing new drugs. Once they have isolated microbes of interest, they can grow them in the laboratory.

The temperature in Tennessee caves is a uniform 57 degrees Fahrenheit. That is the same as the recommended temperature for storing wine. So Bachmann and his colleagues got a cheap wine cooler from Target to store and grow their cave organisms.



STEVE GREEN

At times the researchers leave specially designed "bacteria traps" – hockey puck-shaped silicon wafers with hollow centers filled with nutrient agar and covered top and bottom by thin membranes – and pick them up in a month or two.

"The kind of bacteria we are interested in have the capability to cut through the membrane and take up residence in the chamber," Bachmann said. When they get the samples back to Bachmann's laboratory on the Vanderbilt campus, they purify the microbes and take DNA fingerprints to determine if they are distinct from known bacteria.

They then grow the isolated microbes in large-scale fermentations and use various chemical extraction methods to pull out potential drug-like compounds from the fermentation broths. The complex extracts are then separated into their components and run through high-throughput drug screening tests that look for individual compounds with interesting drug activity.

The process of separation and identification of biological activity is automated by equipment and software specially developed by Bachmann and his collaborators. Compounds that show anti-microbial, anti-fungal, anti-cancer or other potentially useful activities are stored in the Vanderbilt High Throughput Screening Center's compound storage system, where they can be tested by any researcher at the university.

So far, out of 21 interesting compounds, the scientists have isolated 13 that are totally new.

"That is a remarkably good ratio. Normally, this ratio is about 5 percent, not 50 percent," Bachmann said. "It's actually hard to find something that isn't new."

Even finding known compounds can be valuable. Normally, these known compounds are not publicly available and have been assayed for only one type of bioactivity. Bachmann's group can produce enough of the compound so that it can be screened for a number of different biological activities on campus.

When a new compound is discovered, an extra step is required: The chemists must determine its structure. Using nuclear magnetic resonance equipment at Vanderbilt, data is collected, processed and analyzed to determine the three-dimensional structure of the unknown molecule, a process that Bachmann likens to solving a 3-D crossword puzzle using mostly only four letters – C, H, O and N, standing for carbon, hydrogen, oxygen and nitrogen.

Bachmann's ultimate dream is not only to discover important new drugs, but also to lift the natural products discovery process out of the "grind and find" paradigm and make it competitive with the combinatorial chemical synthesis method that displaced it. **VM**

WEB LINK
To view a video of Bachmann's underground efforts, please visit www.mc.vanderbilt.edu/vanderbiltmedicine

Prison of BONE

A scientist and his zebrafish offer the best hope for a cure for a rare and disabling bone disease.

WRITTEN BY **NANCY HUMPHREY**
ILLUSTRATION BY **DIANA DUREN**

Greek mythology is rich with stories of gods and goddesses who suddenly and tragically turn to stone.

But for fewer than 3,000 people in the world, this mythological metamorphosis to stone is no Greek legend. A rare and disabling disorder, fibrodysplasia ossificans progressiva (FOP), happens episodically throughout life, replacing soft tissue like muscle and ligament with bone and, at its worst, turning bodies into living statues.

People with FOP basically form a second skeleton over existing bone that permanently locks parts of the body in place. About one in 2 million people are affected by the congenital disease that can remain dormant in the body until triggered by an injury or bumping or bruising of the body. Many patients with the disease have shortened lifespan when the growth of additional bone restricts breathing. Steroids help in some patients, but only minimally. Any attempt to remove the extra bone leads to the explosive growth of even more bone, only making the condition worse.

Hope for a treatment for the disabling disease rests squarely in the hands of a handful of physician scientists including Vanderbilt's Charles Hong, M.D., Ph.D., an assistant professor of Medicine, Pharmacology and Cell and Developmental Biology, whose drug discovery research has uncovered a compound that could prevent the progression of this disabling disease.

"You wouldn't wish FOP upon your worst enemy. It's a horrible disease," said the Harvard and MIT-educated Hong who had never heard of FOP until 2006.

DANIEL DUBOIS

SCIENTIFIC SYNERGY

Sharon Kantanie of Brentwood, 41, was diagnosed with FOP when she was 6. Over the past 35 years most of her joints have been fused, but she is hopeful that new findings, including those from Hong, can help stop the progression in FOP patients, specifically in children who are just beginning their battle with the condition.

Although her Nashville home and Hong's Preston Research Building lab are separated by only 12 miles, Hong and Kantanie first met in 2007. Her FOP physician, orthopaedic surgeon Fred Kaplan, M.D., of the University of Pennsylvania, one of the world's leading authorities on the condition, put her in touch with Hong, shortly after he learned of the Vanderbilt physician scientist's promising research.

The close-knit community of FOP patients and their families has long been included in frequent symposia about the disease and know many of the physicians and scientists working to unlock them from their prison of bone.

"This is a classic example of what academic research is all about," Hong said. "I do basic science, so it's very rare that my research has a chance to make a direct impact on somebody. This was my first experience where ordinary people wanted to visit my lab and really cared about our work. We almost see a finish line, and without raising false hope, we want to give it a full effort."

In 2006, the FOP gene was discovered by Kaplan, Eileen Shore, M.D., and their colleagues at the University of Pennsylvania, and scientists found that the exact same mutation occurred in a bone-forming protein, the bone morphogenetic protein (BMP) receptor, in every FOP patient.

"It's absolutely invariant," Kaplan said. Children of an FOP parent have a 50 percent chance of inheriting the disorder, but it can't be accurately detected during pregnancy screenings.

That same year, Hong and his colleagues at Harvard Medical School discovered a compound they named dorsomorphin that could inhibit all BMP receptors. Betting that chemicals that control signaling pathways in early development might also be useful as drugs to treat human diseases, Hong exposed zebrafish, a tiny freshwater fish used in drug discovery research, to thousands of different compounds and evaluated the embryos for changes in their body development.

They identified dorsomorphin, which made the embryo's back-side (dorsal) structures more prominent, and also mimicked genetic changes to the BMP signaling pathway. Hong and his colleagues reasoned that the compound might act as an inhibitor of BMP signaling.

"We kind of stumbled into it, and through our discovery have made some really good friends who have treated FOP patients for years," Hong said. "I'm new to this field, but our friends at the University of Pennsylvania have dedicated their entire careers trying to find the cause and a cure."

Over the past 35 years most of her joints have been fused, but she is hopeful that new findings, including those from Hong, can help stop the progression in FOP patients, specifically in children who are just beginning their battle with the condition.

WORKING TOWARD A CURE

Hong's lab houses tanks of zebrafish, originally from the Ganges River in India. Zebrafish embryos are useful in understanding how all vertebrates, including people, develop from the moment that sperm fertilizes an egg. The eggs are clear and develop outside of the mother's body allowing scientists to watch them grow into newly formed fish under a microscope.

A cardiologist with the Vanderbilt Heart and Vascular Institute, Hong studies chemicals that control how different parts of the body form at the precisely specified locations. When he found that dorsomporphin was an inhibitor of the gene involved in FOP, his research suddenly went in a very different direction.

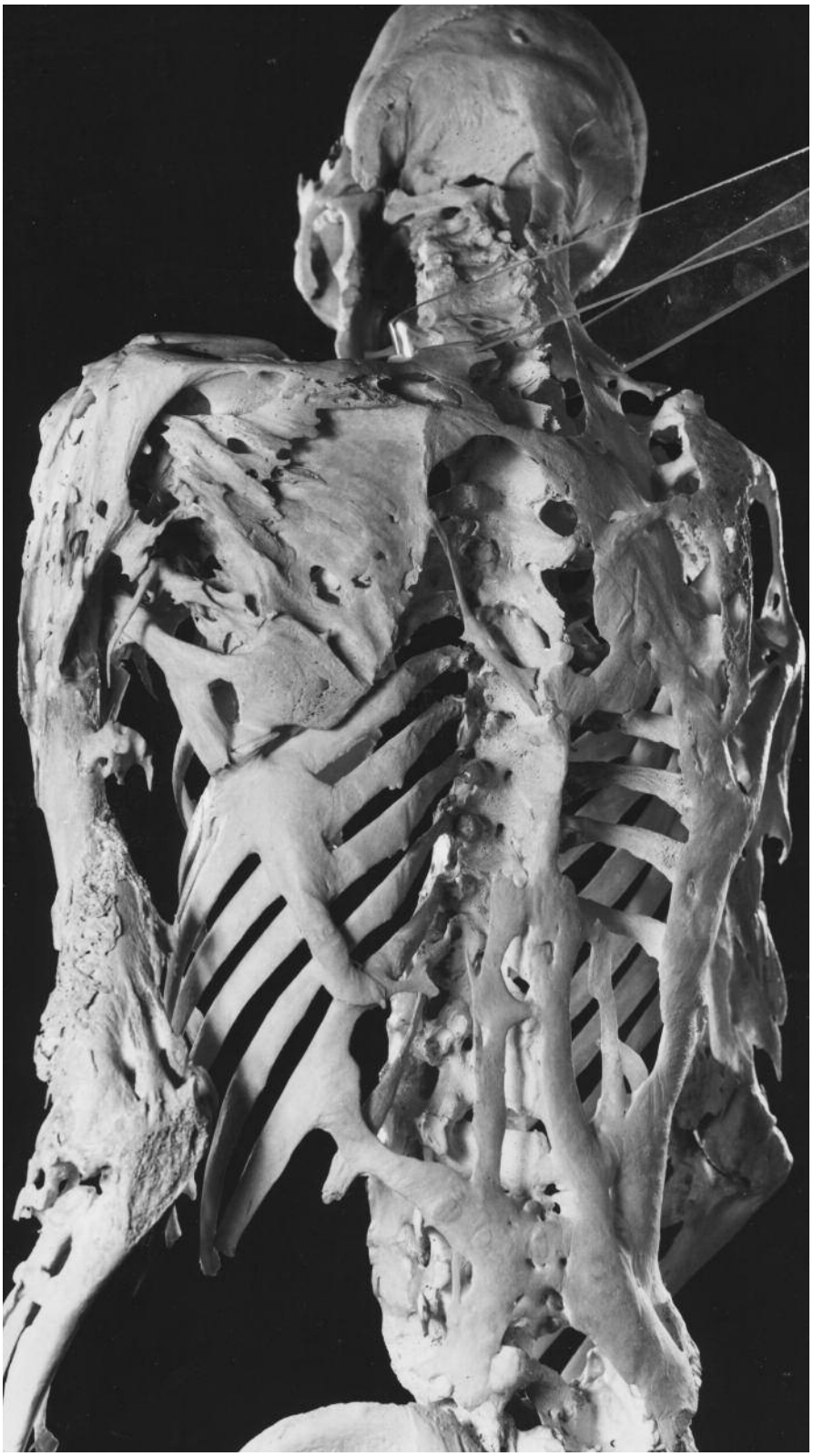
"We could wait for drug companies to do it, but they aren't going to spend a hundred million dollars on a disease that affects fewer than 3,000 people. It's not cost effective for them. But that's one of the great things about Vanderbilt. We have resources that other universities simply don't. We can take full advantage of the drug discovery expertise of the Vanderbilt Institute of Chemical Biology, and make improved versions of dorsomorphin and test them on mice, with the ultimate hope of delivering these in the first trials for people with this disease in the next few years."

Kaplan, who saw his first FOP patient in the 1980s, a decade after he entered practice, calls the condition "devastating" and is watching Hong's research with interest.

"Nobody else is working on it. Nobody. And it's the worst orthopaedic condition I have ever encountered," said Kaplan, the Isaac & Rose Nassau Professor of Orthopaedic Molecular Medicine and Chief of the Division of Molecular Orthopaedic Medicine at the University of Pennsylvania School of Medicine. "Not everybody needs to be working on this, but someone does."

Kaplan said that Hong's research also holds promises for other conditions of heterotopic (extra) bone formation – for those with hip replacements, soldiers in Iraq injured by IEDs. "The 70 percent who survived have severe limb injuries and limited rehabilitation. Dr. Hong's discovery

Vanderbilt University alumna Sharon Kantanie (B.A. '91, M.A.T. '93) was diagnosed with FOP when she was 6 years old.



A skeleton of a man with fibrodysplasia ossificans progressiva, which forms a second skeleton over existing bone. (Courtesy New England Journal of Medicine.)

very likely could have some utility for those people as well. The pathways are the same."

Kaplan said the pediatric patients with the condition are particularly close to his heart. "The difference between seeing an adult and a child with this condition is like going to the World Trade Center site now versus Sept. 11 (2001). You see the hole in the ground now, and yes, it's terrible, but you're seeing the process after it's complete. With children, you're seeing the planes fly into the buildings. The catastrophe is happening right in front of your eyes."

AN UNPREDICTABLE PROGRESSION

Kantanie realizes that a treatment to stop the progression of FOP will be of little help to her since so many of her joints are locked into place, and any attempt to remove the extra bone simply triggers the growth of more bone.

"I think FOP research holds the most promise for children with FOP and their parents who hopefully won't have to watch their children suffer the way my parents did," Kantanie said.

Children with FOP appear normal at birth except for one telltale sign – their big toes are smaller than normal and turned inward. During the first or second decade of life, painful swelling that some physicians have mistaken for tumors, appear on the neck, back and shoulders, and turn into bone. The disease progression is unpredictable. In some, episodes, called flare-ups, occur frequently and close together. A joint can be frozen into place overnight. In others, it's a gradual process.

Although Kantanie's big toes were curved inward, her condition wasn't diagnosed until she was 6 and woke up one morning with a bruised and swollen back.

A SERENDIPITOUS DETOUR

In the world of academic medicine you ever know what doors may be opened by a discussion between great minds.

In 2007, Fred Kaplan, M.D., an orthopaedic surgeon at the University of Pennsylvania School of Medicine and one of the world's leading authorities on fibrodysplasia ossificans progressive (FOP), received a phone call from Greg Mundy, M.D., John A. Oates professor of Translational Medicine who directed the Vanderbilt Center for Bone Biology. Mundy died last year.

"He (Mundy) said 'I just heard a brilliant young scientist lecture about a compound he discovered. I think he has something that can be useful to you," Kaplan said. And just like that, a trans-institutional collaboration was established.

Kaplan invited the Vanderbilt scientist, Charles Hong, M.D., Ph.D., to Penn for a lecture and the two have been collaborating on possible treatments for patients with FOP since.

"Chaz is an extraordinary and visionary scientist," Kaplan said. "He's creative, imaginative and intellectual, but he also has humility and passion. His singular discovery (a compound that could stop the progression of FOP) is one of the best hopes for the FOP community."

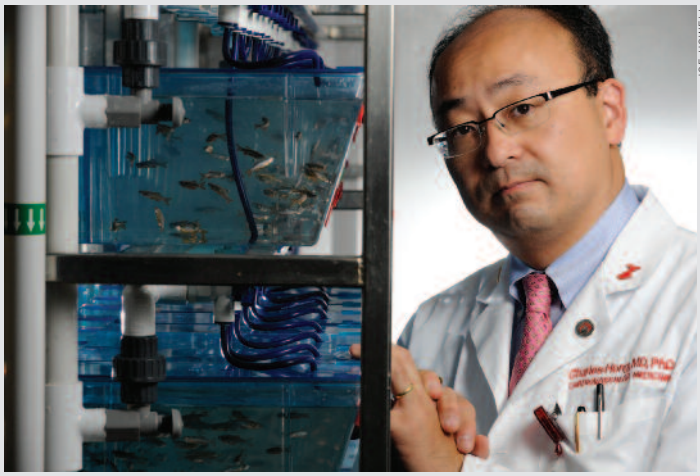
Hong said that when an opportunity presents itself, especially one that could save a life, it's hard to ignore. "It's serendipity. I'm not kidding when I say I'm doing basic research so I can help people, but when there's an opportunity to help people directly, it's very gratifying and puts a little bit of urgency in what I do."

The Penn FOP team has been mentoring Hong, encouraging him to continue his research, he said. They have even provided monetary support for Hong's lab. "I'm really grateful for our colleagues at Penn. A lot of the money they raise is from bake sales and fundraising by FOP families. We take our responsibility very seriously."

Hong and Kaplan attended a meeting of FOP patients, their families and physicians and scientists in Orlando in 2007.

"We participated in clinics all week long," Kaplan said. "Chaz sat there beside me, seeing every patient with me. He was interested in learning about the disease. You could see the wheels spinning in his mind. He's an extremely humble and compassionate man and epitomizes what a clinician/scientist is all about." VM

– NANCY HUMPHREY



JOE HOWELL

Charles Hong, M.D., Ph.D., shown here with his tanks of zebrafish.

She was taken to a doctor in Chattanooga, where the family lived, and a biopsy of tissue was taken from under her arm. Her shoulders, neck and back fused into place after the biopsy.

"The diagnosis came fairly quickly, but my parents were told I'd be dead in a matter of a few years," she said. Her parents searched for other opinions, and ended up at the Mayo Clinic. "The prognosis was much rosier there," she said. Survival would be possible, but her parents were also told that her life would be full of unpredictable flare-ups.

After the initial fusing of her shoulder, her childhood was fairly free of flare-ups, until she turned 9 and her jaw fused after an injection of Novocain at the dentist's office, followed by hip and knee problems in adolescence and restrictions in elbow movement in her late 20s.

Kaplan said FOP strikes both genders and all races equally. He knows of patients on every continent except Antarctica.

The way the disease progresses is particularly unfair to those who have it, he said. "Around the early teens, early 20s, right when a young person is ready to be independent, the hips usually become involved and walking becomes limited. Some people are actually stuck in a standing position. Life as we look at it becomes miserable."

Despite the condition, Kaplan says most of his patients have a positive attitude about their lives. "It's not the life they wanted, or had planned for, but they all have amazing outlooks. They seem to get over flare-ups and find meaning in life."

Kantanie has used a wheelchair full-time since 2007, and is one of those who sees the glass half full. "When I was a child we didn't know a lot about FOP. There's still a lot we don't know, but there's a lot we do know. I try to tell parents of children with FOP that you don't really know what life holds in store for your child, but there are people working on finding treatments, like Dr. Hong, so you have to hope for the best."

Kaplan says that Hong's research holds the "best hope."

"If we can effectively and selectively block this pathway, we might turn FOP from a catastrophic condition into something that's only a minor inconvenience." VM

WRITTEN BY **PAUL GOVERN**
ILLUSTRATION BY **DAVE CUTLER**

When Edward Jenner developed the smallpox vaccine and invented vaccination late in the 18th century, he had no way of understanding the underlying biological mechanisms. It was more a matter of, how about we give you a little cowpox and see if that makes you resistant to the much more virulent smallpox.

Even today, vaccine development tends to be more experimental, less rational than other drug development.

"You don't have to understand much at the beginning. An interesting little secret in the vaccine world is that for a vast majority of vaccines we don't really know exactly how they work. We don't need to know. We only know that they somehow mimic mechanisms of protection that work normally," said James Crowe Jr., M.D., director of the newly launched Vanderbilt Vaccine Center.

Vaccines deliver medical intelligence into the body, instructing the immune system about how to recognize and prepare defenses against attempted colonization by enemy invaders, usually a virus or bacterium. Typical vaccines introduce a weakened form of a pathogen or an inactivated partial pathogen, easy targets designed in most cases to spur production of protective blood proteins called antibodies.

The immune system remembers the target as alien and if actual infection should later occur, the patient is prepared with both an early warning system and a ready means of defense.

Antibodies may break up or otherwise inactivate pathogens themselves or they may simply tag pathogens for destruction by other components of the immune system. Strictly speaking, antibodies attack antigens, that is, some unique feature — a protein, a sugar, a lipid — that conveniently marks out a microbe as alien.

BOOSTER SHOT

Vanderbilt receives $20 million to develop new vaccines for rotavirus, RSV and more.

"I think I'm into antibodies the way some collectors are into orchids," said Crowe, professor of Pediatrics, Cancer Research, and Microbiology and Immunology.

Unlike most proteins, antibodies are made not from single genes but from three or four genes working in concert, genes that have the rare distinction of being permitted to mutate rapidly, allowing huge diversity of gene products. A single antigen usually meets with hundreds of different single-purpose antibodies.

"You could invent a wholly new substance and the immune system would make antibodies for it," Crowe said.

Vaccine development begins by questioning what works naturally, what protects an animal or human from disease. It's about mimicry.

"That's really the theme in all vaccine development: what part of the immune system protects, and then how do you mimic the way an infection induces that? If you delete part of an animal's immune system and the infection is still prevented or cleared, that missing part isn't essential, but if infection proceeds, it suggests the deleted part is very important," Crowe said. "Then we can go in depth, trying to figure out, for example, which antibody is protecting. And with those antibodies in our hand in the lab we can ask how they work. That's when the intellectual fun part occurs — we know they work, but how do they work?"

Sometime there's no immunity to emulate. "Things like HIV stump us because there is no effective immunity after natural infection to mimic," Crowe said.

Creating New Vaccines

With more than $20 million of currently committed research funding, Crowe's new center brings together all vaccine-related activity and signals a new emphasis on creating new vaccines at Vanderbilt University Medical Center. The center has an important institutional partner in Buenos Aires, the INFANT Foundation, headed by Vanderbilt faculty member Fernando Polack, M.D. Researchers at the center are studying the diarrhea-causing rotavirus and viruses that cause dengue fever, and they've also begun dreaming of a universal, one-time vaccine for influenza.

Crowe is well along in developing a new vaccine for respiratory syncytial virus (RSV), an endemic early childhood infection that figures as the leading single cause of pediatric hospitalization, sending 2 percent to 3 percent of children to the hospital at least once with bronchiolitis.

A surface protein called the F protein is the crucial antigen in RSV. Crowe and colleagues have taken the gene that encodes this protein and inserted it in the Venezuelan equine encephalitis virus, or rather in a version of the virus that's been stripped of a number of its genes (by colleagues at the University of

North Carolina), rendering it harmless but leaving intact its ability to move from cell to cell. The harmless zombified virus provides transport for the RSV antigen, and all indications are that this will induce resistance to human RSV.

Crowe hopes to begin human testing within a year, but it can take 25 years to complete a new vaccine. Once you have a new vaccine that works in animals, you purify the substance and pay around $1 million to any one of a number of outfits that are in the business of checking new vaccines thoroughly for germs, toxins and cancer-causing activity. Then come multiple phases of mandated human testing: an initial placebo-controlled safety test in a score of healthy adults, followed by a safety and efficacy test in about 500 people (more precise dosages get set at this stage), followed by a more definitive efficacy test in 50,000 to 70,000 people. Provided you're dealing with a reasonably common infectious disease, with a test group this large you learn quickly how well a vaccine works. After licensing and implementation, regulators may ask the drug maker to follow reports of adverse events, amounting to an extra stage of safety testing. Meanwhile, the Centers for Disease Control and Prevention (CDC) routinely gathers and analyzes vaccine adverse event reports and supports vaccine safety research.

Microbiologists and immunologists want to know fundamentally how things work, and tend to consider vaccines too applied of a discipline. Even those who do choose to develop vaccines can become "enamored with complexity and with new tools, and get bogged down in that complexity," Crowe said. "But the point is we just need to find something that works against disease. I think a lot of people have forgotten the end goal."

In it for the Right Reasons

Lack of commercial interest amounts to another damper on vaccine development. As Crowe notes, vaccines are by far the most successful, most life-saving medical interventions ever devised, providing more benefit than all the world's hospitals and all other drugs combined. But there was a period not long ago when the entire world vaccine market fetched less revenue than the stomach antacid Tagamet. "If you're a drug company, would you rather sell a one-time vaccine or something that people have to take every day? This isn't a great financial area. People don't do it for the money."

Crowe does see a funding bright spot: the Gates Foundation's emphasis on the developing world is encouraging vaccine development for diseases like TB, malaria and HIV. Meanwhile, people in the rich world have become "weird about the cost of vaccine. These vaccines are cheap, typically $50 to $80 for life-long protection, yet people balk. It's patently ridiculous. If a vaccine prevents me from being in an iron lung or dying, and it's $50, who wouldn't use it?"

In the clinic, once risks and benefits are explained, "most people are reasonable about vaccines," Crowe said, "but there's been increasing public visibility of the anti-vaccine movement. I have run into a number of people who are just fundamentally against vaccines without a rational reason for this position. I've personally not been effective in talking to them."

After a 1998 paper in *The Lancet* suggested a link between the MMR vaccine and autism, pediatricians in England and elsewhere saw refusal of the vaccine shoot up. The media picked up the story and the resulting controversy left many doctors around the world unsure about the safety of the vaccine. A lot of ink has been spilled over this controversy. MMR coverage in England fell from 92 percent in 1995–1996 to 80 percent in 2003–2004. Fortunately, since 2005, vaccination rates have been recovering in that country. No link between the MMR vaccine and autism has turned up in the numerous studies touched off by the *Lancet* paper. It eventually came out that the original paper's lead author, gastroenterologist Andrew Wakefield, was at the time developing a competitor vaccine. *The Lancet* published a partial retraction in 2004, followed by a complete retraction in February 2010.

James Crowe's passion is deeply rooted in his experiences on medical missions in Africa, where he saw firsthand the devastation infectious diseases can cause.

SUSAN URMY

SUSAN URMY

Kathryn Edwards, M.D., stresses the need to improve communication to establish trust in vaccines.

Building Trust

Among parents who refuse vaccine for their children, vaccine safety concerns tend to be matched with comparatively low concern about the dangers of vaccine-preventable illness. So say the authors of a May 9, 2009, article in the *New England Journal of Medicine,* "Vaccine refusal, mandatory immunization, and the risks of vaccine-preventable diseases." Some statistics from the article: in the U.S. between 1991 and 2004, the mean state-level rate of nonmedical exemptions for vaccination increased from 0.98 to 1.48 percent; based on nationwide surveillance (1985 through 1992), children with exemptions were 35 times as likely to contract measles as nonexempt children; non-medical exemption rates are often geographically clustered, and in one state (Michigan) the odds ratio for the likelihood that a census tract included in a pertussis cluster would also be included in an exemptions cluster was 2.7.

"Vaccines are one of our most important medical advances. Prevention is much preferable to treatment of infectious diseases. But if the public fails to be immunized the diseases of the past can come back again," said Kathryn Edwards, M.D., professor of Pediatrics and a principal investigator with the Vanderbilt Vaccine Research Program (VVRP). The VVRP evaluates new vaccines, mounts safety studies of recommended vaccines and serves as one of six sites in the Center for Immunization Safety Assessment Network, funded by the CDC to assess reports of suspected adverse patient reactions to vaccine. (Providers can call the VVRP at (615) 322-8792 to submit reports.)

"In trying to inform the public regarding the vaccine safety debate, it's important that we not simply hold to the line that vaccines never cause adverse events, because sometimes they do," Edwards said. "We need to improve our methods of communication with parents. We need to arm them with the facts about vaccine. We need to tell them what reactions can be seen with vaccines and how we might reduce them. We need to train young investigators who are interested in assessing and communicating the safety of vaccine."

Elizabeth Williams, M.D., one of the young investigators working with Edwards, is designing materials that pediatricians can use to aid discussion of vaccine safety with parents.

"One of the real challenges of vaccines is trust in them, the safety aspect," Edwards said. "No matter how exciting and scientific and sexy a new vaccine is, if people are afraid of it, no one is going to get it."

It was in association with compulsory vaccination that the term "conscientious objector" first entered the law (in late 19th century England). Today the Amish and some other communities in Tennessee choose not to immunize. Pediatricians at Vanderbilt periodically see a child with meningitis "who gets brain damaged because he didn't get the vaccine," Crowe said.

"It only takes a small community for bad things to happen. If a high school falls below 95 percent immunity to measles, at some point there will be a measles case. These germs find unvaccinated people." **VM**

Vanderbilt and vaccines

Vanderbilt has earned a spot in the recent history of vaccine achievements with its contributions:

1940s VUMC's Ernest Goodpasture, M.D., develops the method of culturing vaccines in chick embryos.

1953 VUH opens Ward 3320 for adult and pediatric polio patients, who would receive free care.

1954 David Karzon, M.D., collaborates with Harvard researcher John Enders, M.D., to study the polio virus. Enders' team won the 1954 Nobel Prize in medicine.

1957 Randy Batson, M.D., dean of VUSM, receives some of Albert Sabin's new oral polio vaccine to test and helped show that the oral polio vaccine worked in children.

1970s The Vanderbilt Vaccine Clinic is established, founded by Peter Wright, M.D.

1972 Vanderbilt's Sarah Sell, M.D., and Wright lead the first International Conference on Haemophilus influenzae, type b (Hib).

1985-1990 Kathryn Edwards, M.D., leads a large field trial comparing the effectiveness of live and inactivated influenza vaccine in children and adults.

1988 Haemophilus influenzae type b (Hib) conjugate vaccine is licensed and recommended for all infants, thanks in part to Sell's contributions.

1991-1992 Large clinical multicenter trial comparing all new pertussis vaccines available throughout the world is coordinated at Vanderbilt by Edwards.

2005 Vanderbilt establishes a Program in Vaccine Science that is directed by James Crowe, M.D. Vanderbilt receives grants to study a new virus, metapneumovirus.

2009 Edwards and the Vanderbilt Vaccine Research Program perform clinical trials for the H1N1 vaccine.

– COMPILED BY LESLIE HILL

The accidental DRUG developer

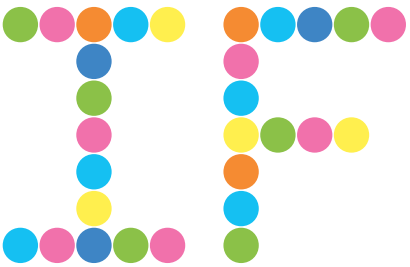
Steady research trek leads from the bench to the bedside of patients with failing hearts

Doug Sawyer wasn't looking for a new treatment for heart failure when he started his research fellowship 15 years ago. As a cardiologist, he was interested in helping patients with the condition, to be sure, but as a scientist, he was more intrigued by the biology of heart muscle cells. He wanted to understand how these cells maintain themselves for a lifetime.

"How do constantly beating cardiac myocytes (muscle cells) withstand the wear-and-tear of contraction? And how do they survive for so many years?" wonders Sawyer, M.D., Ph.D., Lisa M. Jacobson Professor of Medicine and chief of the Division of Cardiovascular Medicine at Vanderbilt University Medical Center.

Sawyer and other investigators have zeroed in on a survival factor – a protein called Glial Growth Factor 2 (GGF2) – that protects cardiac myocytes from stressors in culture and enhances heart function and survival in animal models of heart failure. Now, Sawyer and colleagues at Acorda Therapeutics are poised to test GGF2 for the first time in human patients.

WRITTEN BY **LEIGH MACMILLAN**
PHOTO ILLUSTRATION BY **ADRIANNA WILLIAMS/THE IMAGE BANK/GETTY IMAGES**



the first trials show that GGF2 is safe and well tolerated by patients, the investigators will pursue further clinical trials.

GGF2 represents a potentially new approach for treating heart failure, a chronic condition in which the heart is unable to meet the body's demands, leaving patients short of breath and unable to complete daily activities. Current medications address the symptoms of fluid build-up and aim to modify the heart's workload, but GGF2 appears to enhance the repair of damaged heart muscle.

"I never expected to be so fortunate as to be involved with something that's gone all the way from studies at the bench to the point where we're going to give it to people to see if it might help them," Sawyer says. "I feel very lucky in that regard."

Probing cardiac cell survival

As its name suggests, Glial Growth Factor 2 was first characterized for its growth-promoting actions on glia, cells that support and protect neurons in the nervous system. GGF2 is a member of a family of proteins called neuregulins, which themselves are part of an even larger family of epidermal growth factor (EGF) proteins. Vanderbilt's Stanley Cohen, Ph.D., was awarded the Nobel Prize in 1986 for his discovery of EGF.

GGF2 landed in Sawyer's hands by chance.

He was new to the research group of Ralph Kelly, M.D., and Thomas W. Smith, M.D., experts on cardiac myocyte biology, at Brigham and Women's Hospital, where he had begun to study the effects of cancer drugs called anthracyclines (such as adriamycin) on cultured cardiac myocytes. These drugs were known to cause heart failure in cancer patients, and Sawyer was testing whether they killed heart cells the same way they killed cancer cells. He was also examining factors that might improve cell survival.

Mark Marchionni, Ph.D., at a company called Cambridge Neurosciences, had approached Kelly about looking at the effects of GGF2 on cardiac myocytes. Marchionni had cloned the gene for GGF2 and coined the term "neuregulin."

"The GGF2 project was an orphan in the lab, and Ralph Kelly said to me, 'why don't you study GGF2 in the myocytes while you're doing your other experiments,'" Sawyer recalls.

He included GGF2 in a panel of factors he was testing, and he found that GGF2 regulated myocyte survival – with GGF2 around, the cells lived longer, even after stressors like anthracyclines.

"That result made GGF2 much more interesting to me," Sawyer chuckles.

GGF2 had been studied in other cell types and was known to work through the EGF family of erbB receptors. Sawyer used those previous reports as a starting point for his own examination of the receptors and signaling pathways activated by GGF2 in cardiac myocytes.

Findings were also emerging from other groups that neuregulins played critical roles in the developing heart. Mice missing neuregulin-1 (GGF2 is a version of this neuregulin) or its receptors erbB2 or erbB4 died *in utero* because of failures in heart development.

Sawyer and Kelly speculated that if GGF2 improved cell survival in the setting of heart failure, it might be a good therapy for the condition. So Cambridge Neurosciences patented GGF2 and other neuregulins as potential treatments for heart failure. Sawyer is an inventor on the patent, but he didn't intend to continue his neuregulin research. Instead, after finishing his fellowship, he took a faculty position at Boston University and continued his studies of anthracycline toxicity, oxidant stress, and cardiac cell survival.

"I just went about my business," he says. "I didn't know what was going to happen with the neuregulins, but I figured I was better off pursuing my interest in cardiac myocyte biology and leaving the drug development to the company."

Then chance intervened again. A new cancer drug – Herceptin – was introduced, and it caused heart failure in patients with breast cancer, particularly those who were also taking anthracyclines.

Clues from the clinic

Herceptin was developed to block erbB2 receptors, which are activated by epidermal growth factor family members, including neuregulins. Breast cancers with increased levels of erbB2 receptors – also called HER2/neu receptors – are more aggressive and have a worse prognosis compared to breast cancers that do not overexpress erbB2.

"Herceptin's cardiac effects demonstrated in humans that this neuregulin signaling system matters in the heart – if you interrupt it, it's bad news," Sawyer says.

Genentech, the manufacturer of Herceptin, invited Sawyer and others to submit grants to study the roles of neuregulins, anthracyclines and Herceptin in cardiac biology.

"I never expected to be so fortunate as to be involved with something that's gone all the way from studies at the bench to the point where we're going to give it to people to see if it might help them."

– Doug Sawyer M.D., Ph.D.

JOE HOWELL

Doug Sawyer, M.D., Ph.D., first began studying GGF2 nearly 15 years ago. A successful collaboration between industry and academia has resulted in making it a possible new treatment for heart failure.

Sawyer was awarded a Genentech grant.

"I basically dove back into neuregulin biology," Sawyer says. "And we stayed focused on the biology, rather than the therapeutic development."

Sawyer's team learned which heart cells express neuregulins, and which neuregulin form is most potent in regulating cell survival. They discovered how neuregulins modulate cell metabolism and cell growth. And they explored how the body controls neuregulin expression and activity – and how that might go awry in heart failure.

Other groups found that erbB receptor expression drops in animal models of heart failure and in human tissues from patients with heart failure, further implicating the signaling system in the condition.

During this time, Acorda Therapeutics, a neurosciences-focused company, bought the neuregulin technologies from Cambridge Neurosciences/Cenes and pursued development of GGF2 for a range of neurologic and cardiac conditions, including stroke and heart failure.

In 2006, data supporting the therapeutic potential of neuregulins in heart failure "reached a tipping point," Sawyer says.

Researchers at Zensun, a company in China, reported that a version of neuregulin-1 (different from GGF2) improved cardiac function and survival in animal models of heart failure caused by ischemic injury (like a heart attack), cancer drugs and viruses.

"I was happy – and surprised – to see those results," Sawyer says. "I honestly never believed neuregulin was going to go anywhere therapeutically because in cancer it could promote growth."

Therapeutic development was never his mission, he says, rather, he was interested in maintaining a grant-funded basic science lab and in training new investigators to study cardiac myocyte biology.

But another chance occurrence – a new grant mechanism – brought Sawyer into the drug development arena.

Back to the bedside

Just after the Zensun findings were reported, the National Heart, Lung and

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The road from research to remedy

Bringing a new drug to market is an increasingly daunting – and expensive – task.

Today it costs more than $1 billion and takes more than seven years, on average, to complete the human studies required for a drug to be approved for marketing.

Only about one in five drugs makes it through the clinical trial pipeline. And that's not counting the thousands of promising compounds that are eliminated before they get to human testing.

In the first stage of drug discovery, called "preclinical development," pharmaceutical companies and, increasingly, their university partners, screen thousands of compounds for an effect, for example, on a receptor in the brain that may be involved in depression.

The yield is tiny: only a few hundred will show sufficient activity to proceed with laboratory and animal testing. Of these, only a handful will meet the criteria for studies in humans.

They must be absorbed by the body and reach their target tissue at a just-enough concentration to do the job. Then they must be effectively eliminated from the body so they don't reach toxic levels.

More than four years of work may be required to get through the preclinical stage. Then it's on to human testing, which is conducted in three "phases."

In Phase I, the compounds are tested for safety in up to 100 healthy volunteers. Phase II involves further safety and efficacy testing in 100 to 500 patient volunteers who have the condition the compounds are meant to treat. In Phase III, the potential drugs are tested in thousands of patient volunteers to confirm effectiveness, determine appropriate dosage and detect adverse reactions.

While the average time to complete clinical trials has declined in recent years, drug safety regulations have only gotten stricter.

– BILL SNYDER

Sources:
"Spending on New Drug Development" by Christopher Paul Adams and Van Vu Brantner, published online in Health Economics on Feb. 26, 2009, http://onlinelibrary.wiley.com/doi/10.1002/hec.1454/abstract

"Outlook2010," Tufts Center for the Study of Drug Development, 2010, http://csdd.tufts.edu/_documents/www/Outlook2010.pdf

Blood Institute introduced the Cardiac Translational Research Implementation Program (C-TRIP) to advance research on promising new therapeutics for heart failure and arrhythmias.

Vanderbilt and Acorda received a C-TRIP grant in 2010, which is supporting additional studies of GGF2 in animal models of heart failure and a Phase I clinical trial to assess the safety of GGF2 in human patients with heart failure. Acorda is sponsoring another Phase I trial of GGF2 at Vanderbilt.

"C-TRIP has been a great mechanism for pulling academic and industrial groups together," says Anthony Caggiano, M.D., Ph.D., vice president of Preclinical Development at Acorda and a co-principal investigator with Sawyer on the C-TRIP grant.

"Our collaboration over the years, and now with this grant, has been ideal in that our strengths are complementary and only somewhat overlapping. Acorda has strength in drug development science, while Dr. Sawyer and his colleagues have basic science and cardiology expertise."

The Phase I trials of GGF2, being led by Daniel Lenihan, M.D., professor of Medicine, and Carrie Geisberg, M.D., assistant professor of Medicine, are designed to study GGF2 safety and dosing. The investigators also will be looking at measures of heart function – using blood biomarkers and non-invasive imaging including echocardiography – to gather information that would support further clinical testing.

"We're really excited about these trials," Lenihan says. "We have a lot of room for improvement in treating heart failure," which he notes is the most common reason for hospital admission in the United States.

"We think that GGF2 is going to enhance the repair of damaged heart muscle, no matter what has caused the damage," Lenihan says. "That's really a whole line of therapy for heart failure that we haven't investigated. There are no therapies that do that right now."

"I think it's a good experiment. It's worthwhile to test GGF2 in people," Sawyer says. "We know that the chances of success for any experimental therapeutic are small, but we're hopeful that GGF2 will help patients with heart failure."

Chance, after all, seems to be on Sawyer's side. VM

A Picture Worth 1,000 Words

WRITTEN BY **LESLIE HILL**
PHOTOGRAPH BY **JOE HOWELL**

Jon Schoenecker, M.D., Ph.D.

Caitlin Lovejoy had Angelman Syndrome, a genetic condition that causes developmental delays and typically results in a happy demeanor with frequent laughing and smiling. It's the way her family will always remember her.

Her oldest sister, Sarah Huckabay, said that although Caitlin couldn't speak or walk without assistance, she never missed out on family activities.

"Growing up, my sister Rachel and I knew Caity was different from others' siblings. But she was never treated any different. She rode rollercoasters, went swimming, and went on airplanes to vacations just like any other family member. She was just one of the gang – always along for the ride," said Huckabay, who is a nurse on the surgical step-down unit at Vanderbilt University Medical Center.

Caitlin also had scoliosis and came to the Monroe Carell Jr. Children's Hospital at Vanderbilt in February 2008 to have rods placed in her spine.

"After the surgery her back looked awesome, and we were joking we would have to buy her longer pants because she was so much taller," Huckabay said. "On post-op day one or two she wasn't waking up. The doctors were worried she was over-sedated, but a CT showed she had had a stroke and she just went downhill from there."

Caitlin, 22, died from complications following surgery.

The family asked that donations be made to the Children's Hospital in her memory and spent a lot of time deciding where to designate the funds.

"My parents were proactive that the donations go toward something meaningful. It is nice to see it materialize into something that can have real results, and it is nice that Cait is remembered in that way," Huckabay said.

Memorial contributions were given to Jon Schoenecker, M.D., Ph.D., a pediatric orthopaedic surgeon, to purchase the Synergy 2 plate reader for his lab. The $40,000 machine has aided his research in coagulation, which could have effects in health issues as far reaching as cancer metastasis, infection and wound healing.

Caitlin's father, Steven Lovejoy, M.D., a pediatric orthopaedic surgeon at the Children's Hospital, had mentored Schoenecker when he was a resident at Vanderbilt. When he found out Schoenecker was returning after a fellowship at Children's Hospital Boston, there was no doubt where the memorial funds would go.

"My one little exposure to research at [the University of Kentucky] was to count bacteria, and that machine would never work," Lovejoy said. "I've always remembered that, and I wanted Jon to buy something that would help him work and make his research easier."

Right above the lab bench holding the plate reader, beside pipettes and microscopes, hangs a framed portrait of the Lovejoy family – three beautiful, smiling daughters, their mother, Carolyn, and father, Steven.

Each time a researcher loads a new plate into the machine, they are reminded of the generosity that is making their work possible.

Schoenecker said having the plate reader has accelerated his work tremendously.

"Before, we had to beg, borrow and steal a plate reader to get anything done. The Lovejoys have been incredible in what their donation has allowed us to do. It is inspiring to see their picture right above the machine and really makes us feel like we have a purpose in what we are doing," he said. VM

WEB LINK
To read more about the Synergy 2 plate reader, please visit www.mc.vanderbilt.edu/vanderbiltmedicine

PRESIDENT'S LETTER

Dear Canby Robinson Society Members:

At Vanderbilt, we continue our long-standing commitment to leadership and our vision for making a transformational impact on health care. That all starts with the education and mentoring we offer to our medical students.

At a recent meeting of the Canby Robinson Society board, John Zic, M.D., walked us through an exercise on the School of Medicine admissions process, designed to deepen our understanding of the caliber of applicants we are attracting and the challenges of selecting a class of students among so many accomplished and talented candidates.

Dr. Zic is associate dean for Medical School Admissions and associate professor of Medicine in the Division of Dermatology. It was quite fitting that he would enlighten us about the admissions process since he was one of the very first CRS Scholars when he was a medical student here.

This interesting simulation exercise included small group reviews of applications, followed by a mock admissions committee discussion. The process really helped to illustrate the thoughtful—but difficult—admissions process that Vanderbilt follows. We learned about the important role of scholarships in making the dream of medical school a reality for our students. We saw firsthand that our endowed scholarship support needs to grow well beyond where it is today. The average debt load for medical students after graduation is $130,000, and we are only able to meet 22 percent of the financial need for medical student scholarships.

These are numbers that need to change. Nothing is more important than helping our students. Supporting our educational programs through philanthropy will make us great and secure our future.

As leaders of the Canby Robinson Society, we have recommitted ourselves to fully participating in the educational mission of Vanderbilt University School of Medicine, and we encourage others to join us in this effort. Unrestricted gifts to the School of Medicine at the $1,000 level and above support scholarships as do the many endowed scholarship funds created by committed supporters.

I send my thanks to everyone who helps to train our country's future leaders in health care by making a Vanderbilt medical education a reality.

You can learn more about giving to support scholarships at www.vanderbilthealth.org/givetomedicine.

Paul Sternberg Jr., M.D.
Canby Robinson Society president

REUNION GIVING SUPPORTS SCHOOL OF MEDICINE

Medical alumni in classes celebrating a reunion in 2010 gave back in a big way, collectively contributing more than $2.5 million to support the School of Medicine.

Scholarships—an ever-present need—received an extra push this year with four reunion classes launching group efforts to raise funds for scholarship support. The Class of 1989 surpassed $100,000 to create the Class of 1989 Scholarship Fund. The classes of 1975, 1979 and 1990 are well on their way to doing the same. The Class of 1961 focused its efforts on encouraging each other to make a planned gift in memory of the 13 classmates who are deceased.

"It's wonderful to see this large expression of support for the institution in which we share so much pride," Richard Johnston, M.D., MD'61, told the crowd gathered for Reunion 2010. Johnston co-chaired the reunion's giving effort with Robert Moorman, M.D., MD'60, and Cauley Hayes, M.D., MD'61.

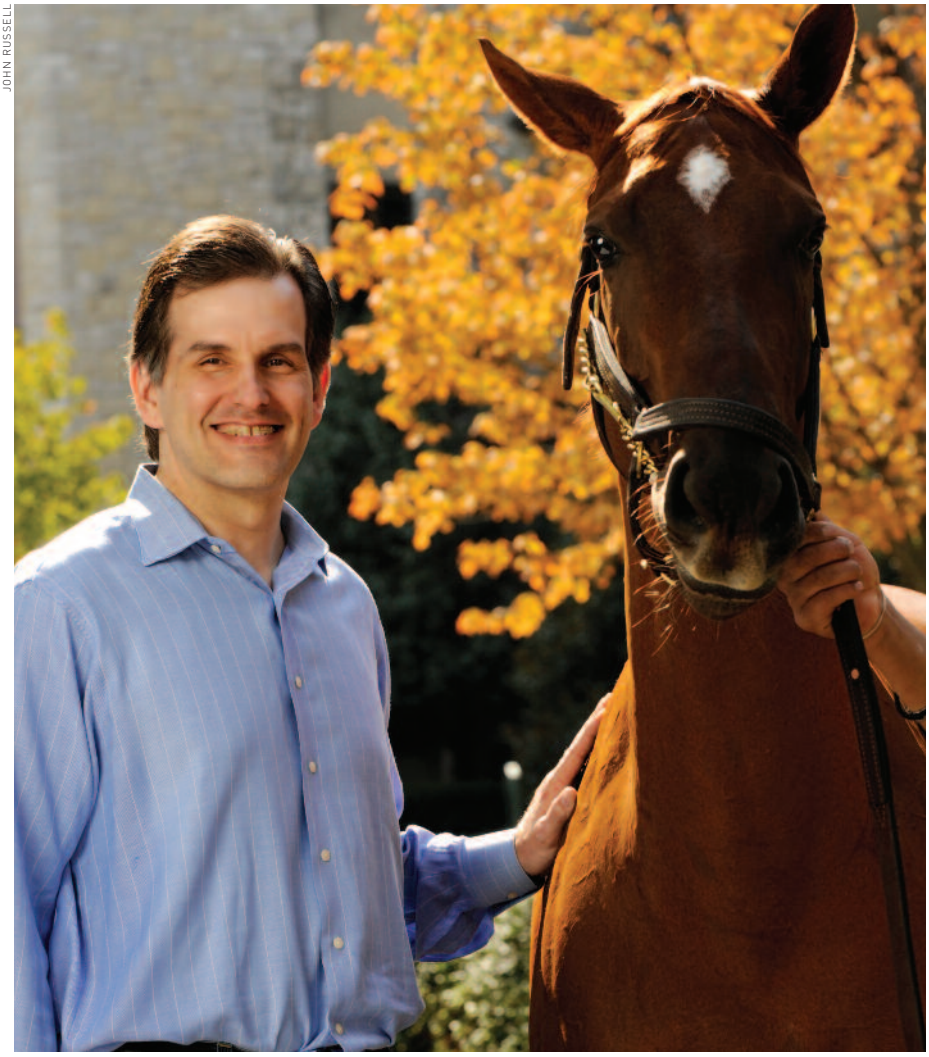
"My wife, Mary Anne, and I are sure the money will be applied to do good because of the school's leadership," he said. "Jeff Balser is one of the very smartest, most creative, and finest human beings to lead any American medical school. He's also one of the youngest. So if he'll eat right, exercise regularly, and continue to make it home to his wife and children by suppertime, we can benefit for a long time."

$2,599,028
was given by School of Medicine alumni in classes celebrating Reunion 2010 to benefit scholarships and many other programs (as of January)

39%
of alumni in School of Medicine Reunion 2010 classes gave a gift

A GIFT OF GRATITUDE

JOHN RUSSELL



John Zic, M.D., left, was honored when his patient Beth McDaniel and her husband, Roger, decided to name their racehorse after him and donate the filly's winnings to Vanderbilt.

Conventional wisdom says never to look a gift horse in the mouth, but on a typical day seeing patients in the clinic, John Zic, M.D., found himself staring down at a literal gift horse, not quite sure how to react.

His patient Beth McDaniel and her husband, Roger, had just proudly presented Zic with a manila envelope. Inside he found a glossy 8x10 photo of a racehorse striding for the finish line.

"I thought they were giving me a horse," he recalled, the shock still evident in his voice.

The McDaniels quickly explained that they were the horse's owners and had named her Dr. Zic in honor of their physician.

"I really didn't know what to say. You're always honored when a patient even brings in a case of peaches from their farm or cookies for the staff. But this is really on a different level," said Zic, associate professor of Dermatology at Vanderbilt University Medical Center and associate dean of admissions at Vanderbilt University School of Medicine.

In 2005, the McDaniels started Derby Lane Farm near Lexington, Ky., and around the same time, Beth began to have mysterious itching on her abdomen. She saw specialists around the country, but no one could find a solution.

Finally, a doctor in Lexington referred her to Zic who made the diagnosis – cutaneous lymphoma. In this relatively rare disease, cancerous cells infiltrate the skin.

"The hallmark of this disease is that you itch to death," Beth said. "My skin is often red all over and it dries and peels constantly. I feel as if I have full-body dandruff."

Later, when the McDaniels' trainer suggested they purchase a promising filly, they knew just who to name her after. Dr. Zic surprised everyone by winning her very first race, and she just kept winning.

"Dr. Zic (the horse) won quite a bit of money, and my husband wanted to get me something for my birthday. I kept saying I have everything I want, so he came up with the idea that we would give to Vanderbilt," Beth said.

Their gift was split in half between a fund for immediate use and an endowment so the funding opportunities will continue in the future. The funds support cutaneous lymphoma research, including the work of two new Dermatology faculty members, Laura McGirt, M.D., and Jeffrey Zwerner, M.D., Ph.D., who are chomping at the bit to research the disease.

"There have been great strides in diagnosing the disease earlier and some significant discoveries in new treatments, but we need more," Zic said.

"My thinking is that it probably won't help me," Beth said, "but maybe my kids might have this disease and it would help them. I don't want anybody else to go through this misery."

After her initial burst of success, Dr. Zic had to be taken out of racing for nearly a year for an ankle injury. Now she is in great shape, and won a prestigious race this spring.

The McDaniels have pledged future winnings from Dr. Zic to the cutaneous lymphoma research fund.

"Dr. Zic may never win another race in her life, but we plan on adding to the fund when she does," Beth said.

– LESLIE HILL

CYNTHIA MANLEY

Members of the newly formed Young Ambassadors group have pledged to raise funds for research at Vanderbilt-Ingram Cancer Center.

GROUP FORMS TO RAISE CANCER RESEARCH FUNDS

Nearly two dozen young professionals are harnessing their social, work and family networks to raise money for innovative cancer research at Vanderbilt-Ingram Cancer Center.

This Young Ambassadors group initially made a commitment to raise $35,000 to fund a VICC Discovery Grant, awarded to young cancer investigators who don't yet have significant government or industry support to test their scientific theories.

Over the course of the last year, the group raised more than $41,000, and Vanderbilt-Ingram's Board of Overseers secured $20,000 in additional funding for a second, smaller grant.

Members of the newly formed organization say the mission is personal. Emily Blake (EB) Jackson, chair of the philanthropic group, has watched three of her grandparents struggle with or succumb to cancer. EB's husband, Todd, and his family have had their own cancer challenges.

"Nearly everyone has a cancer story. My mother had breast cancer, my father had esophageal cancer and I had a brain tumor," said Todd Jackson.

The group decided to focus on young cancer investigators who need a financial jumpstart to make inroads in cancer research.

"These are new researchers coming in with passion and vision and they may be the ones to develop a new cure for cancer," said Kate Steinbeck.

Kate, and sister Carrie Steinbeck, joined the Young Ambassadors because of the care their father received at Vanderbilt while he was battling lung cancer.

Most members of the Young Ambassadors didn't previously know one another, but they have found common ground in their commitment to cancer research. They are using e-mail, Twitter, Facebook and other social media in addition to traditional outreach to raise funds. Beth Franklin, VICC Board of Overseers member, local philanthropist, and mother of Young Ambassador Ruth Franklin, has served as a mentor to the group.

The group awarded the first grant in the fall to Ryoma (Puck) Ohi.

Ohi has identified a potential weakness in cancer cells and if he is correct, this Achilles' heel could be a good target for chemotherapy treatments in multiple cancers.

For more information about the Young Ambassadors initiative, go to www.vicc.org/youngambassadors.

– DAGNY STUART

FIRST-YEAR CANBY ROBINSON SCHOLARS

Irene Mathieu

Scott McCall (M.D./Ph.D. program)

Kristen Ploetze

Jessica Solomon

Shannon Skinner

Catherine Meador (M.D./Ph.D. program)

For more information about the Canby Robinson Society, contact Robin Kumar, Vanderbilt University Medical Center, 2525 West End Ave., suite 450, Nashville, Tenn., 37203, (615) 343-8677, fax (615) 322-3193, e-mail: robin.kumar@vanderbilt.edu; www.mc.vanderbilt.edu/crs

IN BRIEF

THE VANDERBILT KENNEDY CENTER AWARDS FIVE 2010 HOBBS DISCOVERY GRANTS

Five 2010 Nicholas Hobbs Discovery Grants have been awarded to the following interdisciplinary teams led by Vanderbilt Kennedy Center (VKC) researchers. Nicholas Hobbs Discovery Grants, made possible by the generosity of donors, provide essential seed funding that contributes to the discovery of new knowledge to improve the lives of individuals with disabilities and their families. A gift of $1,000 to VKC also provides the benefit of CRS membership.

Time-delimited Manipulation of CaMKII Activity During Development

Roger Colbran, Ph.D., in collaboration with Louis Muglia, M.D., Ph.D., and Danny Winder, Ph.D.

Stress-induced Alterations in Serotonin 2C Receptor Editing and Behavior

Ron Emeson, Ph.D., in collaboration with Louis Muglia, M.D., Ph.D., and Melinda Arnett, Ph.D.

Air Pollution and Mortality Among Infants with Down Syndrome

Robert Hodapp, Ph.D., in collaboration with Richard Urbano, Ph.D., and Eva Pantaleoni, Ph.D.

Epilepsy and Disrupted Thalamic Physiology in Mouse Model of Angelman Syndrome

Andre Lagrange, Ph.D., in collaboration with Kevin Haas, M.D., Ph.D., and Mark Grier.

Angelman Syndrome and Rett Syndrome as Genetic Models of Autism Spectrum Disorder

Sarika Peters, Ph.D., in collaboration with Alexandra Key, Ph.D., and Rachel Hundley, Ph.D.

MARY DONALDSON

THE EYES HAVE IT

The Vanderbilt Eye Institute Advisory Board recently hosted a community tour and educational session, highlighting the low-vision clinical program at the VEI. Here, Irene Wills, left, uses a vision aid to inspect the fine-print text on a cereal box held by Dudley White.

TOMMY LAWSON

SURVIVORSHIP CLINIC TOUR

Anne Washburn, left, associate director of Patient Affairs and Community Education, leads a tour of the REACH for Survivorship Clinic with members of the board of Canby Robinson Society and guests of the Medical Center, from left: Lonnie Burnett, M.D., Ann Bumstead, Arnold Malcolm, M.D., Carol O'Hare, Ann Robinson, Fran Hardcastle and Robin Kumar.

web links

Please look for more photos online at **www.mc.vanderbilt.edu/crs**

ANN H. PRICE, M.D.
Associate Dean for Alumni Affairs,
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medalum@vanderbilt.edu
https://medschool.vanderbilt.edu/alumni

Vanderbilt Medical Alumni Reunion 2010

Many thanks to all of you who attended Reunion 2010. With 1,170 attendees, this was our largest VUSM Reunion event ever. I hope you enjoyed your time back on Vanderbilt's campus. A special thanks to all of our class chairs, class gift chairs and class party hosts for making this Reunion a truly wonderful weekend. Of note, along with our special class anniversary celebrations, this year's VUSM Reunion also featured meetings for the Amos Christie Society (Pediatrics), the Lonnie S. Burnett Society (Obstetrics and Gynecology), and the Thomas E. Brittingham Society (Medicine). If you were not able to attend Reunion 2010, please refer to the back two pages of this issue for photographs from various Reunion festivities.

VMAA Board Meeting in conjunction with Reunion 2010

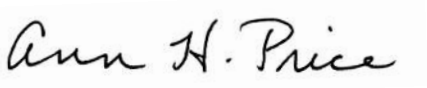
The Vanderbilt Medical Alumni Association (VMAA) welcomes our new VMAA president, David W. Patterson, M.D., MD '85. Dr. Patterson, an Internal Medicine specialist engaged in private practice in the Washington, D.C., area, has served as a Northeastern regional representative to the VMAA Board since 2004. His tenure as VMAA President extends from Reunion 2010 until Reunion 2012. The VMAA also welcomes Clifton R. Cleaveland, M.D., HS '64, FE '70, who has previously served as a Tennessee regional representative as the new president-elect. Our sincere thanks goes out to outgoing VMAA President Wyatt E. Rousseau, M.D., MD '69, from Dallas. He and his wife Carolyn have been strong supporters of the VMAA for many years, and we look to him for future leadership for our regional events in the Dallas area.

VMAA Events and Dinners

For the past two quarters, the VMAA has been actively involved with alumni, student and trainee events on and off campus. For example, in September the VMAA and regional representative, Mitchell S. Steiner, M.D., FAC, FE '93-95, hosted a dinner in Memphis, Tenn., with featured speaker, Vice Chancellor Jeff Balser, M.D., Ph.D. In November, VMAA board president, David W. Patterson, M.D., hosted another regional dinner in Washington, D.C., (in conjunction with the AAMC meeting). Other events of interest include the H. William Scott Society Dinner (in conjunction with the October American College of Surgeons annual meeting in Washington, D.C.); the September postdoctoral picnic, the launch of our VMAA 2010 Host Program, participation in a new graduate student white coat program; a July Nashville Sounds game with House Staff; a book signing event for the BRET Office's Career Symposium and our fourth annual VMAA "Halfway There" celebration for the VUSM Class of 2012.

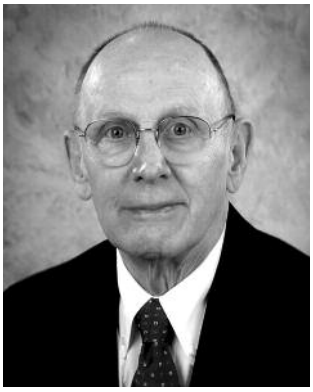
Worthy of Note News

The VMAA always welcomes your submissions for our alumni news "Worthy of Note" section in *Vanderbilt Medicine* magazine. Submit news and digital photographs to medalum@vanderbilt.edu; or fax to (615) 936-8475; or mail to VUMC, 21st Ave South and Medical Center Drive, MCN D-8212, Nashville, TN 37232-2106.



Read *Vanderbilt Medicine* online, and send in your alumni news at www.mc.vanderbilt.edu/vanderbiltmedicine. Digital photos (200-300 dpi and at least 4 by 6 inches) are always welcome and will be included as space permits.

KEY
MD - Medical School Graduate
HS - House staff
FE - Fellow
FAC - Faculty
* Indicates CRS member



***Carl Grote, M.D., MD '54, received the Samuel Buford Word Award at the Medical Association of the State of Alabama's Annual Session. The award is the highest honor given by the Medical Association and is presented in recognition of service to humanity beyond the usual scope of medical practice, with such services having been rendered at some personal sacrifice.**

50s

***Paul Barnett, M.D.,** MD '58, FAC '67-'08, and veterinary surgeon Trey Calfee collaborated to design an animal hospital that will be open 24 hours a day to care for critically ill pets. Barnett had lost two beloved pets in recent years and identified the need for such a facility. The new hospital opened on Sidco Drive in Nashville in October.

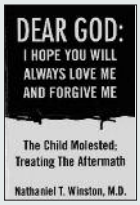
Saul Haskell, M.D., MD '55, is bicycling across southern Spain.

60s

***John B. Neeld Jr.,** M.D., MD '66, HS '67, received the Crawford W. Long Award of the Georgia Society of Anesthesiologists. The award is the highest recognition of a GSA member and honors people who have made exceptional contributions to society. Neeld is a past president of the American Society of Anesthesiologists, a member of the board and past chair of AMPAC, the American Medical Association Political Action Committee, a past chair of the board of directors of Northside Hospital in Atlanta and past president of VMAA.

William G. Wheeler, M.D., MD '60, HS '67, has an Orthopaedics office practice in Lexington, Ky. He has eight children and eight grandchildren.

book focus



Nathanial T. Winston, M.D., MD '53, HS '55, has authored the book "Dear God: I Hope you Will Always Love Me and Forgive Me" (Xlibris Corporation). Winston was born in the mountains of East Tennessee and served as the first psychiatrist in that area. He has been in practice for 51 years. In 1961 he opened a new 150-bed psychiatric hospital in Chattanooga, Tenn. He served as commissioner of mental health for Tennessee under two governors and is considered an authority in the treatment of childhood sexual molestation.

Jim L. Story, M.D., MD '55, right, helped celebrate the beginning of the fourth generation of physicians in his family when he outfitted his granddaughter, Holly Held Volz, center, with her white coat at the University of Texas Health Science Center (UTHSC) in July 2010. His daughter, Kristin Story Held, M.D., Holly's mother, left, graduated from UTHSC in 1985. Story's grandfather, George Washington Story, graduated from the University of Nashville School of Medicine in 1855, which later joined Vanderbilt University School of Medicine. Story sees a bright future ahead for his granddaughter. "Medicine provides a marvelous opportunity to serve the sick, the poor, and, above all, to advance the field of science. I think that carries across in every area of medicine. I know my daughter carries it, and I know Holly will carry it as well," he told the *San Antonio Express News.*

70s

John Michael Conoyer, M.D., MD '75, president of Midwest ENT Center, P.C., in St. Peter's, Mo., is pleased to announce the fifth partner in his practice, his son, **Matt Conoyer, M.D.,** MD '03, who completed his ENT residency at Vanderbilt in 2008 and then joined his father's practice. **Benjamin Conoyer, M.D.,** HS '08, is training in ENT at St. Louis University and plans to join his father and brother in 2013.

***H. Edward Garrett Jr.,** M.D., MD '79, was honored for his legacy of service to Baptist Memorial Health Care with the dedication of the Baptist Memphis Education Center and the Dr. H. Edward Garrett Sr., Auditorium. Located on the campus of Baptist Memorial Hospital-Memphis, the auditorium was named for the elder Garrett, a renowned cardiovascular surgeon who helped perform the world's first successful coronary artery bypass operation in 1964 and performed the first one in Memphis in 1968 at Baptist Hospital.

Steve Jones, M.D., MD '78, visited classmate **Tom Nygaard, M.D.,**

In August 2010, Gordon Flake, M.D., MD '66, HS '66, and his wife, Cristina, visited the Durham, N.C., home of Dean and Verne C. Lanier Jr., M.D., MD '66, HS '66. Lanier said they spent the evening "reflecting on their lives, careers and friendship," in honor of the July 19, 2010, passing of their classmate, John B. Breinig, M.D.

***A. Everette James, M.D., FAC '75-'94, pictured here (seated) with his family in Chapel Hill, N.C., is on the board of directors for the Center for the Study of the American South at the University of North Carolina Chapel Hill.**

***W. Bedford Waters, M.D., MD '74, professor of Urology at the University of Tennessee Medical Center, was named Cambridge Who's Who Professional of the Year in Medical Education. He was chosen for his professional accomplishments, academic achievements and leadership abilities. He is a recognized authority in Urology and Oncology.**

MD '78, in Virginia and together they hiked Mt. Pleasant Wilderness in July 2010. Jones recently left Hawaii and is now working on the merger of Walter Reed and Bethesda Medical Centers.

Steve Podgorski , M.D., MD ' 78, HS '81, was named one of the best Ophthalmologists in *5280* (Denver's Magazine) annual list featuring more than 280 of Denver's best physicians.

80s

John Anderson, M.D., MD '86, HS '86, has been named vice president of Medicine & Science for the American Diabetes Association. Members who are elected to this position must have demonstrated the ability to translate scientific findings into clinical care and be a leader in the medicine and science profession.

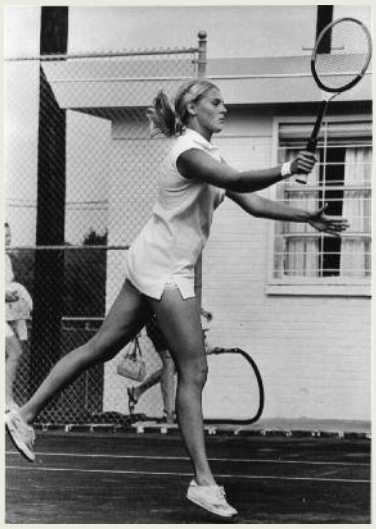
Robert D.B. "Jake" Jaquiss, M.D., MD '86, has been named chief of Congenital Heart Surgery at Duke Children's Hospital. Jaquiss joined Duke from the University of Arkansas for Medical Sciences where he served as the professor and chief of Pediatric Cardiothoracic Surgery at Arkansas Children's Hospital.

Neal Meropol, M.D., MD '85, is the new chief of Hematology and Oncology at University Hospitals Case Medical Center and Case Western Reserve University of Medicine. He is also the associate director for clinical research at the Case Comprehensive Cancer Center, where he is also a researcher. Meropol joined UH and CWRU in August from Fox Chase Cancer Center in Philadelphia.

Marc Shelton, M.D., MD '84, HS '87 has been elected governor of the Illinois division of the American College of Cardiology (ACC). Shelton will act as the ACC Governor for Illinois for a three-year term. He currently serves as the president of Prairie Cardiovascular and is a physician

Brian Riedel, M.D., MD '84, HS '87, FE '88, has been named chief of Pediatric Gastroenterology and Nutrition for the West Virginia Department of Pediatrics. His special interests include treating inflammatory bowel disease, liver disease, and short bowel syndrome in children. He also has expertise in treating nutrition disorders in children.

worthy of note



***Ann H. Price, M.D., MD '78, associate dean of Alumni Affairs for Vanderbilt University School of Medicine, was one of 10 new members inducted into the Vanderbilt Athletics Hall of Fame in September 2010.**

Price, shown here in 1971, played for the women's tennis team in the days before Title IX, meaning the program was non-scholarship and essentially self-coached. Nevertheless, she was a Southern and national standout at both singles and doubles.

Vanderbilt's Hall of Fame Weekend was Sept. 3-5. The Class of 2010 was presented during the football game with Northwestern.

Other inductees in this third Hall of Fame class are Shan Foster, Ernest "Bucky" Curtis, Heidi Gillingham Jackson, Chris Groer, Frank Lorge, Ed Martin, Jeff Peeples, Grantlin Rice and Will Wolford.

William F. Hefley Jr. M.D., MD '85, entered an Orthopaedic Surgery private practice in Little Rock, Ark., in 1990. In 1996 he joined Scott Bowen, M.D., and they now have a group of seven surgeons known as OrthoSurgeons. His practice is limited to hip, knee and shoulder surgery, primarily joint replacement and sports medicine. He and his wife, Lisa, celebrated their 22nd wedding anniversary. They have four children, Bailey, 19, Hannah, 16, Will, 14, and Ren, 10. They live on a farm west of Little Rock and raise cutting horses and barrel horses.

Dominique Delbeke, M.D, HS '89, FAC '90-present, is the new president of the Society of Nuclear Medicine. Delbeke is the director of Nuclear Medicine at VUMC.

at the Prairie Heart Institute at St. John's Hospital.

90s

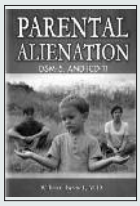
Maria Aaron, M.D., MD '95, received the Parker J. Palmer award, given to 10 residency program directors in all specialties in the country. She also received the Straatsma Award for Excellence in Resident Education this year, which goes to one Ophthalmology Residency Program Director in the country each year.

Jasminka Criley, M.D., HS '98, Associate Director of St. Mary's Internal Medicine Residency Program, and Clinical Professor of Medicine at the UCLA School of Medicine, was recently chosen by the American College of Physicians as one of the top 10 hospitalists throughout the nation. Criley was recognized for her clinical skills, leadership, mentorship and involvement in quality improvement projects which include efforts to decrease falls, improve medication reconciliation at discharge and facilitation of handoff communication.

Richard Gustafson Jr., M.D., MD '98, a pediatrician who was a 1993 graduate of Washington State University (WSU), is a winner of the school's Alumni Achievement Award, which honors graduates who have proved significant service and contributions to their profession, community and/or WSU.

Albert Holt IV, MBA, M.D., HS '97, has been appointed chief medical officer for Paradigm Management Services, a leading provider of catastrophic medical management services. Holt is board-certified in Internal Medicine and Critical Care. He has faculty appointments to Harvard Medical School, Georgetown Medical School, and the George Washington University School of Medicine and Health Sciences.

book focus



William Bernet, M.D., professor of Psychiatry, FAC '92 - present, has published a book, "Parental Alienation, DSM-5, and ICD-11" (published by Charles C. Thomas). The book centers on the reasons why parental alienation should be included in the "Diagnostic and Statistical Manual of Mental Disorders" as either a "mental disorder" or a "relational problem."

Henrietta Ukwu, M.D., FE '90, is senior vice president of global regulatory affairs for PPD, Inc., a leading global contract research organization, celebrating 25 years of providing drug discovery, development and lifecycle management services. Ukwu most recently served as vice president of global regulatory affairs at Wyeth Pharmaceuticals, Inc.

2000-

Robert Boykin, M.D., MD '06, is finishing up a five-year Harvard combined Orthopaedic Surgery residency and will begin a Sports Medicine fellowship at the Steadman-Hawkins Clinic in Vail, Colo., this year.

Nancy Louise Dubuisson, M.D., HS '06, and Zachary Jacob Barker were married June 26, 2010, in New Orleans, La. Nancy is an anesthesiologist with the Surgery Center in Lafayette, La.

Anita Gupta, M.D., MD '06, moved to Boston, in September and is working as a newborn nursery hospitalist at Cambridge Hospital, one of the Harvard teaching hospitals.

Bennett Hooks, M.D., HS '05, started his practice in Gastroenterology after finishing a fellowship in Advanced Endoscopy. He joined the Diagnostic and Medical Clinic at Mobile Infirmary in Mobile, Ala., in July 2010.

***Robert Steele, M.D., MD '93, a pediatrician with St. John's Regional Health Center in Springfield, Mo., has been named a Top Doctor by his peers every year that *417* magazine has conducted its survey. Last year he was also named one of the magazine's 10 "hot husbands." In his free time, he works on restoring his 1979 International Scout 2, working out and serving as chairman for the advisory committee on childhood immunization for the state of Missouri.**

Gustav Blomquist IV, M.D., MD '04, and his wife, Lisa, welcomed twins, Gus and Lars, born May 1, 2010, in Birmingham, Ala., where Blomquist was finishing a fellowship in Musculoskeletal Radiology. He is now on faculty at the University of Kentucky.

William Lea, M.D., MD '08, and his wife, Kerry, welcomed a son, Bradford James, on Sept. 9, 2010. He entered the world at 9 pounds, 11 ounces and 22 inches long.

Cindy McCloskey, M.D., MD '04, HS '04, a pathologist, has established her practice with OU Physicians in Oklahoma City, OK. McCloskey is board certified in Clinical Pathology and Medical Microbiology. She came to OU Physicians from Emory University Hospital in Atlanta, where she completed fellowships in molecular genetic pathology and medical microbiology.

Karen Meredith, M.D., MD '02, HS '06, and her husband, Todd, welcomed their third child, Elise, in March 2010. She joins big sisters, Ava, 5, and Claire, 2.

Lynn Bunch O'Neill, M.D., MD '02, and her family moved to North Carolina in the September. O'Neill has accepted a position as a palliative medicine physician at Duke Hospital and Durham Regional Hospital. She is an assistant professor, Division of Geriatrics, at Duke University School of Medicine.

Amy Whigham, M.D., HS '04, is a Pediatric Otolaryngology fellow at Children's National Medical Center in Washington, D.C.

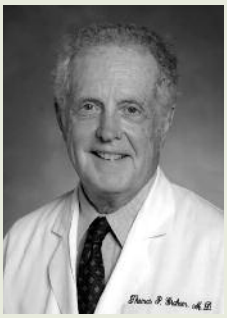
John Belletti, M.D., MD '06, and Alexandra Linden were married on Oct. 16, 2010, at the Plaza Hotel in Manhattan. Belletti is a consultant in the Florham Park, N.J., office of McKinsey & Company. Linden is the policy officer for the Australian Consulate in Manhattan.

Autumn Jackson, M.D., HS '08, and Aaron McRee were married July 17, 2010, in Nashville. They will reside in Chapel Hill, N.C., where she is employed with the University of North Carolina's Cancer Hospital, completing a fellowship in Hematology and Oncology.

Eric Edwards, M.D., MD '05, completed a residency in Internal Medicine and Pediatrics at the University of North Carolina in Chapel Hill and is currently a hospitalist at UNC. He and his wife, Cara, welcomed the arrival of twin girls, Eleanor and Caroline, in February 2010.

Celeste Ojeda Hemingway, M.D., MD '06, HS '10, and Graham Hemingway, M.S. '07, proudly announce the birth of their first child, Penelope Rose, born Nov. 20, 2009. Celeste completed her residency in Ob/Gyn at Vanderbilt and has joined Vanderbilt's Ob/Gyn department as an assistant professor and assistant residency program director.

worthy of note



The Duke Medical Alumni Association honored pediatric cardiologist *Thomas P. Graham Jr., M.D., FAC '71-present, with a Distinguished Alumnus Award on Oct. 15, 2010. Graham, who earned both his undergraduate and medical degrees at Duke, is professor emeritus of Pediatrics at the Monroe Carell Jr. Children's Hospital at Vanderbilt.

He came to Vanderbilt in 1971 and established the Medical Center's first pediatric cardiology program. In 1975 he became a full professor, and in 1985 he received the first Ann and Monroe Carell Family Endowed Professorship. Graham spent the majority of his career researching congenital heart disease and right ventricular function.

Under Graham's leadership Vanderbilt's pediatric cardiology program grew from two cardiologists into a division of 20 pediatric cardiologists and nine fellows. He stepped down as chair of the Division of Pediatric Cardiology in 2004, and the annual Thomas P. Graham Lectureship in Pediatric Cardiology was established. An endowed chair and the Division of Cardiology have also been named in his honor. Graham stopped seeing patients in 2007 but continues to write and teach.

Joe G. Allison, M.D., HS '64, died June 7, 2010. He was 79. Dr. Allison graduated from the University of Tennessee Memphis in 1960. He practiced Ob/Gyn for 40 years, delivering more than 7,000 babies. He was a devout UT fan and attended every game possible. Dr. Allison is survived by his wife of 58 years, Dorothy "Dot"; children, Sloan, Stacy, Joseph and John; 10 grandchildren; and one great-grandchild.

H.R. Anderson, M.D., HS '51, FAC '68 – '88, died May 28, 2010. He was 87. A captain in the U.S. Air Force during the Korean War, he was chief of the Medical Service at Stewart Air Force Base Hospital. Dr. Anderson spent 20 years in private practice as an internist and was on the staffs of Vanderbilt, Saint Thomas, Baptist and Parkview Hospitals in Nashville. He was a clinical faculty member of the Vanderbilt University School of Medicine. Dr. Anderson was retired from the State of Tennessee where he served as Medical Director of the Division of Chest Disease Control for many years. He is survived by his wife of 65 years, Susan; children, William and H. R.; two grandchildren; and one great-grandchild.

Ryan Arnold, D.D.S., HS '03, died Aug. 2, 2010. He was 34. He passed away four days after donating part of his liver to his brother Chad who had PSC, a disease of the liver for which there's no cure. Dr. Arnold was an orthodontist in Watertown, S.D. He is survived by his wife, Shannon; and three children, ages 1, 4 and 6.

John B. Breinig, M.D., MD '66, died July 19, 2010. He was 70. He completed his Cardiology specialty training at the University of Alabama in Birmingham after serving two years with the Public Health Service in Washington, D.C. During his years of practice, he was a partner in the Page-Campbell Cardiology Group. While retired, he pursued his interests in music, photography and travel. He is survived by his wife, Mary; children, Miriam and Anne; and his grandchildren.

Richard M. Christian, M.D., MD '42, died Nov. 24, 2010. He was 93. He served with the mobile Medical Corps of the U.S. Army in the European theatre during World War II. He was recruited by the Duke Foundation to practice Internal Medicine and Hematology at Self Memorial Hospital in Greenwood, S.C. He practiced in Greenwood from 1950 until 1991, when he retired to Fripp Island, S.C. He is survived by his wife of 67 years, Martha; four children, Elizabeth, Margaret, Richard and Thomas; and eight grandchildren.

***Joe G. Cromeans, M.D.,** MD '53, died Oct. 24, 2010. He was 82. He and his wife moved to Scottsboro, Ala., in February 1957, and Dr. Cromeans was honored for 50 years of practice at a meeting of the Medical Association of the State of Alabama. "I think I am addicted to helping people," Cromeans said, when asked what had kept him in practice for 50 years. Cromeans delivered more than 4,000 babies and performed countless surgeries on patients in Jackson County and surrounding areas. He is survived by his wife of 58 years, Mary Ann; and children, Gray and Randall.

Calvin H. Curry, M.D., HS '61, died July 30, 2010. He was 76. Dr. Curry began his medical career as a captain in the U.S. Air Force at Eglin Air Force Base before practicing Ob/Gyn in Tallahassee, Fla., for 45 years. He was a member of many organizations, including the Sons of the American Revolution, Society of Cincinnati, St. Andrews Society and the Sons of Confederate Veterans. He also served on the Board of Directors of Tallahassee State Bank and the Governor's Club, as well as in many hospital leadership roles. Dr. Curry was predeceased by his first wife, Mary Anne, and is survived by his wife, Ann; children, Calvin, John, Margaret and Elizabeth; three stepdaughters; and eight grandchildren.

Ted Eastburn, M.D., MD '80, FE '87, died Aug. 17, 2010. He was 56. Dr. Eastburn received his Cardiology fellowship training at Vanderbilt University School of Medicine and subsequently teamed with William Frist, M.D., former Senate Majority Leader, in establishing the university's heart transplant program. Dr. Eastburn joined Pikes Peak Cardiology in Colorado Springs in 1991 and became a senior partner. He served as City Councilman for the City of Colorado Springs from 1999 – 2003 and ran for mayor at the end of his term. He was well known for his easy disposition and congenial manner.

***Michael A. Gilchrist, M.D.** MD '68, died Oct. 31, 2010. He was 66. He served with the U.S. Air Force as a flight surgeon during the Vietnam War. He began his career in Chelmsford, Mass., with Medical Associates. For the last 20 years, he had his own pediatric practice. In recent years his son, Mark, joined him in that practice. Dr. Gilchrist was on the staff of Lowell General Hospital for 36 years. He is survived by his wife of 39 years, Carol; two children, Gregory and Mark; and one grandchild.

Richard E. Gordon, M.D., HS '72, died Aug. 27, 2010. He was 63. He served 10 years in the U.S. Army reaching the rank of lieutenant colonel before leaving the service in 1989. Dr. Gordon was a well-respected surgeon and his patients appreciated his peaceful demeanor. He fulfilled a lifetime dream of sailing to the South Pacific with his family. He continued sailing every summer, which was the "family activity." Dr.

***David T. Karzon, M.D., FAC '68 – '10, died Aug. 26, 2010. He was 90. Dr. Karzon was a professor of Pediatrics emeritus, chair of the Department of Pediatrics at Vanderbilt University Medical Center from 1968 to 1986, and the founder of Vanderbilt Children's Hospital, now the Monroe Carell Jr. Children's Hospital at Vanderbilt. He bridged the gap existing among Vanderbilt and the community pediatricians and persuaded the Junior League to join forces with him. He started the Friends of Children's Hospital volunteer organization and under his auspices, the Iroquois Steeplechase began donating their proceeds to the Children's Hospital. He held faculty positions at Johns Hopkins and at State University of New York at Buffalo before coming to Vanderbilt in 1968. Karzon's legacy continues today at Vanderbilt. John A. Phillips III, holds the David Karzon Chair in Pediatrics and The David Karzon Award is presented each year to the resident at the Children's Hospital who best exemplifies Karzon's natural curiosity, love of science and dedication to research. Dr. Karzon is survived by his wife, Allaire; children David and Elizabeth; and three grandchildren.**

Gordon is survived by his wife, Patty; children, Madison, Megan, Michelle, Andrew, David, Amy, Luke and Emily; and 13 grandchildren.

Herschel A. Graves Jr. M.D., MD '48, HS '48, died Aug. 7, 2010. He was 85. He served as a medical officer in the U.S. Navy for two years. He began practicing General Surgery in Nashville in 1955 with his uncle, James C. Gardner, M.D., and later with Robert N. Sadler, M.D., until 2000. He was a member of the Nashville Academy of Medicine, the Nashville Surgical Society, serving as President in 1979, and many other organizations. He served as president of the American Cancer Society. He was preceded in death by his daughter, Ann. He is survived by his wife, Bobbi; children, Alice, Elizabeth, Miller and H. Andy; and eight grandchildren.

Samuel T. Haddock, M.D., HS '61, died June 19, 2010. He was 80. Dr. Haddock practiced Pediatrics in Anderson, S.C., for 50 years. He was predeceased by his daughter, Julia, and is survived by his wife, Doris; children, Ellen, William and Samuel; and seven grandchildren.

Halcott T. Haden, M.D., MD '50, died June 11, 2010. He was 83. He served as a medical officer in the U.S. Air Force during the Korean Conflict. Dr. Haden joined the staff of the McGuire Veterans Administration Hospital in Richmond, Va., in 1957, where he served as chief of the Hematology section, acting chief of medical service, and then as chief of the nuclear medicine service until his retirement in 1989. He also served on the faculty of the Medical College of Virginia as associate professor of Internal Medicine and associate professor of Radiology. Dr. Haden is survived by his wife, Phyllis; children, Adrienne and Janet; and three grandchildren.

Pratt Irby, M.D., MD '36, died July 23, 2010. He was 97. Dr. Pratt served in the U.S. Army during World War II and was awarded the Bronze Star for meritorious service. Following the end of World War II, Pratt completed a Urology residency at the University of Tennessee in Memphis, Tenn. He then returned to Fort Scott, Kan., and practiced Urology until his retirement in 1984. Dr. Pratt was also known as an avid trumpet player. He was preceded in death by his wife of 61 years, Pauline, and is survived by children, Robert, Mary and Janet; and four grandchildren.

J. Frederic Kolhouse, M.D., HS '68, died June 17, 2010. He was 67. Dr. Kolhouse was a physician at Anschutz Cancer Center of the University of Colorado Hospital, specializing in Hematology and Oncology since 1977. From 1972 to 1974, he served as a lieutenant commander of the U.S. Navy at Naval Hospital Memphis in Millington, Tenn. He served as director of the University of Colorado Clinical Cancer Center from 1999 - 2010 and as chairman of the board of directors of the Clinical Cancer Center from 2003 - 2010. Dr. Kolhouse also received an abundance of awards, including the J. William Hillman Award for excellence in teaching at Vanderbilt University School of Medicine in 1971. He is survived by his children, Ronald, Christopher and Nicole; and two grandchildren.

Andras Kollar, M.D., Ph.D., HS '98, FE '99, died May 10, 2010. He was 52. Dr. Kollar had been a cardio-thoracic surgeon at the University of Texas Medical Branch since 2003. He recently received tenure and was promoted to associate professor in the Department of Surgery. He was also a fellow of the Royal College of Surgeons of Edinburgh, United Kingdom, and the Royal College of Physicians and Surgeons of Canada. He completed his medical training in Hungary and later in Great Britain, Germany and France. He began his training in the United States in 1994. He served in residencies in Charlotte, N.C., Buffalo, N.Y., and finally at Vanderbilt, where he completed his fellowship in Cardio-thoracic Surgery. He is survived by his wife Debbie; and children, Anna, Eszter, Balint and Warren.

Stewart "Pat" Lawwill Jr., M.D., MD '50, died Sept. 26, 2010. He was 83. Dr. Lawwill began his practice with his father in 1955, eventually joining Chattanooga Eye Associates, which became Chattanooga Vision Center. He was instrumental in the residency program of Baroness Erlanger Hospital, later University of Tennessee Medical School of Chattanooga. He helped design the Erlanger Eye Clinic and the Miller Eye Center. He is survived by his wife of 53 years, Alice; children, Stewart, Elleanor, Mary Margaret; and six grandchildren.

Jay F. Lewis III, M.D., MD '58, HS '58, died June 2, 2010. He was 78. He served in the U.S. Navy, achieving the rank of lieutenant commander. He was a Pathologist in private practice at Erlanger Health System in Chattanooga, Tenn., for more than 36 years and was a professor at University of Tennessee College of Medicine. Dr. Lewis was involved in the formation of the St. Jude Children's Hospital local chapter and the Ronald McDonald House. He was preceded in death by two sons, Jay and David, and is survived by his wife of 53 years, Joy; children, William, Robert, Elizabeth and Barbara; and two grandchildren.

Joseph B. Longino, M.D., MD '43 died Nov. 13, 2010. He was 92. He was a lieutenant in the U.S. Army and joined his father in medical practice in Sulphur Springs, Texas, in 1947. He believed that the highest calling of a man is to be of selfless service to others. This he displayed in his own life caring deeply about his patients' well-being. Frequently, he would make house calls to patients' homes in the '40s, '50s and '60s, up to his retirement. Dr. Longino was preceded in death by his wife, Joan, and their daughter, Stephanie. He is survived by his son, Joseph, and three grandchildren.

Steven E. Mayer, Ph.D., visiting professor, died June 29, 2010. He was 81. After earning a Ph.D. degree in Pharmacology at the University of Illinois, Chicago, he performed postdoctoral work at the National Institutes of Health and at Washington University. In 1985, he relocated to Nashville as visiting professor in Pharmacology at Vanderbilt University School of Medicine until he retired in 1995, as Professor Emeritus at the University of California at San Diego. Dr. Mayer is survived by his wife of 22 years, Elaine; children, Stephanie and Alex; stepdaughter, Kate; and four grandchildren.

Robert W. McCollum, M.D., HS '49, died Sept. 13, 2010. He was a prominent infectious disease researcher who was involved in the development and field trials of several vaccines, including polio and hepatitis B. He conducted research and taught at Yale, became dean of Dartmouth Medical School in 1982 and played a key role in the creation of the newly integrated Dartmouth-Hitchcock Medical Center in Lebanon, N.H. Dr. McCollum was the husband of psychotherapist and author Audrey McCollum. He is also survived by his children, Cindy and Doug; and two grandchildren.

Jeff R. Moore, M.D., MD '53, died July 17, 2010. He was 81. Dr. Moore

served as a captain in the U.S. Army from 1955-1957. He went to Amarillo, Texas, in 1961 as the first plastic surgeon in the northern tri-state area of Texas, Oklahoma and New Mexico. His practice focused primarily on reconstructive surgery, repairing birth defects, the damage of burns and industrial and motor vehicle accidents. He retired in 1998. He is survived by his wife of 57 years, Valee; children, Ruthann, Jeff and Christina; and five grandchildren.

Chelsea Jane S. Nevitt, M.D., HS '93, died July 15, 2010. She was 45. Dr. Nevitt founded and practiced at Wall Street Internal Medicine in Jeffersonville, Ind., from 2000 until the onset of her illness in September 2009. She is survived by children, Jessica and John; her mother, Dorcas "Sam"; and her ex-husband and friend, John S. Nevitt.

Robert A. Partain III, M.D., BA '56, MD '59, died May 25, 2010. He was 75. He was a veteran of the U.S. Army based at Fort Lee,Va., and co-founded Neurosurgical Associates in San Antonio, Texas, where he worked to restore health and comfort to many people. He was past president of the Rocky Mountain Neurosurgical Society, was an avid fan of the San Antonio Spurs, and a season-ticket holder from their inaugural season. Dr. Partain is survived by his wife, Brenda; children, Robert and Geoffrey; and four grandchildren.

Charles L. Pope Sr., M.D., MD '45, died May 14, 2010. He was 79. He served as a physician in the military, ending his service at MacDill Air Force Base. In their medical partnership, Dr. Pope and Victor Knight, M.D., practiced Internal Medicine in Tampa, Fla., from 1951 to 1987, serving Tampa General, St. Joseph Hospital and Memorial Hospital. Dr. Pope served as associate chief of staff at Memorial Hospital and held various officer positions in the Hillsborough County Medical Association. He was preceded in death by his first wife, Rosa, and is survived by his wife, Mary; children, Patricia, Charles and Henry; stepchildren, Pat and Paul; 13 grandchildren; and seven great-grandchildren.

Willem K. Rivenburg, M.D., HS '74, died June 6, 2010. He was 58. In 1977 Dr. Rivenburg began private practice in Fort Oglethorpe, Ga., where he was director of respiratory therapy at Hutcheson Medical Center and chairman of infection control and intensive care. He returned to Columbus, Ohio, in 1986, where he was an instructor in Pharmacology, before settling in Indianapolis in 1987. He continued his practice of internal medicine and critical care and was affiliated with Methodist Hospital / Clarian Health until his retirement in 2006. Dr. Rivenburg is survived by his wife, Kathleen; and children, Richard, Albert and Ann.

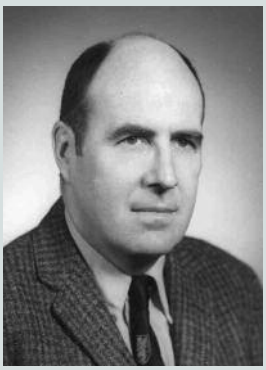
Samuel E. Scott, M.D., MD '57, died Oct. 12, 2010. He was 81. Dr. Scott was a Korean War veteran where he was part of the first Army Mash Unit. He retired after 40 years of medical practice in Livermore, Ky., where he served every patient like family. Dr. Scott was a long-term member and past president of the Livermore Lions Club. He also enjoyed hunting and was a member of the N.W.T.F. Greenville Chapter. Dr. Scott is survived by his sister, Eugenia; brothers, Ewart and W. R.; and several nieces and nephews.

David G. Stroup Sr., M.D., MD '48, HS '49, died July 7, 2010. He was 87. He served as a captain in the U.S. Army Medical Corp from 1950-1952. Dr. Stroup was board-certified in Ob/Gyn and practiced in Atlanta, Ga., from 1954-1992. After retirement, he and his wife Betty moved to Skidaway Island. In 2003, they moved to Brentwood, Tenn. He was a life member of the American College of Ob/Gyn, Georgia Representative of South Atlantic Conference-Ob/Gyn, President of Atlanta Ob/Gyn, Chief of Staff at South Fulton Hospital in Atlanta, Ga., founding member of Arlington Schools and Adjunct Instructor of Interns for Emory University. He is survived by his wife of 60 years, Elizabeth; children, David, Susan and Betty Anne; and four grandchildren.

Richard "Dick" C. Stuntz, M.D., MD '50, HS '51, died Aug. 6, 2010. He was 88. Dr. Stuntz was a captain in the U.S. Army. He served as an Ob/Gyn for almost 30 years, and later completed a residency at Johns Hopkins where he subsequently served in the Department of Psychiatry for more than 25 years. Dr. Stuntz enjoyed artistic interests, serving as the director of the Performing Arts Guild in North Carolina. He is survived by his wife of 31 years, Suzanne; children, Dede, Rick, Rebecca, Leah, Peter, Christofer, William and Kristine; 11 grandchildren; and eight great-grandchildren.

Horton E. Tarpley, M.D., MD '50, died May 24, 2010. He was 90.

Kwok-Yin S. Yu, M.D., HS '80, died Aug. 2, 2010. He was 60. Dr. Yu was a native of Guangdong, China, and received his medical training at Kaohsiung Medical College, Taiwan, R.O.C. and Vanderbilt University Medical Center, where he served his residency in Anesthesiology, and a cardiac anesthesia fellowship. Dr. Yu was in practice from 1983 until 2008 in Gadsden, Anniston and Boaz, Ala. He was a retired major and a veteran of the Gulf War as a member of the Army Reserve, serving as a physician. Dr. Yu is survived by his wife, Grace; and children, Felicia, Patrick and Jonathan.



John L. Norris, M.D., FAC, died Oct. 2, 2010. He was 91. He completed a shortened internship and joined the U.S. Army, serving as a medical officer. Dr. Norris embarked on a career in academic medicine at Cornell Medical College. In 1957, he accepted a position at Vanderbilt University School of Medicine. He taught anatomy at Vanderbilt and then at Meharry Medical College. He retired from Meharry in 1997 at age 78. Dr. Norris thoroughly enjoyed his interactions with bright, enthusiastic medical students and relished the opportunity to help them master skills and knowledge critical to their work as healers. He is survived by his wife of 62 years, Margaret Norris, M.D.; children, John Jr., Tom, Charles and Edith; and six grandchildren.

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TOMMY LAWSON

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MARY DONALDSON

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STEVE GREEN

Medical Reunion

Oct. 22-23, 2010

1) The Thomas E. Brittingham Society dinner was at the Hutton Hotel during Medical Reunion 2010. Front row (l-r) Clifton Meador, M.D., (MD 55), Ann Meador, Roy Elam III, M.D. (FAC '76-present), Kaye Elam; Back row (l-r) Margaret Spickard, Anderson Spickard III, M.D. (MD '89), Susan Spickard, Anderson Spickard Jr., M.D. (MD '57).

2) The Quinq Medical Society Class of 1960 was inducted in Langford Auditorium.

3) William Schaffner, M.D., professor and chair of the Department of Preventive Medicine, received a Distinguished Alumni Award, along with Robert Frye, M.D., professor of Medicine at the Mayo College of Medicine, during Vanderbilt's Alumni Reunion weekend.

4) Medical Alumni enjoyed dinner and presentations at the Grand Dinner at the Loews Vanderbilt Hotel. (l-r) Irvin Heimburger, M.D., (MD '57), Elizabeth Heimburger, Douglas Heimburger II, M.D., (MD '78), Robert Heimburger, M.D., (MD '43), Richard Heimburger, M.D., (MD '61).

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TOMMY LAWSON

1) Members of the Class of 1961 were inducted into the Quinq Society.

2) Vanderbilt University School of Medicine 1994 classmates (l-r) Thomas Quinn, M.D., Henry Harrell, M.D., and Chetan Mukundan, M.D., celebrate at Fleming's Restaurant.

3) Vanderbilt University School of Medicine Class of 2004 class party at Bound'ry Restaurant.

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JOE HOWELL

Robert Rosenfeld, MD '94, has maintained his family tradition—as both a doctor and a supporter of the Helen and Louis Rosenfeld Endowed Scholarship Fund, established by his parents in 1994. Today, Rosenfeld and his wife, Rebecca, are helping two Vanderbilt University School of Medicine students, Jolene Mariotti, Class of 2012, and Mi Jin Yoo, Class of 2011.

"Medical education is extraordinarily dear, and whatever help we can give is worthwhile," Rosenfeld says. "Remembering why I went into medicine in the first place makes me want to support the next generation of physicians."

To make a difference to a student, visit www.vanderbilthealth.org/givetomedicine or contact Mary Beth Thompson at mary.beth.thompson@vanderbilt.edu or (615) 322-8846.

"Thanks to my scholarship, I can cover the cost of tuition without having to apply for private educational loans. It makes a big difference."

—Jolene Mariotti, Vanderbilt University School of Medicine Class of 2012