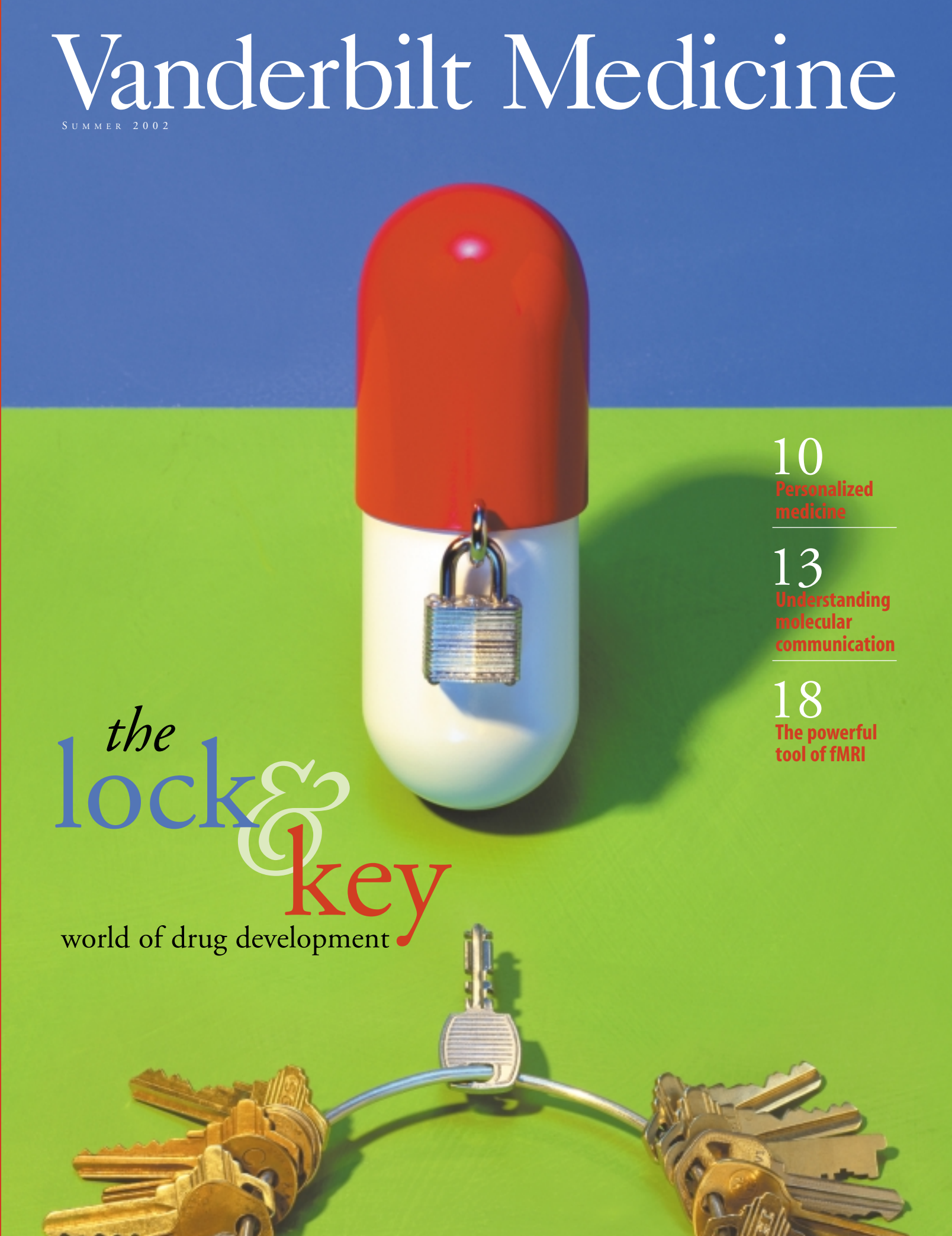
Vanderbilt Medicine

Summer 2002



the lock & key

world of drug development

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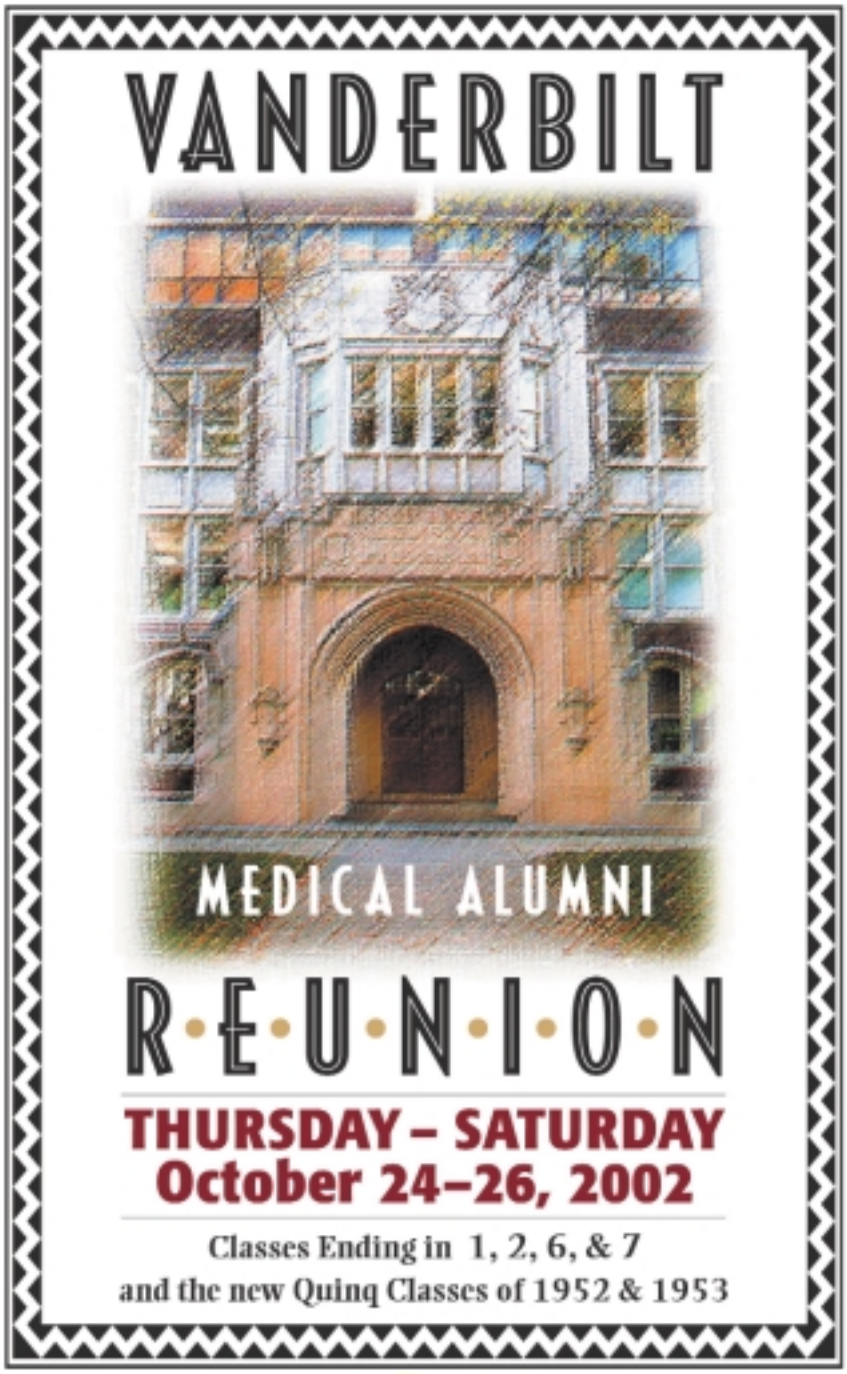

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Vanderbilt Medicine

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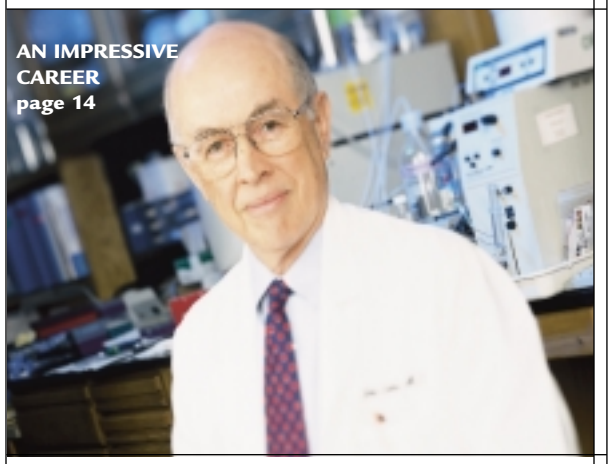

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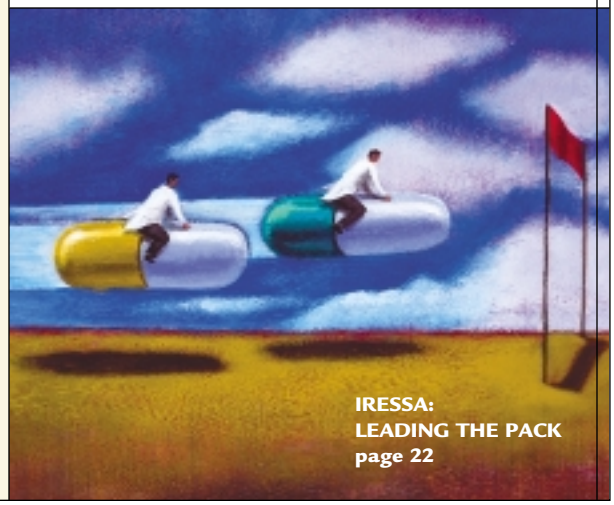

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DEAN DIXON

BY HARRY R. JACOBSON, M.D.
Vice Chancellor for Health Affairs

unlocking a torrent of discovery

Some of the most powerful tools that we as physicians have at our command are the chemical compounds we wield to fight infection, fend off pain and restore normal function. The pharmacopoeia at our fingertips today is a marvel of invention drawn from rigorous scientific study, serendipitous observation and sheer luck.

The scientific processes underlying drug discovery are evolving. The classic mainstay of drug discovery is observation – studying things in the natural world and drawing useful therapeutics from those observations. Our bodies, whether performing well or poorly, are driven by an intricate communication between and within our cells. The "Morse code" of that communication is described, not in dots and dashes, but in organic molecules – binding together, pulling apart, folding in upon themselves and transforming. There is an emerging belief that if we can begin to decode that cascade of chemical "words" we will unlock a torrent of discovery.

To begin translating this new language we have the tools of the structural biologist – mass spectroscopy, X-ray crystallography and computational biology. Structural biologists read the record of our cellular biochemical communication and will look for those telltale words that alter an essential process, that change a normal function to a disease process. It is the first step toward finding a pharmaceutical "spell-check" that can re-write a molecular paragraph. The first breakthroughs will be molecular diagnostics. We'll identify a unique molecule produced in a faulty cellular communication and then use our knowledge of that molecule to screen individuals at highest risk. But the real goal will be to develop therapies that help our cells correct themselves, the long sought and elusive process of rational drug design.

The last three decades have been notable in drug discovery both for the remarkable progress that has been made but also for the frustrating near misses of promising drugs. As human beings we share 99.1 percent of our genotype. All the variation in human beings is accounted for by less than .9% of our genes. Yet it is in that less than 1 percent variation that we may find both the cause of these frustrating near misses and the resolution. The recent past is littered with promising drugs that could not be used because they created unacceptably high risks for a small fraction of the population. Proteomics holds the key to this puzzle.

What if you could identify that fraction of the population who might predictably be harmed by a drug through a protein fingerprint? We as doctors could avoid prescribing the drug for those at risk and be able to use the drug confidently with those at low risk. We might even in the future use that proteomic fingerprint to not only select the appropriate therapy but also to calibrate an optimal dosage.

This issue of Vanderbilt Medicine explores a number of topics in drug discovery. With our investments in structural biology, proteomics and combinatorial chemistry, Vanderbilt will play an important role in this new, evolving and exciting area.

Hill to lead diversity initiative at School of Medicine

George C. Hill, Ph.D., professor of Microbiology at Meharry Medical College, has been appointed to a newly created position at Vanderbilt University School of Medicine - Associate Dean for Diversity.

Hill, who will begin his new role on July 1, will oversee efforts to promote Vanderbilt as a "receptive, positive environment" for minority faculty, house staff, students and patients. He will report directly to Dr. Steven G. Gabbe, dean of the School of Medicine.

Hill also will be a tenured professor of Microbiology and Immunology, and will hold the newly created Levi Watkins Jr. Professorship for Diversity in Medical Education at Vanderbilt. The professorship is named for the renowned Johns Hopkins University heart surgeon who was the first African-American to earn his medical degree from Vanderbilt in 1970.

Gabbe said Vanderbilt was "very fortunate" to have attracted Hill, who has a national reputation in medical education and research, and who also is very knowledgeable about the medical school and its alliance with Meharry. He is a member of the Institute of Medicine of the National Academy of Sciences and was elected this year as a Fellow of the American Academy of Microbiology. He currently serves on the Advisory Council for the National Institute for General Medical Sciences (NIGMS) of the National Institutes of Health.

Hill understands "how we could expand our diversity not only of medical students but at all our educational levels, including residents, graduate students, post-doctoral fellows and faculty," Gabbe said.

"I am excited about joining Vanderbilt University School of Medicine and helping to achieve the vision and goals of Dean Gabbe," said Hill, former Vice President for Sponsored Research at Meharry.

"I think Dr. Hill will make an outstanding contribution to Vanderbilt's endeavor to enhance the diversity of its programs, student body and faculty," said Meharry President Dr. John E. Maupin Jr. "He has made tremendous contributions to Meharry Medical College ... and he will continue to be of great value to Meharry while he serves in his new role at Vanderbilt."

"Our faculty, staff and students need to reflect the society in which we live," said Dr. Harry R. Jacobson, vice chancellor for Health Affairs. "For too long, Vanderbilt has trailed its peer institutions in attracting applicants from a broader spectrum. Dean Gabbe and Dr. Hill will make a huge difference in this effort."

Several programs already are underway at Vanderbilt to recruit and train medical and graduate students from underrepresented minorities. They include the Office of Minority Medical Student Affairs, the Office of Biomedical Research Education and Training, and the Bridges program, a pathway from the master's degree to the Ph.D. that is designed to increase the number of minority biomedical scientists.

Gabbe said Hill and other Vanderbilt administrators would visit college campuses across the country "to make certain their students understand the opportunities at Vanderbilt." Hill will help residency program directors in their recruitment efforts, and will be part of the faculty and chair search committees, the dean said.

- BILL SNYDER

VUH commended for patient safety measures

Representing tremendous health care buying power, the Leapfrog Group, a consortium of Fortune 500 companies and other large private and public employers, has singled out Vanderbilt University Hospital as being among a select few hospitals providing safety measures that the rest of the nation should emulate. The strong endorsement of VUH comes at a time of increased awareness of patient safety by purchasers and the public alike.

In the Leapfrog Group's survey of 241 hospitals in seven regions, VUH was among a small number of hospitals commended for using computerized physician order entry and for ample physician coverage of intensive care units. In fact, VUH was one of only two hospitals to indicate full implementation of both these safety standards. Vanderbilt is also cited as exceeding patient volume criteria for various surgical procedures dealt with in the survey. Patient volume is considered a marker of how well a hospital is likely to perform a given major surgical procedure.

Members of the Leapfrog Group provide health benefits to more than 24 million Americans and spend more than $45 billion on health care annually. Sponsored by the Business Roundtable, the group was formed in response to a 1999 Institute of Medicine report attributing an estimated 98,000 deaths per year to preventable medical errors made in hospitals.

The group is limiting its focus to three initiatives, order entry, ICU coverage and surgical volume, to quickly spur major advances in safety. Leapfrog research consultants, led by well-known health systems researcher Dr. John Birkmeyer of Dartmouth Medical School, estimate that universal implementation of the three safety standards in urban centers could save up to 58,294 lives per year and avoid up to 522,000 serious medication errors.

"Vanderbilt is one of only a handful of medical centers nationwide to perform so well on the Leapfrog criteria," said VUMC Chief Medical Officer Dr. John S. Sergent.

- PAUL GOVERN

contemplating cholesterol at bodega bay

When Dr. Robert Mahley wants to relax from his busy schedule, he often drives north to his weekend retreat in Bodega Bay, Calif., a quiet fishing community, popular for its quaint hometown feel and proximity to the vineyards of Napa and Sonoma Valleys. He walks on the beach with Linda, his wife of 39 years, and perhaps his two young grandchildren, reflecting on his career as a scientist and physician and looking forward to future projects.

Mahley, the first graduate of Vanderbilt's formal M.D./Ph.D. program in 1970, has produced seminal research into lipid metabolism and heart disease. He founded a dynamic and growing research institute, The J. David Gladstone Institutes, and has guided its growth for more than 20 years. His research has been recognized by many honors, including election to the National Academy of Sciences and the Institute of Medicine. In 2000, he received the Distinguished Alumnus Award from the Vanderbilt University School of Medicine.

His experience at Vanderbilt provided the basis for his life's work. At Vanderbilt, he began his research on lipoproteins—complexes of fats and proteins that transport cholesterol throughout the body—and their role in heart disease. Today, HDL and LDL are fairly well known among health-savvy Americans. But in 1963, when Mahley was beginning his doctoral studies with Dr. Virgil LeQuire in Pathology and Cell Biology, lipoproteins were the subject of cutting-edge research.

"I embraced it totally because it was a new area of research about which we knew very little," he said. "We knew cholesterol was involved with heart disease, but we didn't know how."

After completing a pathology internship at Vanderbilt in 1971, Mahley was recruited to work at the National Institutes of Health, where he became head of the comparative atherosclerosis and arterial metabolism section of the National Heart, Lung, and Blood Institute. "Excitement at the NIH was at a fever pitch," said Mahley. "We were making fundamental discoveries about lipoprotein metabolism. It was the beginning of a whole new field."

One of the exciting new findings was a high-density lipoprotein that was induced by cholesterol feeding in experimental animals. This lipid-binding complex contained only a single protein, which ultimately became known as apolipoprotein E. Studying the biology of apoE and its role in decreasing blood cholesterol levels became the focus of his scientific work.

"I was extremely fortunate that apoE turned out to be such an interesting protein," he said. "For essentially all of my scientific life, some 30 years now, I have been following where apoE chose to lead me. And it has been fun."

Then came the call from the trustees of the J. David Gladstone Foundation, named for a southern California real estate developer who bequeathed his fortune to medical research. Their proposal to establish a research institute sounded good to Mahley although, at 37 years of age, Mahley believes he was simply too young to realize what he was getting into. But the enthusiasm and vision of the trustees sold him on the idea.

Gladstone opened its doors in 1979 with a staff of seven scientists, all of whom had worked with Mahley at the NIH. His team continued their research on apoE. They determined the amino acid sequence of the protein and identified the amino acids that enable it to interact with lipids and other lipoproteins to deliver cholesterol from the blood to the liver and other parts of the body. Their work helped to establish that apoE is a key regulator of plasma cholesterol levels.

Gladstone has grown to include three institutes, each focusing on a specific area of research: cardiovascular disease, AIDS and immunology, and neurological diseases. The institutes are home to the laboratories of 22 researchers, all with faculty appointments at the University of California, San Francisco, an institution known for its world-class research.

In 1988, Mahley proposed that apoE was not only involved in heart disease but also played a key role in the normal functioning of the nervous system. Since then, he and others have shown this insight to be accurate. Researchers at Gladstone demonstrated that apoE is produced in the central nervous system and is deeply involved in neuron extension and repair. This work provided the context for the discovery, made by researchers at Duke University, that an isoform of apoE (apoE4) is currently the single most predictive genetic risk factor for Alzheimer's disease.

CHRIS GOODFELLOW

DR. ROBERT MAHLEY

In 1990, Mahley began to study risk factors for heart disease in Turkey, where there are clear-cut regional differences in dietary fat consumption and cardiovascular disease is common. The international team revealed that Turks have extremely low levels of HDL, the "good cholesterol," regardless of their diet. The low level of HDL placed them at high risk of heart disease. Now Mahley's goals are to train Turkish physicians in the treatment and prevention of cardiovascular disease and to unravel the genetic mechanism for the low HDL levels in this population.

Mahley's work is not yet done. Gladstone continues to grow, and is expected to nearly double in size to more than 500 employees within the next few years. To accommodate this growth, the institutes will build a research facility at UCSF's new Mission Bay campus. And apoE has not yielded all of its secrets. There is much more science to be done. This bright and exciting future gives Mahley plenty to contemplate on his weekend walks on the beach at Bodega Bay. Ⓥ

by Laura Lane

match day 2002

PHOTOS BY DANA JOHNSON

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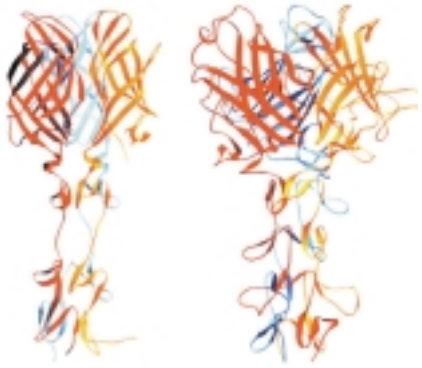
Study finds evolutionary link between two viruses



Researchers at Vanderbilt University Medical Center, in collaboration with Harvard University Medical Center, have linked two different virus families, reovirus and adenovirus, which may lead to the development of new antiviral drugs and a better understanding of the strategies microbes use to dock and internalize inside cells to begin the process of infection.

Dr. Terence S. Dermody, professor of Pediatrics, and Harvard structural biologist, Thilo Stehle, Ph.D., led the study that has revealed remarkable similarities in the attachment proteins of two quite dissimilar viruses, suggesting a common ancestor.

The five-year study began with a phone call from Stehle to Dermody, asking the Vanderbilt researcher if he would like to work with Stehle's group in solving the structure of the sigma 1 protein.

Dermody then contacted Dr. James Chappell, who had been Dermody's first graduate student and who is now back in the lab as a clinical pathology resident. Chappell was enthusiastic about trying to express the protein and purify it in an attempt to crystallize it and solve the structure. So, the Vanderbilt team of Dermody and Chappell began the collaboration with the Harvard team of Stehle and his post-doctoral fellow, Andrea Prota, Ph.D.

Dermody's lab has an interest in determining how viruses cause disease in the nervous system, and specifically how one virus may cause a sore throat while a different virus may incapacitate a patient with hepatitis or encephalitis. A key determinant of the different cell selection within the host is the attachment protein.

Some viruses resemble spherical objects with thin protein fibers that protrude from the sphere and are used to attach to the surface of the cell by binding to specific receptors. The cell can become infected if the viral attachment protein can bind a particular cell-surface receptor. For reovirus, the attachment protein is known as sigma 1.

The process to solve the sigma 1 structure, expected to take a year or two, stretched into five years as conditions were modified to generate the right constructs to facilitate the expression of the protein.

- ELIZABETH ROTH

DEAN DIXON

Dean's office restructured

The Office of the Dean of Vanderbilt University School of Medicine has been restructured.

Gabbe will serve as chief executive officer of the School of Medicine with the following new positions: Senior Associate Dean for Clinical Affairs, held by Dr. John S. Sergent; Associate Dean of Clinical Affairs, Dr. F. Andrew Gaffney; Assistant Dean of Admissions, Dr. J. Harold Helderman; Chief of Staff, Lynn E. Webb, Ph.D.; and a restructured Dean's Executive Council, which now includes Lee E. Limbird, Ph.D., Dr. Alastair J.J. Wood, and Dr. Mark A. Magnuson.

Current administrative positions within the medical school have not been affected. Leadership roles for Dr. Deborah C. German, senior associate dean for Medical Education, Dr. Gerald S. Gotterer, senior associate dean for Faculty and Academic Administrative Affairs, Dr. Roger Chalkley, senior associate dean for Biomedical Research, Education and Training, Dr. Bonnie Miller, associate dean for Medical Students, and Dr. Fred K. Kirchner, associate dean for Graduate Medical Education, will remain the same.

The School of Medicine has also created an office for Diversity. George C. Hill, Ph.D., professor of Microbiology at Meharry Medical College will serve as Associate Dean for Diversity.

This addition is critical to Vanderbilt's goal to be among the top 10 U.S. medical schools, according to Gabbe. On average, 12 percent of U.S. medical students are from underrepresented minorities compared to only 6 percent of Vanderbilt medical students. Four percent of VUSM faculty are minorities.

Other recently announced leadership positions are also an integral part of VUMC's future. In the past year, the following people were recruited and/or appointed to key leadership roles: Dr. Jeffrey R. Balser, chair of Anesthesiology; Pat Levitt, Ph.D., director of the Kennedy Center; Susan Wente, Ph.D., chair of Cell and Developmental Biology; John Gore, Ph.D., professor of Radiology and Radiological Sciences and Biomedical Engineering; Dr. Larry Churchill, Stahlman Professor of Ethics; and Billy Hudson, Ph.D. director of the Center for Matrix Biology and professor of Medicine.

Ongoing searches are also being conducted to recruit chairs for Ophthalmology, Pathology, and Psychiatry, and a vice-chair position for Biostatistics in Preventive Medicine.

- JON COOMER

the lock & key

world of drug development

Medicine increasingly is about medication.

Traditionally scientists have relied on trial and error to test potential new drugs in large robotic screens, cells and animal models. That approach is rapidly evolving into a new field called "rational drug design," where molecules are designed to interact with specific enzymes like a key turning a lock. Another new field – pharmacogenomics – uses genetic testing to identify patients whose illnesses are most likely to respond to treatment, and who are least likely to experience side effects. The aim is to improve diagnosis and treatment, and perhaps one day to prevent disease from happening in the first place.

Will these efforts accelerate the pace of drug discovery? Will they lead to new drugs that are more effective and have fewer side effects than current medications? Will the computer revolution, by automating and speeding laborious testing procedures and by storing and analyzing huge amounts of data, ultimately save money and cut the cost of pharmaceuticals?

The answers to these questions are hard to predict. The more scientists learn about the splendidly complex chemical circuitry that cells use to communicate with each other, the more they realize how much more there is to understand. If indeed science is engaged in a "war" on disease, it must be like the current war on terrorism – an engagement with an enigmatic enemy whose array of weapons and defenses is scarcely understood. No one knows how long the battle will last, or how much it will cost.

A recent Tufts University study estimated that the average cost of developing a new prescription drug is $802 million – a 250 percent increase in little more than a decade – in large part because of the expense of the rigorous and lengthy clinical trials that are required to prove drug safety and efficacy. Critics challenged the estimate, arguing that it ignored the tax breaks and government grants drug companies receive, but other experts argue that increasing cost is inevitable.

While rational drug design and screening will likely speed the development of more specific medications, "I don't think it's going to be easy or any less challenging than what we do now," said Dr. Carlos L. Arteaga, Ingram Professor of Cancer Research at Vanderbilt. "Although it will be a lot of fun, the cost of this enterprise could be mind-boggling. But in the end, savings could be enormous if one factors in the years of life extended and saved."

Dr. Alastair J.J. Wood, professor of Medicine and Pharmacology and assistant vice chancellor for Research, agreed. "Supposing in the future people's diseases were treated by medication and … we didn't need surgeons and maybe not hospitals," he said. "Then drug costs are going to be a much bigger proportion of the health care dollar."

This issue of *Vanderbilt Medicine* explores some of the frontiers of drug development being explored at Vanderbilt University Medical Center, including the search for new COX-2 inhibitors; the role of epidermal growth factor in cancer therapy; and the "eureka moment" that ultimately led to the development of the first effective drug treatment for severe hypertension – a landmark in history.

While many questions remain, Vanderbilt researchers hope their efforts will lead to many more "eureka" moments.

– BILL SNYDER

personalized medicine

An ideal medicine, most agree, is one that effectively treats an illness without making us feel lousy — or worse — in the process. Despite rigorously regulated efforts in this country to produce efficacious and safe drugs, serious adverse drug reactions sometimes occur and medications are rarely effective in all patients. One person might show a very good response to a drug, while another shows a poor response or no response at all.

by Mary Beth Gardiner

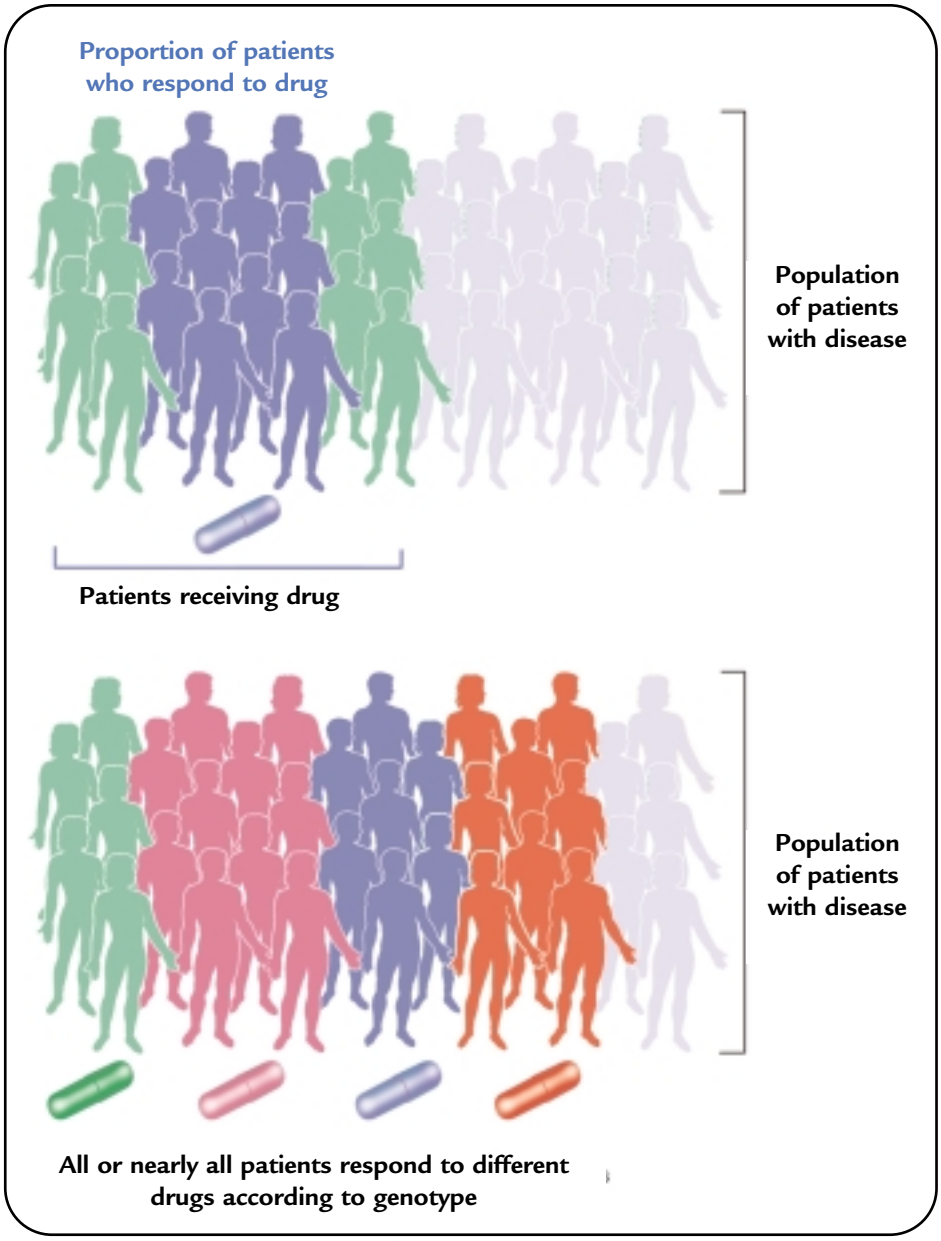
The relatively new field of pharmacogenomics holds the promise of removing some of the uncertainty in drug prescription. The field is based in the premise that much of the variability in drug response can be explained by genetic factors.

Each of us is genetically unique. Yet we all have in common at least 99.9 percent of the DNA code in our genome. Variations in the remaining 0.1 percent account for individual differences in physical appearance, in susceptibility to disease, and, scientists are learning, in the way a person responds to drug therapy.

With the recent publication of the first draft of the human genome sequence, researchers are beginning to pinpoint areas of "flex" in the genome, where substitutions of one or more nucleotides in the DNA sequence can occur. These changes – called polymorphisms – and other genetic variants, such as the mutation, duplication, or deletion of a gene, cause no discernible alteration in appearance, but may affect physiology, including how the body responds to medications.

The long-term vision of pharmacogenomics is to develop personalized medicine: to tailor, based on an individual's genetic profile, the selection of each prescribed drug and drug dosage in order to maximize positive effects and minimize risk. That goal, however, will probably not be reached for decades for most drugs.

In the near-term, researchers at Vanderbilt and elsewhere focus on isolated examples in which knowing a variant in a gene helped them understand an unusual response in a patient. One commonly prescribed drug serves as an example. Codeine is a widely used pain reliever that in most people is metabolized to a much more potent agent, morphine. Research from the lab of Dr. Alastair J. J. Wood, professor of Medicine and Pharmacology at Vanderbilt, showed that about 7 percent of African-American and Caucasian populations lack the ability to convert codeine due to a



genetic polymorphism. Consequently, those people experience less pain relief taking codeine.

One of the reasons the effect is interesting, said Dr. Dan M. Roden, William Stokes Professor of Experimental Therapeutics, is that it is tied to ethnicity.

"That's one of the themes that resonates through pharmacogenomics," he said. "The variants we identify in one ethnic group, or other subpopulation, don't exist – or don't exist in the same proportions – in another group."

Roden is the principal investigator of a four-year, $11.2 million grant from the National Heart, Lung, and Blood Institute that places Vanderbilt among a select group of institutions taking the lead in pharmacogenomic research. Each of the 13 institutions in this initiative supported by the National Institutes of Health has a specific area of specialization; Vanderbilt's is cardiac arrhythmia.

"One of the striking things about drugs that regulate heart rhythm is the spectrum over which they work," Roden said. "There are patients for whom a dose of medication makes a heart rhythm problem melt away and others for whom a dose of the same medication causes a catastrophic, perhaps even life-threatening side effect. We need to find a way to target the right drug to the right patients. Understanding why there is this variability may also help design better and safer drugs."

Roden and colleague, Dr. Alfred L. George Jr., Grant W. Liddle Professor of Medicine and director of the Division of Genetic Medicine, have spent years studying the area of drug-induced arrhythmias. It's well recognized that certain drugs, both heart rhythm-regulating drugs and other kinds of drugs, can actually cause people to have fatal or potentially fatal abnormal rhythms. Until recently, it's not been well understood why some people seem to be more susceptible than others.

"Alastair's work showed the effect of genetically-determined drug metabolism. Our work with anti-arrhythmic drugs has shown that there are specific genetic abnormalities, not in the way these drugs are metabolized, or burned up," Roden said, "but in the way they interact with their target proteins, called ion channels."

Most anti-arrhythmic drugs work by interfering with the function of ion channels, the specialized pore-forming proteins found in the membrane of heart cells that control electrical activity. The genes that encode sodium and potassium ion channels turn out to have variants, which the investigators think might explain increased susceptibility to drug-induced arrhythmias in about 10-15 percent of those people having them.

"This has been the Achilles heel of the

drug development industry for anti-arrhythmics," George said. "It limits their usefulness and makes them dangerous."

This is a problem not only with anti-arrhythmic drugs, George said. Some antibiotics are known to trigger abnormal heart rhythms. And a number of drugs have been taken off the market recently for this same reason, including the allergy drug Seldane and the gastric motility drug Propulsid. Because of the increasing incidence of this effect over the past few years, the FDA now requires that pharmaceutical companies provide evidence that their non-cardiac-related drugs don't affect the heart electrical system in a way that could trigger a fatal arrhythmia.

"Drug companies now have the burden of proof to show that their drug does not block critical ion channels in the heart," George said, "so they're very interested in knowing whether there is a subset of patients who should not receive their drug."

It is during drug development, rather than after the fact, that having genotyping information will be particularly useful, saving both time and money, according to Wood, who is also assistant vice chancellor for Research in charge of clinical research initiatives at Vanderbilt.

"If at an early stage in the drug development process we can identify patients, who, because of their genetic makeup, respond to a drug," he said, "then by including only such patients in our clinical trials we could substantially reduce the number of patients who have to be entered into the pivotal trials for drug approval.

"Conversely," he said, "the ability to identify patients at particular risk for side effects will also affect the risk-benefit profile of a drug. Drugs which might otherwise be considered too toxic for widespread use may be safely developed if we can exclude patients at risk of toxicity from the trials."

In Wood's view of the future, research from the field of pharmacogenomics will ultimately yield a complex of information for each individual – drug response genotypes, disease genotypes, toxicity genotypes, and drug sensitivity genotypes – to be taken into consideration by a physician in selecting a drug and deciding on proper dosage. All this in addition to the usual factors involved, including age, medical history, and current medications, among others. Clearly, this is a lofty goal that will be some time in coming.

"Until that nirvana of personalized medicine is achieved," Wood said, "research will proceed in the continuous search for safer and more effective drugs."

The long-term vision of pharmacogenomics is to develop personalized medicine: to tailor, based on an individual's genetic profile, the selection of each prescribed drug and drug dosage in order to maximize positive effects and minimize risk.

A study of arrhythmia patients

To identify the genetic factors involved, Drs. Dan Roden and Alfred George Jr. have launched a retrospective study of people who have had documented drug-induced arrhythmias. About 10 percent of the 140 individuals studied to date have some variants in the genes coding for potassium or sodium channels in the heart. Most are rare mutations. However, one polymorphism common to both patient and control groups appears to be more common in patients.

"This polymorphism is present in about 8 percent of our drug-induced arrhythmia patients and in about 2 to 4 percent of the controls," Roden said. "Lab studies and computer modeling support our idea that this polymorphism doesn't do anything to the way the heart works at baseline, but it dramatically increases the risk of arrhythmia on exposure to certain drugs. This is what we're looking for because it may be common enough to make an impact on public health."

Prospective studies are also planned. The researchers will follow Vanderbilt patients prescribed certain anti-arrhythmic or anti-coagulant medications to monitor their response. A project with Drs. Jeffrey R. Balser and Brian S. Donahue in the department of Anesthesiology involves collecting outcomes data and DNA samples on all heart attack patients having cardiac surgery at Vanderbilt to address whether there are predictors of post-operative atrial fibrillation, a very common event following bypass surgery.

Both Roden and George believe this kind of science is highly multi-disciplinary, requiring the expertise of basic scientists, genetic scientists, clinicians, database managers, statisticians, and bioinformaticists, among others. Orchestration of this effort is what the NHLBI grant is all about, they said.

- MARY BETH GARDINER

understanding molecular communication

by Mary Beth Gardiner

Think of the cell as a molecular chat room. The multitude of activities within cells results, in essence, from molecules communicating with one another. Understanding how biomolecules communicate – how they interact physically at the atomic level – is the basis of high-resolution structural biology, a field of study central to current strategies of drug design among pharmaceutical companies and academic centers alike.

Interference with how biomolecules communicate is, perhaps, the simplest way to think about the relationship between structural biology and drug development, according to Walter Chazin, Ph.D., director of the Center for Structural Biology.

"Once we understand how two molecules interact," he said, "what we try to do is design a small, bioavailable molecule that can interfere with that process to inhibit or eradicate an overactive or aberrant activity."

There are a number of different strategies for this type of rational drug design, but the basic principle is built around knowing the shape and chemical properties of the active site of a protein and the partner molecules that activate it. Understanding this relationship allows for the design of a drug that slips into the place where the usual partner interacts, preventing activation.

Several drugs are now on the market that originated from this structure-based design approach. The most well known examples are the HIV protease inhibitors and the anti-flu drug Relenza.

Chazin was recruited to Vanderbilt in 1999 to develop a transinstitutional initiative in structural biology, an area identified for strategic investment by the faculty and Board of Trust. He arrived with a plan to do something "very unique on the national level."

Traditionally, there are three separate disciplines of atomic resolution structural biology — NMR spectroscopy, X-ray crystallography, and computational biology — that have the same objectives but make distinctly different contributions. Chazin wanted to create a new entity that used all three tools not just to determine structures, but also to attack biological problems.

Chazin is recruiting additional faculty with expertise in these disciplines to hold appointments in a variety of departments across campus, with the Center lending an overarching focus.

In addition, Chazin is developing what he calls the Structural Biology Resource, a facility where faculty, students, and post-doctoral fellows can meet with Ph.D. level experts to learn how structural approaches can enhance their research. The Resource will provide consultation and education, as well as training and the requisite infrastructure.

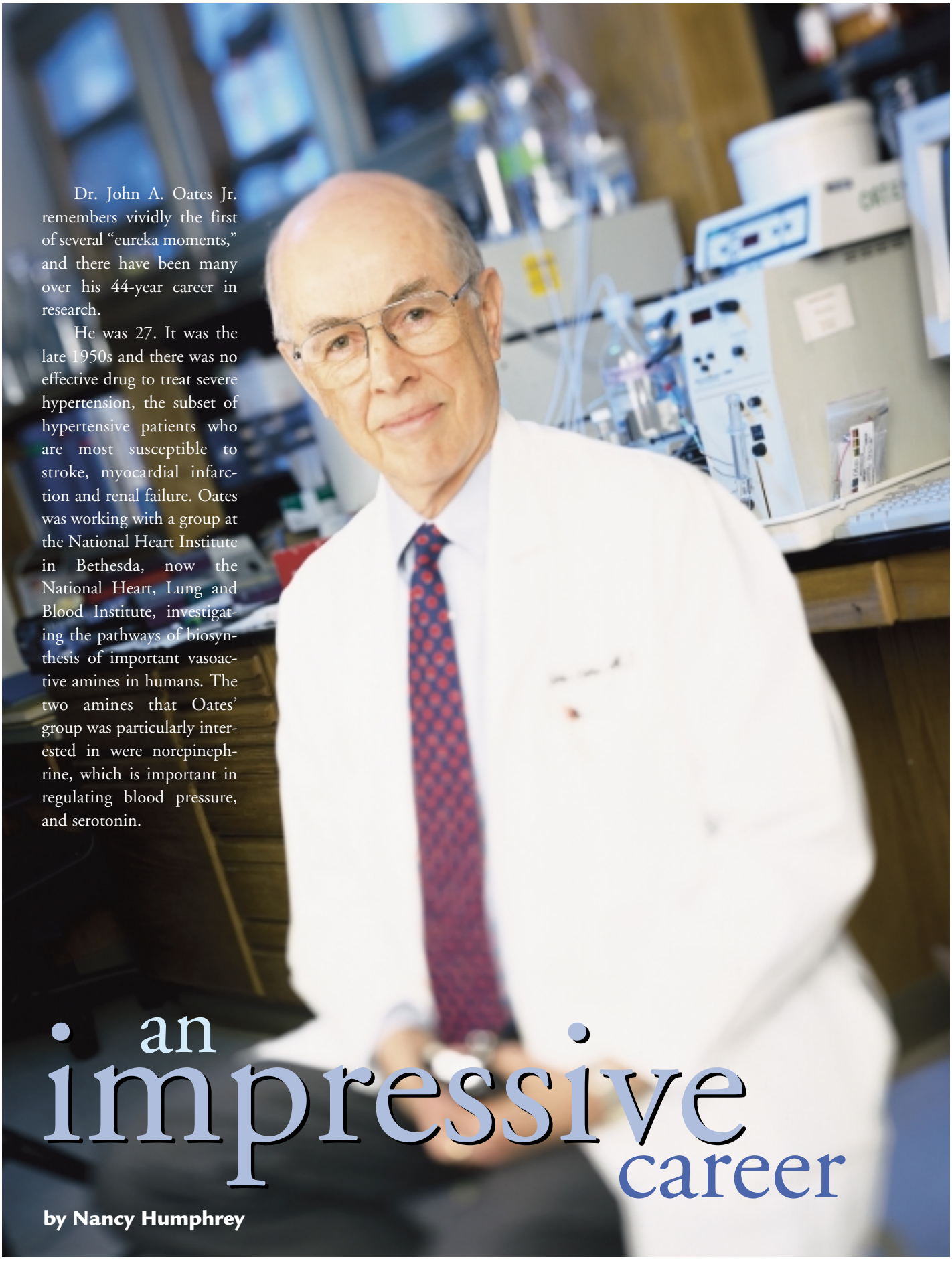
Chazin's own research takes a structural biological approach to understanding how calcium is used, not just in bones and teeth, but in all cells, to regulate numerous biochemical processes. He studies calcium-binding proteins, which are the key players required for all of these activities. One of the proteins under study — calcium-dependent protein kinase, or CDPK — is unusual because it has a built-in structural control mechanism that enables it to regulate its own biochemical activity.

WALTER CHAZIN, PH.D.

It turns out that, in the animal world, the CDPK protein is found only in protozoa, such as the parasites that causes malaria, and is essential to their survival. Finding a molecule that would structurally inhibit CDPK activity should shut down such an organism. And since CDPK doesn't occur in human beings, a drug that inhibits the enzyme could be used to prevent disease in those who become infected with a parasite, with little chance of harming the patient.

Chazin's project illustrates how understanding the structures and interactions of molecules within cells can contribute to solving important biological and clinical problems. When all of the tools available to structural biologists are coordinated, they form a powerful foundation for rational drug discovery.

DEAN DIXON



an impressive career

by Nancy Humphrey

Dr. John A. Oates Jr. remembers vividly the first of several "eureka moments," and there have been many over his 44-year career in research.

He was 27. It was the late 1950s and there was no effective drug to treat severe hypertension, the subset of hypertensive patients who are most susceptible to stroke, myocardial infarction and renal failure. Oates was working with a group at the National Heart Institute in Bethesda, now the National Heart, Lung and Blood Institute, investigating the pathways of biosynthesis of important vasoactive amines in humans. The two amines that Oates' group was particularly interested in were norepinephrine, which is important in regulating blood pressure, and serotonin.

"Our group did a number of studies to quantify and measure the formation of these amines in human beings, and in particular, the enzymatic steps in their formation," Oates said.

So the group, headed by Albert Sjoerdsma and Sidney Udenfriend, decided to focus on one particular enzyme, the aromatic amino acid decarboxylase, and measure the enzyme activity in humans as a basis for assessing drug effects. The group chosen: hypertensive patients.

A general assumption underlying many of the studies being conducted by the group was that new knowledge regarding the biochemistry and pharmacology of aromatic amines held a potential for improving the understanding and treatment of hypertension.

Udenfriend began discussing the experiments with scientists at Merck pharmaceutical company who had synthesized methyldopa as a potential decarboxylase inhibitor. The chemical had not been found to have any cardiovascular effects in animals and was "sitting on a shelf," Oates said. The NIH group asked to use methyldopa as an experimental tool since there was officially no evidence that it lowered blood pressure.

"The study began using methyldopa as an experimental tool, not as a potential drug," Oates said.

"The investigators gave increasing doses of methyldopa and were gratified when they achieved a dose of the drug that inhibited the decarboxylase enzyme. From the multiple blood pressure measurements on that patient's chart, it was not possible to draw a conclusion, but it looked like there was a trend toward dropping the blood pressure.

"That night I went back to the lab and plotted a graph, averaging each day's blood pressure on a bar graph and it became quite clear that the blood pressure was being lowered by the drug," Oates said.

He excitedly called one of his colleagues at home, calling him back to look at the data. Albert Sjoerdsma was in Sweden on sabbatical. Oates sent him an urgent message, and he cancelled his sabbatical and came home.

"I was so excited that night I could hardly go to sleep. There have been several eureka moments but that was certainly the first," he said.

"After it was found that methyldopa in a single daily dose produced significant reductions in blood pressure in three patients, the observations were sufficiently impressive that Merck put the drug into pilot plan production, making kilograms instead of grams of the drug," Oates said. The NIH group extended the initial findings in a placebo-controlled trial in 10 hospitalized patients, most of whom had very severe hypertension. The study concluded once again that methyldopa lowered blood pressure in all of the patients. This was quite in contrast to the lack of such an effect in experimental animals. That decision to evaluate in hypertensive patients was crucial," Oates said. The study was published in *Science.*

The NIH group went on to find that the hypotensive effect of methyldopa was not related to decarboxylase inhibition, but the reduction in blood pressure was due to an active metabolite of the drug.

The widely used drug, with the trade name of Aldomet, was used for about 15 years, from 1960 to 1975 as the major drug to treat severe hypertension. It proved to be a multi-billion-dollar drug for Merck Pharmaceuticals, and is still the drug of choice in certain patient populations such as pregnant women.

"It was such a valuable discovery for that window of time," Oates said.

Oates, Thomas F. Frist professor of Medicine at Vanderbilt, left his senior investigator position at the National Heart Institute and joined the department of Pharmacology at Vanderbilt in 1963. He was recruited to Vanderbilt to lead clinical pharmacology, a program which is recognized internationally as the best residency training program in this discipline. "I saw Vanderbilt as an environment where there was a vision of bridging basic sciences with clinical medicine."

At Vanderbilt, Oates was involved in another exciting discovery – that of one drug blocking another. He found that a certain group of tricyclic antidepressant drugs blocked the action of some common anti-hypertensive drugs, such as guanethidine.

A woman treated in the medicine clinic was taking a very large dose of guanethidine. She was also taking desipramine, one of the tricyclic anti-depressants. Because the anti-hypertensive drug was not working, Oates took her off the antidepressant and left the blood pressure drug as it was.

"I saw Vanderbilt as an environment where there was a vision of bridging basic sciences with clinical medicine."

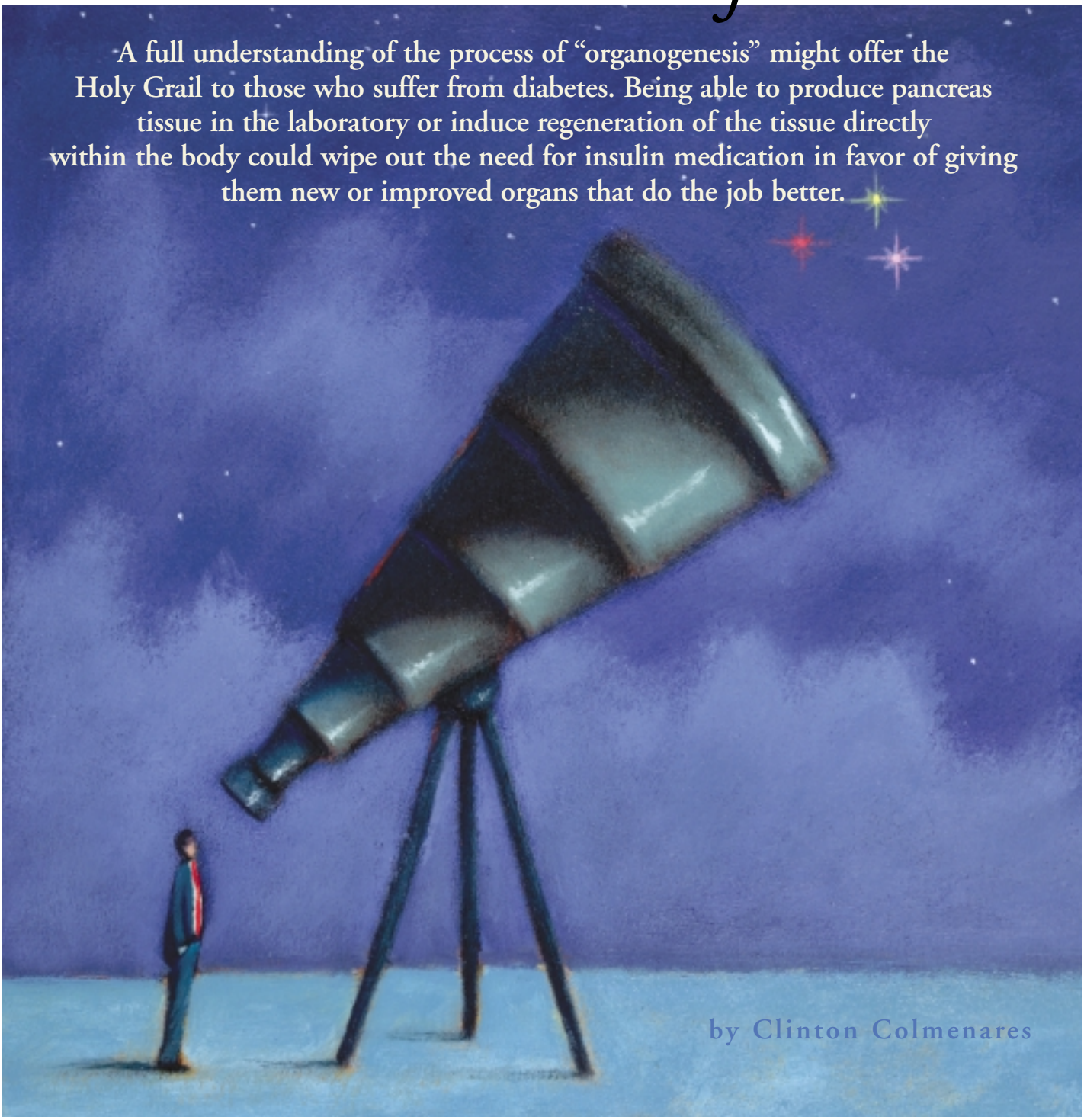
"A few days later we received a call from the patient. She couldn't stand up. The same drug that was not working before, was now working excessively. So with one patient in the clinic, we observed a very potent clinical drug interaction of one drug blocking the action of another."

To further study this observation Oates worked with Jerry Mitchell, then a Vanderbilt M.D/Ph.D. student, who would become president of Upjohn, to carry out studies that characterized this drug interaction. In the investigations that defined the mechanism of the drug interaction, the mechanism for guanethidine's selective action on blood pressure was also elucidated.

A Fellow of the American Academy of Arts and Sciences for his overall contributions to the field of medicine through teaching, research and writing and a member of the Institute of Medicine, Oates served as chair of the Department of Medicine from 1983 until 1997.

finding *the* Holy Grail *of* diabetes

A full understanding of the process of "organogenesis" might offer the Holy Grail to those who suffer from diabetes. Being able to produce pancreas tissue in the laboratory or induce regeneration of the tissue directly within the body could wipe out the need for insulin medication in favor of giving them new or improved organs that do the job better.



by Clinton Colmenares

Christopher Wright, D.Phil, professor of Cell and Developmental Biology and director of the Vanderbilt Developmental Biology Program, has been working on this process since 1987 when he was a postdoctoral fellow with Eddy De Robertis. He was studying fundamental developmental processes, and focusing on homeobox genes – which encode proteins regulating batteries of other genes that direct the development of entire body parts. These genes are present in vertebrates, but were first discovered in *Drosophila*, more commonly known as fruit flies.

Wright was studying another model system, frogs (*Xenopus laevis*) and was the first to find a homeobox gene in vertebrates, dubbed *Pdx1*, that is responsible for forming the pancreas, where insulin is produced. The expression pattern of Pdx1 was so specific to the pancreatic region of the embryo, and unlike any other gene found previously, that he predicted: "If you knock out Pdx1 in a mouse, it won't develop a pancreas," he said.

He was right. The pancreas was completely missing in mice lacking the Pdx1 gene, achieved experimentally with gene "knock out" strategies. Subsequent studies from other laboratories have found the same defect in infants with mutations in the human Pdx1 gene.

If Wright and his collaborators at Vanderbilt and at other research institutions are successful, they will determine the precise combinations of genes that work together during the formation of precursors for organs like the pancreas during embryogenesis, and determine if similar cells exist in and can be purified from the mature pancreas. Such "organogenesis" work might make an end-run around drug therapy.

"It would be a gratifying success if we were able to find a reliable and reproducible way of converting a fraction of another organ, say the liver or small intestine, into pancreas tissue that's long-lived, functional and normal (non-cancerous)," Wright said.

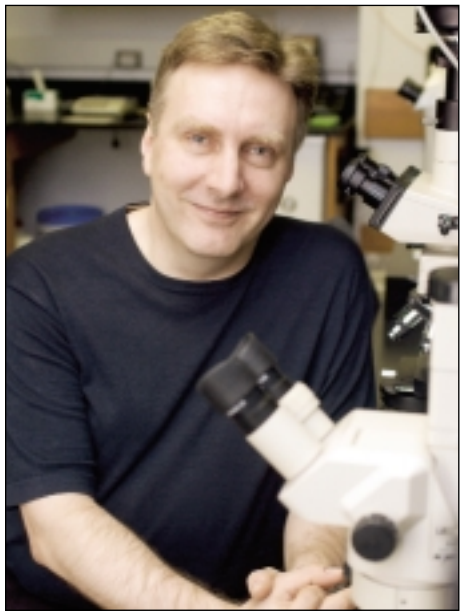
The past 12 years have seen the first molecular inroads into the basic cell biology of how pancreatic tissue is formed in embryos and how pancreas tissue functions in adult mammals. There is strong evidence that the information generated from mouse studies can be directly applied to humans, Wright said.

Wright and scientists from other departments, including Dr. Mark Magnuson and Roland W. Stein, Ph.D., both professors of Molecular Physiology and Biophysics, and Maureen Gannon, Ph.D., assistant professor of Medicine – who make up part of the Beta Cell Biology Consortium, an international group of research laboratories attacking diabetes at the biochemical, cellular and physiological levels – are trying to understand how to activate Pdx1 and similar genes, in exactly the right way and at the right time, to use them as a series of molecular switches to spark other cells into forming a pancreas.

It would be a gratifying success if we were able to find a reliable and reproducible way of converting a fraction of another organ, say the liver or small intestine, into pancreas tissue that's long-lived, functional and normal (non-cancerous).

It may be possible to activate the switches in undifferentiated embryonic stem cells, directing them to form proper pancreatic tissue, or at least form cells that carry out the pancreas' normal functions, Wright said. Such converted cells could one day be implanted into an organ, like the liver, to carry out the pancreas' function in addition to its own.

The liver is the best location for these cells because it has a heavy network of blood vessels. There have been recent successes in Canada in which islet cells derived from organ donors were transplanted into the liver, removing the need for diabetic patients' daily insulin injections. If researchers could reprogram an individual's own hepatic cells to act as pancreatic islet cells, responding to blood glucose levels, then the blood vessels could deliver insulin (and, under different signals, other pancreatic hormones) rapidly into the blood stream, thereby mimicking the most basic functions of the pancreas.



DANA JOHNSON

CHRISTOPHER WRIGHT, D. PHIL

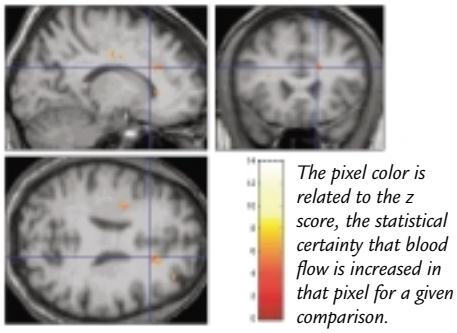
Part of learning how to make a surrogate or substitute pancreas involves knowing what might go wrong in embryonic development or in certain forms of cancer, so scientists know which of Mother Nature's errors can and should be avoided.

"It's really exciting being on the brink of discovering exactly how such an important organ is formed, and linking this to what goes wrong, genetically and functionally, in diabetes, with the real hope of providing life-enhancing therapies," Wright said.

by Elizabeth Roth

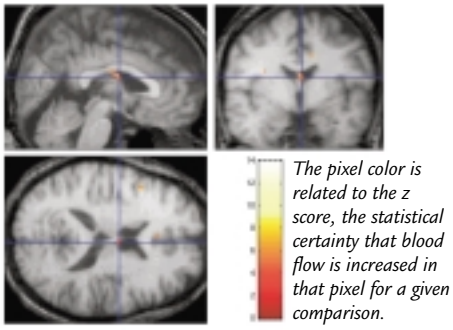
For many years, scientists had only a rudimentary grasp of how the brain operated, with most of their research based on the brains of other mammals or human cadavers. The fundamentals of brain biochemistry and function, much less how this three-pound organ responded to various drugs, eluded even the most erudite scientists.

the powerful tool of fMRI



The pixel color is related to the z score, the statistical certainty that blood flow is increased in that pixel for a given comparison.

In this study of brain activation with fMRI in patients with Irritable Bowel Syndrome, the subjects were undergoing painful rectal distension which simulates IBS pain during the scans. The image shows brain activation during amitriptyline, an antidepressant used for pain, subtracted from placebo activation. This image depicts activity in the anterior cingulate gyrus, an area thought to mediate pain and suffering.



The pixel color is related to the z score, the statistical certainty that blood flow is increased in that pixel for a given comparison.

Brain activation during amitriptyline subtracted from placebo activation. This image depicts activity in the dorsomedial thalmus, a limbic-related area that is thought to be involved with suffering during pain.

Profound advances in technology now offer researchers unprecedented opportunities to understand how the brain works, a prelude to a glimpse of how the mind works. Noninvasive imaging techniques can be used to gather hard to obtain information on *in vivo* physiology and biochemistry in experimental subjects. For example, functional magnetic resonance imaging (fMRI) and data analysis allow researchers to identify parts of the brain that are performing or monitoring certain functions.

Drug discovery and development are natural applications for fMRI research. Armed with a better understanding of brain circuitry, physiology, and function, scientists can now work toward developing targeted therapeutic interventions. *In vivo* brain imaging approaches such as single photon emission computed tomography (SPECT), magnetic resonance spectroscopy (MRS), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI), are becoming multimodal approaches to building a better understanding of the pathophysiology of a disorder.

Vanderbilt's commitment to imaging technology and the tremendous promise it offers is evident in the recent hiring of John Gore, Ph.D, professor of Radiology and Radiological Sciences and of Biomedical Engineering, who is bringing a team of investigators with him from Yale University as he assumes his new role as a Director of the VU Imaging and Research Center on July 1.

"Imaging can provide important information on the effectiveness of drugs," said Gore. "In the brain, functional MRI can provide pictures of the networks of brain regions that are active in performing specific tasks and the manner in which new pharmacologic agents affect brain activity so that the treatments of psychiatric disorders such as schizophrenia can be measured."

Pat Levitt, Ph.D., director of the John F. Kennedy Center for Research on Human Development at Vanderbilt, said the recruitment of Gore marks an unparalleled opportunity for advancing the understanding of brain development and disabilities that affect children.

"Noninvasive technologies such as fMRI and magnetic resonance spectroscopy provide a window into the developing human brain that is already elucidating, for the first time, the ways in which children use their functional circuitry differently compared to adults," Levitt said. For the study of children with developmental disabilities, new imaging methods will help us define the very circuitry we wish to improve through intervention."

Physicians like Vanderbilt gastroenterologist Dr. Howard Mertz, associate professor

of Medicine, are interested in physiological differences in the brains of individuals afflicted by Irritable Bowel Syndrome (IBS).

Mertz studied control subjects and patients with IBS, performing fMRI scans as a rectal balloon was inflated to mimic IBS symptoms. He observed marked differences in the brain scans of the two groups, suggesting that IBS patients respond to pain more vigorously.

IBS patients also were scanned following either drug or placebo treatment. The scans of the patients taking medication revealed a significant difference in some areas of the brain. Objective findings such as these provide patients with peace of mind – their symptoms are not psychosomatic nor is their response to drug therapy. Additionally, they encourage the scientific and medical community to envision extensive possibilities offered by advancements in current fMRI technology, Mertz said.

Vanderbilt Diabetes Center investigators are also hopeful about the applications of the fMRI.

"fMRI provides a non-invasive way of studying lipid and carbohydrate metabolism," said Dr. Daryl K. Granner, Joe C. Davis Professor of Biomedical Science and director of the Vanderbilt Diabetes Center, adding that there are very few places in the United States with the equipment and professional expertise to do these studies. "This procedure offers a unique window through which one can look at what is happening in liver, skeletal muscle, heart and adipose tissue in normal persons as compared to those with a metabolic disorder such as diabetes. After establishing a baseline value, one can measure the effectiveness of an established or new therapeutic agent."

Vanderbilt schizophrenia researcher Dr. Herbert Y. Meltzer, Bixler/Johnson/Mays Professor of Psychiatry, views fMRI as the best means of studying the intricate neural circuits in living subjects. Neural circuit abnormalities underlying core symptoms, such as auditory hallucinations, and cognitive deficits, such as working memory or attention, can be mapped with fMRI as can the effects of drugs administered to improve or partially correct these defects.

Schizophrenia studies conducted by Meltzer have already revealed abnormal patterns of activation of the cortex and hippocampus, two brain regions believed to be key to various types of memory deficits present in schizophrenia.

"fMRI is a most important tool for research into the etiology and pathophysiology of schizophrenia and for understanding the mechanism of action of antipsychotic drugs," Meltzer said.

Ronald R. Price, Ph.D., professor of Radiology and Radiological Sciences and director of the division of Radiological Sciences, said it's possible that fMRI may make it possible to one day understand and treat complicated diseases like autism or manic depression, but he cautions against looking at fMRI as an instant solution.

Victoria L. Morgan, Ph.D., assistant professor of Radiology and Radiological Sciences assists investigators in designing a research study using techniques that are likely much different from their past research endeavors. Additionally, fMRI research requires proper collection of the data as well as a strong knowledge of the analysis software.

"It's a very powerful tool, and I think that its first limitation is the ingenuity of the person using it," said Price. "Both the initial research and the subsequent analysis can be time consuming, but are necessary components to ensure the integrity of the results."

measuring molecules

Like fMRI, mass spectrometry can provide scientists detailed data that can be used for developing more efficacious, targeted drugs. Scientists such as Vanderbilt's Richard M. Caprioli, Ph.D., Stanley Cohen Professor of Biochemistry, are hard at work, pioneering new strategies to fight disease through the use of this technology.

In addition to the structure, mass, and molecular weight, the sequence of proteins can also be deduced using mass spectrometry. Because almost every drug is targeted to proteins, mass spectrometry is used in the course of development for many drugs. Understanding what proteins are affected by a particular drug therapy can provide scientists and physicians with invaluable ammunition in their battle with disease.

"Once we understand what the molecular events are within the disease, we have a chance of controlling them," Caprioli said. "With mass spectrometry, you're measuring molecules so you know exactly what has changed, exactly what it has changed into, and where it went. The thinking is to uncover the molecular events and then design drugs that will stop a tumor in many places."

Nowhere are such innovations more promising than in the field of cancer. The insidious nature of the disease allows it to withstand treatment and in some cases, come back stronger than before, unresponsive to previous drug treatments. With a solid understanding of the molecular events in an individual cancer, physicians can bombard the cancer with multiple drugs, cutting the disease off at every pass and inhibiting it in so many ways that it cannot recover.

Such promising advances in mass spectrometry are amazing even to those who have been in the field for years.

"Even 10 years ago, what we're doing now would have been unthinkable," Caprioli said. "The pot of the gold at the end of the rainbow is so inspiring – there is a chance that the work we're doing can contribute one day even in a small way to the elimination of disease."

– ELIZABETH ROTH

DANA JOHNSON

hoping *for a* touchdown

If he were a National Football League quarterback, Larry Marnett estimates his team would be positioned at about his opponent's 25-yard line, steadily making its way toward the end zone.

by Cynthia Manley

The biochemist at Vanderbilt University Medical Center is working to develop new aspirin-like compounds that hold the potential for relief of pain and inflammation, prevention and treatment of cancer, and benefits for patients with a host of other diseases.

Since reporting the first of these compounds in the journal *Science* in 1998, Marnett and his team in the A.B. Hancock Jr. Memorial Research Center have developed about 380 compounds of varying chemical structure. The goal is to develop a partnership with a pharmaceutical company to take their discoveries further – and ultimately into the marketplace.

So far, the large pharmaceutical companies that Vanderbilt has approached have deemed the work too "early stage" for their interest, but Marnett's group is working to advance the research, looking at smaller companies that might have an interest and carefully watching the market for similar drugs.

"The big companies want us to get it to the five-yard line, so they can pick it up and run it in for a touchdown from there," said Marnett, Ph.D., director of the Hancock Lab and Mary Geddes Stahlman Chair in Cancer Research.

These new compounds selectively inactivate an enzyme called cyclooxygenase-2 (COX-2) while sparing its stomach-protecting cousin, COX-1. This selectivity provides benefit with less risk of gastrointestinal toxicity, as is found in drugs like aspirin and non-steroidal anti-inflammatories that affect both enzymes.

The overwhelming success of the first two selective COX-2 inhibitors to reach the market – Celebrex (developed by Monsanto, now a product of Pharmacia) and Merck's VIOXX – has dampened interest in new drugs to target the enzyme. Combined, these had more than $5 billion in sales last year in only their second year on the market. "They are juggernauts," Marnett said.

However, the landscape may be changing. Concerns have been raised about potential cardiac toxicity with VIOXX, and in March, Merck withdrew its new drug application to the Food and Drug Administration for a second-generation form of VIOXX, saying it wanted to include more safety data and indications for a new use in its application.

"The question is, how serious is the cardiac toxicity and is it compound-specific?" Marnett said. "Would another chemical structure avoid that? So the timing is probably good to look at new structures. I believe the opportunity for our compounds is stronger now."

Marnett and his team have developed two classes of compounds that selectively target COX-2. One group of about 80 compounds effectively "kill" the enzyme by permanently binding to it. The other group, of which the team has made about 300, ties up the enzyme temporarily but eventually breaks away, freeing the enzyme for activity.

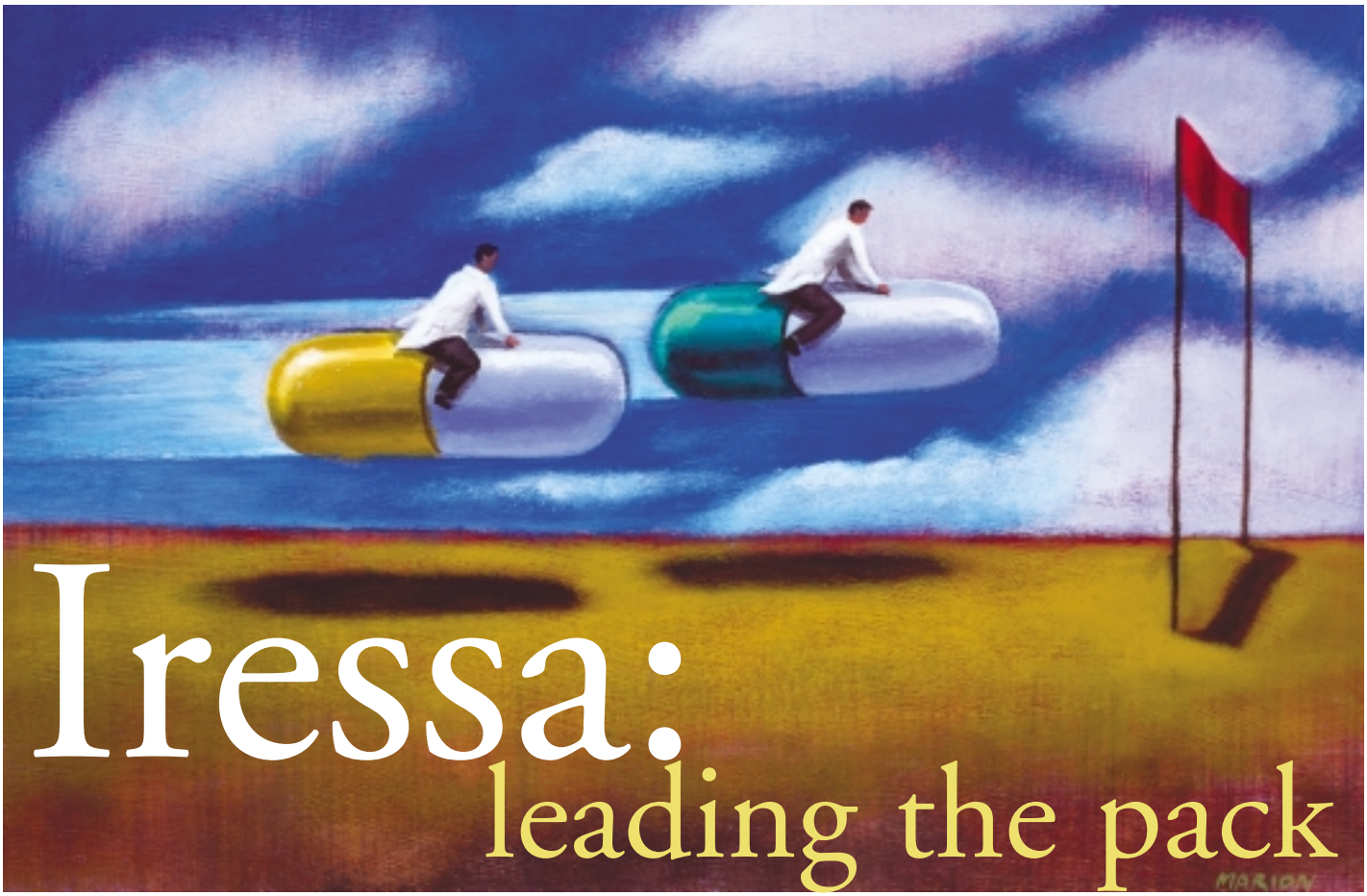
"We've made a few hundred compounds, but that's nothing in the pharmaceutical world," Marnett said. "Monsanto made 6,000 derivatives before zeroing in on the Celebrex compound." He added that such a high volume of production is impossible for an academic center like Vanderbilt with its limitations in space and personnel.

Marnett and his team are exploring new opportunities for the technology, including targeting smaller pharmaceutical companies that would be interested in "niche markets" for selective COX-2 inhibitors and would be willing to further develop the compounds. "A smaller company might be interested in a compound with the potential to generate sales of $100 million, whereas the big companies are looking for much larger returns," Marnett said. "That would still result in an income of maybe $5 million to the university."

In the meantime, the research is paying off in other ways.

They are working to develop X-ray detection of COX-2 in tumors, which would help physicians target therapy combining COX-2 inhibitors with other anti-cancer drugs. And they are further exploring the basic functioning of COX-2. This work has led them to discover a new class of COX-2 substrates (the raw material the enzyme uses to produce prostaglandins). This finding may provide other targets for interfering with the enzyme's activity and may also lead scientists to an explanation for why both COX-1 and COX-2 exist, Marnett said.

"All this is the direct result of our drug discovery work," he said.



Iressa: leading the pack

When Vanderbilt's Stanley Cohen won the Nobel Prize in 1986 for the discovery of the epidermal growth factor, news articles noted his work's "important implications" for cancer treatment.

Decades after his discovery, drugs that selectively target the complex signaling pathway that involves EGF and its receptor are generating much excitement and anticipation in the cancer community.

Leading the pack in the drug development process appears to be Iressa, which blocks the activity associated with the EGF receptor tyrosine kinase. Abnormal EGF signaling may be involved in a third of cancers, including common tumors such as lung, colon and breast. The U.S. Food and Drug Administration is currently reviewing Iressa for potential approval later this year. Vanderbilt-Ingram Cancer Center investigators have been closely involved in all phases of clinical testing of Iressa. This involvement includes Dr. David Johnson's leadership of a national, multi-institutional trial of Iressa in patients with non-small cell lung cancer.

"The excitement about this drug and others like it is that they appear to be very selective in their action with few side effects," said Johnson, Cornelius Abernathy Craig Professor of Medical Oncology and deputy director of the Vanderbilt-Ingram Cancer Center.

"The other major advantage is that many of them can be given in an oral form, which makes treatment much more convenient for the patient."

The national lung cancer trial has closed and its results are being analyzed, but Vanderbilt-Ingram is currently enrolling patients in trials with Iressa in colon and breast cancer.

Not all patients have responded to Iressa. In fact, Dr. David Carbone, Ingram Professor of Cancer Research, told participants in a lung cancer education event last fall that it appeared that fewer than 20 percent of patients who had failed previous chemotherapy would respond to Iressa.

by Cynthia Manley

"It's not a miracle," he said. "But for that percentage, it appears to be working very well."

And, Carbone said, this scenario may well be the future of cancer therapy.

"We're hoping to build up an entire set of new drugs," he said. "Maybe each drug will only work for 5 percent of patients, but for that 5 percent, it will be just what they need."

A good example is Dorothy Arvin, a patient of Carbone who may hold the distinction of having had the first complete response to Iressa. In January of 1999, the grandmother from southern Indiana faced a particularly lethal form of cancer, bronchioalveolar carcinoma. After taking two Iressa pills daily for more than two years, there is no visible sign of the cancer that had taken hold in both lungs – and she is living life to its fullest. "I'm not taking anything for granted anymore," Arvin said.

Dr. Carlos Arteaga, whose laboratory has focused on understanding the EGF receptor and its role in cancer, shares his enthusiasm about Iressa and other EGF-receptor targeted therapies with moderate skepticism. While they represent a large step forward, Arteaga anticipates that as they are combined with other drugs, unexpected toxicities may become apparent.

He is also skeptical that these "magic bullets" used alone would be enough to cure advanced metastatic cancers. Cancer cells protect themselves from destruction through complicated and redundant signaling programs. Stopping the signal at a single point is probably not enough to halt cancer progression and/or eliminate the tumor cell, he said. "Unless we think cancer cells are that naive – and they are very smart – we have to think about targeting these signaling programs, like the EGF receptor network, simultaneously in combination with other anti-signaling approaches and molecular therapies."

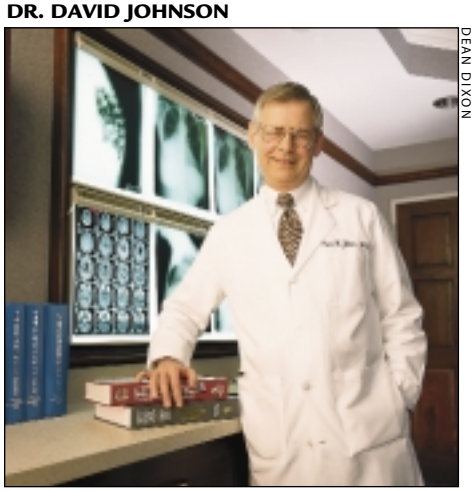
The most logical use of Iressa and other targeted therapies will be in combination with each other or with more traditional therapies, Arteaga said. One trial at Vanderbilt-Ingram, for example, combines Iressa with Herceptin in breast cancer patients. Herceptin targets a mutant receptor molecule, called HER2/neu that is part of the EGF signaling family.

"One of the reasons tumor cells overexpress these signals is to have a survival advantage," he said. "If we administer something like chemotherapy or radiation that threatens the cells' survival, then add Iressa or a similar targeted agent, we may enhance the treatment's effectiveness."

Dr. Robert Coffey, director of Vanderbilt-Ingram's Specialized Program of Research Excellence in Gastrointestinal Cancer, noted that the EGF receptor signaling pathway provides a variety of targets. These include the points where EGF is released from the cell surface, the point on the cell surface where EGF binds and the point inside the cell where the newly received signal is passed along toward the nucleus through a chemical reaction.

The GI SPORE, funded with a $13 million grant from the National Cancer Institute, includes projects to test Iressa in colorectal cancer as well as to evaluate combinations of drugs that target the EGF receptor pathway as well as another cancer-related enzyme, cyclooxygenase-2 (COX-2).

DR. DAVID JOHNSON



DEAN DIXON

The latest on EGF receptor inhibitors

The big cancer news last year was the approval of Gleevec, the so-called "leukemia pill" that targets an enzyme specifically involved in chronic myelogenous leukemia and a rare tumor of the stomach.

The excitement went beyond a significant improvement in care for the relatively small number of patients with these types of cancer. For many scientists it was proof that agents could specifically target molecules found only or primarily in cancer cells themselves.

Gleevec and other drugs coming along behind it inhibit a group of enzymes inside cells called tyrosine kinases. These enzymes represent critical steps in the chain that carries signals from outside the cell to its control center, the nucleus.

The first tyrosine kinase, the epidermal growth factor receptor (EGFr), was discovered at Vanderbilt by Nobel laureate Stanley Cohen, Ph.D., and Graham Carpenter, Ph.D., Ingram Professor of Cancer Research. Other tyrosine kinases include HER2/neu, a cousin to EGFr, both of which are found in breast and other cancers; platelet-derived growth factor receptor, which is overexpressed in some brain tumors; the TRK and RET proto-oncogenes, found in high levels in neuroblastomas and thyroid cancers, among many others.

In a growing number of cases, scientists have figured out the three-dimensional structure for these kinases, which allows drugs to be developed to fit into these molecular "pockets" and block kinase activation.

"Typically, these inhibitors are small enough to be given orally, be absorbed quickly and exhibit good penetration into the tumor tissues," said Dr. Carlos Arteaga, Ingram Professor of Cancer Research, who is conducting laboratory and clinical research with EGF receptor inhibitors.

EGF and its receptor are part of a complicated signaling network that includes four known receptors and eight known ligands (like EGF, the molecules that bind to the cell-surface receptor to send the signal into the cell). In addition, the four receptors can work together in various "two-headed" combinations with which different ligands can interact. Potentially any of these ligands, receptors and combinations give scientists targets for therapeutic agents to shut down the signaling and interrupt cancer growth.

– CYNTHIA MANLEY

the story behind the story of Viagra

by Mary Beth Gardiner

Audiences don't snicker as much as they used to when Jackie Corbin talks about his research. It seems that the public has gotten used to hearing about – and even talking about – male erectile dysfunction.

In the days and months after news of Viagra hit the papers and then filtered into magazine and television ads, Corbin took a lot of ribbing. Now, people are generally eager to hear the story behind the story, so to speak, and Corbin is happy to provide the details of how the search for a means to lower blood pressure gave rise to one of the best selling drugs in history.

JACKIE CORBIN, PH.D.

DANA JOHNSON

Corbin, professor of Molecular Physiology & Biophysics, has been interested in cell signaling since his days as a Vanderbilt graduate student. His research has focused specifically on how two signaling molecules – called cyclic AMP and cyclic GMP – affect a broad range of functions in the body, from vision to heart function to the breakdown of fat.

When Corbin joined the faculty in 1971, he turned his attention to cyclic GMP and its role in regulating smooth muscle function in blood vessels. Buttressed by the expertise of fellow faculty member Sharron Francis, the two labs joined forces to identify a new protein in smooth muscle called phosphodiesterase-5, or PDE-5, that breaks down cyclic GMP. Knowing that increased levels of cyclic GMP cause smooth muscle relaxation, the researchers reasoned that inhibition of PDE-5 might lower blood pressure.

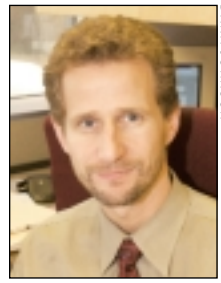
A number of drug companies tried to harness PDE-5 in a drug, but were largely unsuccessful. Pfizer Pharmaceutical, however, had results promising enough to warrant a small clinical trial.

By chance, the physician of one of the enrolled patients learned that the man's ability to sustain penile erection was enhanced while taking the drug. When Pfizer questioned the other men in the study, they reported the same effect. The company hastened to arrange a clinical trial with the new goal in mind of producing a treatment for male impotence, and the drug Viagra was born.

Corbin was delighted, but not entirely surprised by his contribution to the discovery of Viagra.

"Most of the time discoveries in the lab build on others," he says. "New concepts are somewhat rare; new observations are more the norm, shedding light on how different processes relate to one another. A scientist should always keep in mind how things fit into the bigger picture."

Heart study looks at ethnicity factors


DANA JOHNSON

DR. DON CHOMSKY

It's been nearly 20 years since a study showed Ace-Inhibitors were more effective in the treatment of heart failure than the standard drug combination of hydrazaline and nitrates.

Since that time the drug combination has rarely been used. But a cardiologist at Vanderbilt University Medical Center thinks that will change.

Dr. Don B. Chomsky, assistant professor of Medicine and director of Cardiac Transplantation, is enrolling patients in a drug study to take a closer look at the drug combination now thought to have little use in standard therapy.

The original study, VHeFT II, a cooperative study of Veteran's Administration hospitals, explored the use of hydrazaline and nitrates vs. Ace-Inhibitors for use as standard therapy. The patient population for that study consisted mostly of Caucasian males. Based on the results, Ace-Inhibitors proved to be the superior treatment option. It soon replaced the drug combination in the therapeutic protocol.

But a recent review of this study led physicians to reconsider the drug combination's role in standard therapy.

"What is becoming clearer and clearer is that not all medications work the same way in all ethnic groups," said Chomsky. "For example, we see this in some blood pressure medications. When researchers reevaluated the VHeFT II study, they found that the African-Americans enrolled in the study did better on the combination therapy than when treated with a placebo or Ace-Inhibitor.

"But the results of the study were based on the overall outcome, which was based on a patient population made up mostly of Caucasians."

Under the new multi-center study AHeFT (African-American Heart Failure Trial), Vanderbilt will enroll at least 15 patients with moderate to severe chronic congestive heart failure. The study will be a comparison between standard therapy, which consists of Ace-Inhibitors, digoxin, beta blockers and diuretics and a placebo vs. standard therapy along with a drug combination of hydrazaline and nitroglycerine, now called Bidil. More than 600 patients are expected to be enrolled in the nationwide study.

Bidil would act as a vasodilator to decrease resistance to flow in blood vessels and thereby decrease stress on, and increase performance of, the heart. The objective of the study is to demonstrate the efficacy and safety of Bidil when combined with standard therapy.

"Identifying the most appropriate regimen for African-Americans with heart failure also raises greater issues about our decision-making about medical therapies based on studies often using populations that are not representative of the population most affected by a disease," Chomsky said.

African-Americans are diagnosed with heart failure at a higher rate due to the higher prevalence of hypertension, diabetes and coronary disease. The death rate from cardiovascular disease including heart failure in the 1990's was 353 per 100,000 for blacks and 244 per 100,000 for whites. - JESSICA PASLEY

Vanderbilt to create a Comprehensive Diabetes Care Center

The Vanderbilt Diabetes Center marked more than a quarter century of discovery, training, and patient care recently with a day-long scientific symposium and the announcement of a bold new initiative – the planned creation of the Vanderbilt Comprehensive Diabetes Care Center.

Dr. Harry R. Jacobson, vice chancellor for Health Affairs, made the announcement at a celebration dinner that included featured speakers Dr. Phillip Gorden, MD'61, former director of the National Institute of Diabetes and Digestive and Kidney Diseases, Dr. Oscar B. Crofford, professor of Medicine, Emeritus, and Dr. Daryl K. Granner, Joe C. Davis Professor of Biomedical Science and director of the Vanderbilt Diabetes Center.

"The clinic would provide expertise and talent in one physical location to treat patients from first diagnosis throughout life, with seamless transition from pediatric to adolescent to adult care," Granner said.

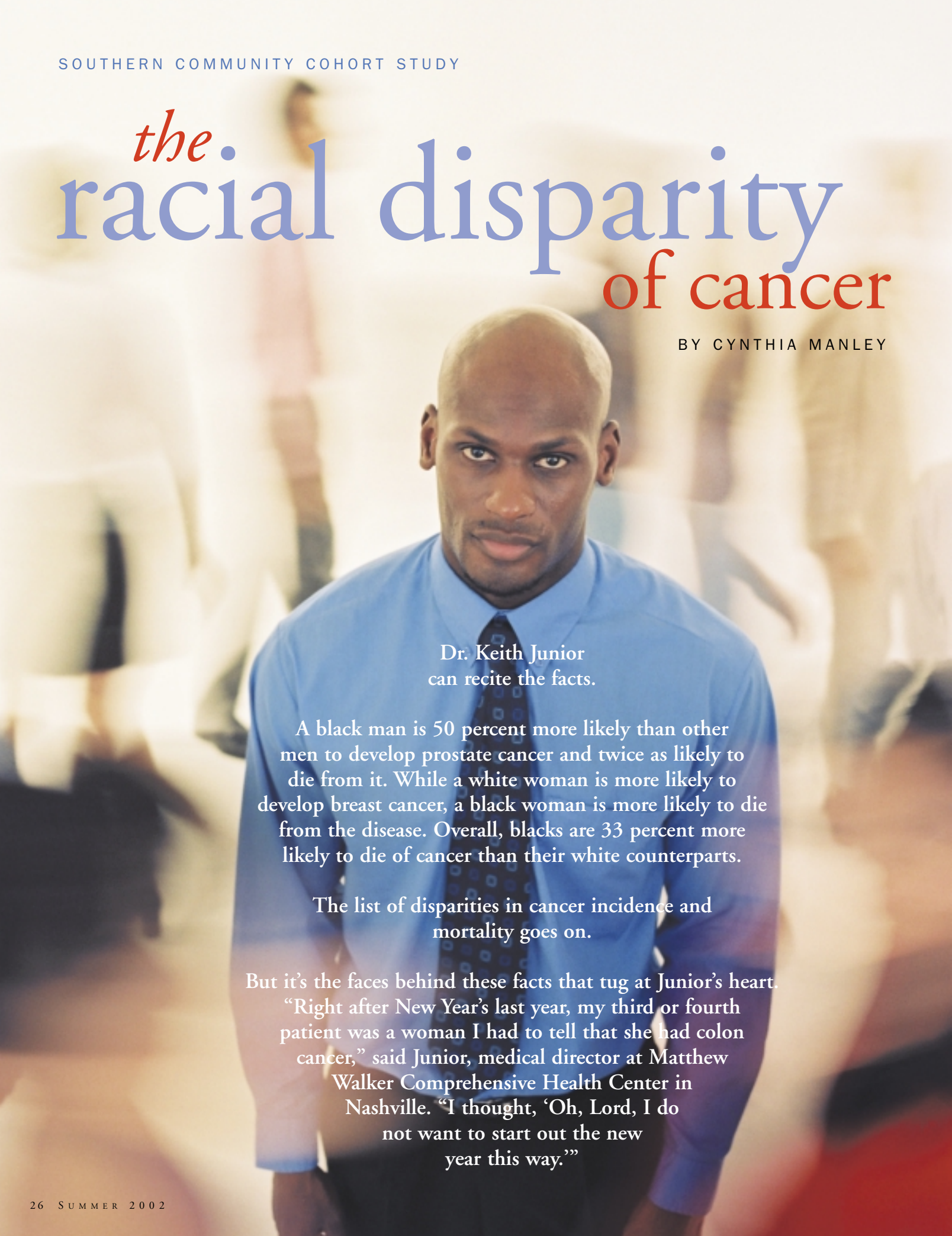
Most diabetes patients see a series of doctors over the course of their disease, often encountering a new philosophy or approach to treatment with each change. The new clinic, as it is planned, would obviate such inconvenience and worry with a broad, multi-disciplinary care program.

"This novel approach would place Vanderbilt among only a handful of centers in the nation that provide extensive, lifelong diabetes care," Jacobson said.

The mission of the VCDCC, pending its approval by the Board of Trust, would embody a number of wide-ranging goals for providing unparalleled patient care. Each patient would be able to expect an effective treatment regimen for normalization of blood glucose levels, a risk reduction regimen for prevention of diabetes-associated complications, effective treatment for existing diabetes complications, and rapid access to innovative therapeutic discoveries from clinical research. - MARY BETH GARDINER

the racial disparity of cancer

BY CYNTHIA MANLEY



Dr. Keith Junior can recite the facts.

A black man is 50 percent more likely than other men to develop prostate cancer and twice as likely to die from it. While a white woman is more likely to develop breast cancer, a black woman is more likely to die from the disease. Overall, blacks are 33 percent more likely to die of cancer than their white counterparts.

The list of disparities in cancer incidence and mortality goes on.

But it's the faces behind these facts that tug at Junior's heart. "Right after New Year's last year, my third or fourth patient was a woman I had to tell that she had colon cancer," said Junior, medical director at Matthew Walker Comprehensive Health Center in Nashville. "I thought, 'Oh, Lord, I do not want to start out the new year this way.'"

Junior is not just doctor to his patients with cancer. He is a fellow cancer survivor, diagnosed and treated for kidney cancer 13 years ago, just before he graduated from medical school. He feels the heavy burden of cancer (and other diseases) faced by African-Americans.

That's why he's giving his time and his name to a potentially historic study that will soon begin enrolling participants at Matthew Walker and 21 other federally funded community health centers in Tennessee, Alabama, Florida, Mississippi, South Carolina and Georgia.

Funded by a five-year, $22 million grant from the National Cancer Institute, the Southern Community Cohort Study will enroll and follow 105,000 people, two-thirds of them African-Americans. The group, or cohort, will be tracked to identify genetic, environmental and lifestyle factors that contribute to cancer development – the reasons why blacks are at higher risk and why residents of the southeastern states face a greater risk than other regions.

"Often in our own lives, we get too focused on the ditch we're digging," said Junior, who personally wrote his patients asking them to consider participating in the pilot study last year. "This study will allow us to pick up our heads and look around. We may not directly benefit ourselves by participating in this study, but I look at it this way. Like Moses, if I don't make it to the Promised Land, I hope God will let me lead someone else to it. And that someone is someone we care about deeply – our children and our grandchildren."

The initiative is a collaboration of the Vanderbilt-Ingram Cancer Center, nearby Meharry Medical College, and the International Epidemiology Institute, based in Rockville, Md. Its funding is a significant accomplishment for the Meharry-Vanderbilt Alliance, launched in 1999 to promote collaboration between the two medical schools. In addition to the community health centers, its partners also include staff from Jackson State University in Jackson, Miss., the University of South Florida, and Westat, a research corporation.

The project will be the first study of its kind in the southern United States and the largest population-based health study of African-Americans ever conducted.

"But it can be done," Junior said. "We have to do it. Information is powerful. The grocery store knows what I eat (by tracking purchases on a bar-coded card). If we can gather that kind of information, we can look at it carefully and say, 'hey, these are the things that are putting you at risk and these are the things you can do about it.'"

"This is a challenge that we must meet to ensure that the benefits from medical advances are shared equally, regardless of race, ethnicity, geography or economic status." – Dr. Harry R. Jacobson

The community health centers and their medical and other staff, like Junior, will play a crucial role to the success of the project, in building relationships with potential participants in the study.

"It's wonderful for the health centers to be involved in this," said Michelle Marrs, chief executive officer at Matthew Walker, which participated in a pilot study. "Many people will participate in this study because of the relationship that exists between them and their community health center."

Lifestyle information gathered in the Cohort study is expected to yield important insights into other health concerns, including diabetes and heart disease.

"This is a challenge that we must meet to ensure that the benefits from medical advances are shared equally, regardless of race, ethnicity, geography or economic status," said Dr. Harry R. Jacobson, vice chancellor for Health Affairs at Vanderbilt University Medical Center.

John E. Maupin Jr., DDS, president of Meharry Medical College, said he is hopeful that this study will shed light on why people behave certain ways and how those behaviors relate to disease. "Once we have a handle on that, the scientific community will be in a position to develop culturally sensitive interventions to impact health behavior and to have a demonstrable effect on health status and outcomes."

The study will explore several specific factors that may play a role in the disparities. These variables include the higher-fat "southern diet" and potential differences in activity levels, body mass index, use of over-the-counter medications (including aspirin and non-steroidal anti-inflammatory drugs), use of folk and herbal supplements, tobacco use, metabolism of carcinogens and genetic factors.

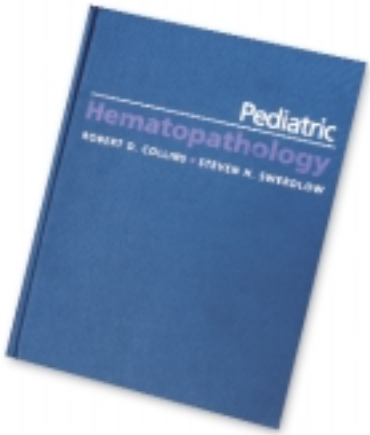
Participants must be 40-79 years of age, not currently diagnosed with or under treatment for a terminal illness, and willing to be contacted (and keep in contact with the study coordinators) in the future.

The study will involve a survey of lifestyle and health history information, follow-up contact every other year, and the optional collection of blood and saliva samples. These samples will be invaluable sources for DNA testing as new genes and proteins are identified and new technologies are developed to identify "markers" of disease risk.

Information will also be gathered from the federal government's National Death Index and state cancer registries to determine whether individuals in the study have died or been diagnosed with cancer.

For more information about the study, visit www.southerncommunitystudy.org.

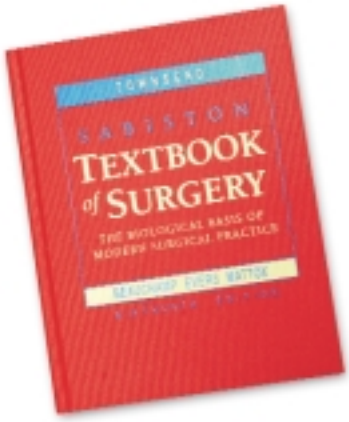
spring book reviews



Pediatric Hematopathology

By Drs. Robert D. Collins, professor of Pathology, VUMC, and Steven H. Swerdlow, professor of Pathology, University of Pittsburgh School of Medicine, 2001, Churchill Livingstone, 422 pages

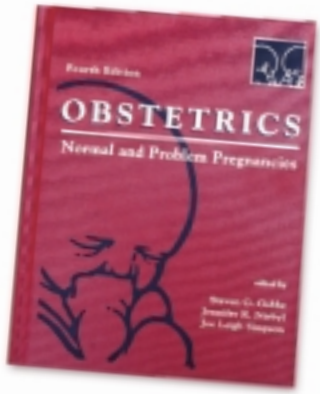
The goal of *Pediatric Hematopathology*, the first pediatric hematopathology text, is to provide the essential diagnostic and biologic information about diseases that affect the lymphatic tissues and marrow in children. The presentation is oriented toward the diagnostic laboratory in a general hospital or in a hospital dedicated to the care of children. The status of pediatric hematopathology in the 20th century is reflected in the contents of this book. The timing of the publication affords the authors a unique opportunity to speculate on the prospects for pediatric hematopathology in the 21st century. The authors point out that although the basic approach in pediatric hematopathology must be similar to that of adult hematopathology, the emphasis is quite different because many diseases common in adults are rare in children, and certain inherited diseases and infections are far more common in children than adults.



Textbook of Surgery
The Biological Basis of Modern Surgical Practice, 16th edition

Editor-in-Chief, Dr. Courtney M. Townsend Jr., The University of Texas Medical Branch; associate editors: Drs. R. Daniel Beauchamp, John Clinton Foshee Distinguished Professor of Surgery, and Director of the Section of Surgical Sciences, VUMC; B. Mark Evers, The University of Texas Medical Branch, Galveston; Kenneth L. Mattox, Baylor College of Medicine, 2001, W.B. Saunders Company, 1750 pages

The 16th edition of the *Textbook of Surgery* is a continuation of a work first published in 1936 – dedicated to the principle of providing the most current, comprehensive information on surgical science and treatment. All contributing authors are distinguished experts and the 13-section book reflects the explosion of knowledge and the continuing evolution in the field. With an eye to the future, the authors pay tribute to the past, to the five editions edited by Frederick Christopher, the four editions edited by Loyal E. Davis and to the six editions edited by David C. Sabiston Jr. For the past 65 years these surgeons and teachers have made certain that the text has reflected the growth of the art and science of surgery by providing "cutting-edge" information for generations of surgical trainees and practitioners.



Obstetrics Normal and Problem Pregnancies
Fourth edition

Edited by Drs. Steven G. Gabbe, Dean of the Vanderbilt University School of Medicine, and Professor of Obstetrics and Gynecology; Jennifer R. Niebyl, University of Iowa College of Medicine; Joe Leigh Simpson, Baylor College of Medicine, 2002, Churchill Livingstone, 1429 pages

Obstetrics: Normal and Problem Pregnancies was published for the first time in 1986. With the fourth edition, the book enters its third decade. During these years remarkable advances have occurred in some areas of obstetrics, and in others, less marked. To provide the reader with the most up-to-date information, three new chapters have been added: Fetal Therapeutic Interventions, Surgical Procedures in Pregnancy, and Endocrine Diseases in Pregnancy. The fourth edition includes 28 authors who are making their first contributions to the textbook.

CRS

THE CANBY ROBINSON SOCIETY

SPECIAL SECTION

President's Corner

On behalf of the Canby Robinson Society, I would like to thank Bob McNeilly for his hard work and leadership during the past two years. His commitment has been outstanding. His cheerful good nature and consistent optimism have had a positive effect on all aspects of the Society. One of the major contributions of his tenure has been the evolution of a plan first proposed by Dr. Robert D. Collins to develop a new scholarship fund that would enable Vanderbilt to offer a partial scholarship to every student accepted into the medical school each year. The goal of the plan is to try to offset the increasing debt that almost all students incur during their first four years of medical school.

The problem of indebtedness can be a factor in the choice of career or training for the graduating physician. All too often this leads to a choice of early employment to pay off the debt and excludes a career path in research, academic or humanitarian service. If Vanderbilt could extend scholarship support to every student it could reduce this problem and would make our school more attractive to the top students who apply each year. Fortunately Bob McNeilly is planning to continue his commitment to this project and to use his considerable experience in fund raising to help make this a success.

The overall health of the Canby Robinson is robust. Imagine what Dr. Robinson would have thought in 1927 if he could have known that 75 years into the future there would be a Society using his name with more than 1,900 members who contribute each year to a great variety of projects that benefit students, housestaff, faculty, research and patient care. He would be both astounded and pleased. In the same way the founders of the Canby Robinson Society must be equally pleased to see that in 24 years it has grown beyond their most optimistic expectations.

The most recent activity of the Canby Robinson Society has been with the committee that selects the scholars for the upcoming school year. There have been several meetings since January to review the achievements and performance of the most outstanding applicants for next fall, and we are blessed with an abundance of talented young men and women. Our hope is that those selected will bring additional scholarship, diversity and dedication to the class of 2006. All of this is made possible by the members of our Society and to all of them, we thank you. CRS

William S. Stoney Jr,. M.D.
President,
Canby Robinson Society

Having your cake and eating it too

Will Oldham wanted to have his cake and eat it too. He's among four Canby Robinson Scholars who are M.D./Ph.D students. This is the first group of scholars who have chosen the M.D./Ph.D route.

"I suppose the (program) is the way I could have my cake and eat it too," said William Oldham, a first-year medical student from Annapolis, Md. During Oldham's freshman year at the University of North Carolina he began studying protein interactions and Parkinson's disease in a molecular biology lab. He was fascinated by the kinds of questions that could be asked and answered with modern experimental techniques. He considered pursuing a degree in pharmacology instead of attending medical school but realized that working with patients would be more fulfilling. He decided that the dual degree would be a way for him to do two things he really enjoyed.

"I want to be one of the physician-scientists helping to apply bench-top discoveries at the bedside, and I think the dual degree program is the best preparation for that sort of research," he said.

Oldham said he is grateful that the CRS supports the program, adding that the National Institutes of Health determines the number of M.D./Ph.D students it will fund for each university depending on the quality of their program. The university can add students to the program.

"The scholarship essentially allows two additional M.D./Ph.D students to attend Vanderbilt, and the more people in the program, the better the quality of the program."

(continued on page 32)

CRS scholars embark on a new journey

For four Canby Robinson Society scholars, graduation from medical school means the end of one wonderful opportunity – attending Vanderbilt University School of Medicine. But it's also the beginning of countless new opportunities as the graduates begin residencies at Vanderbilt and other institutions.

"Medical student well-being is definitely a priority here," said Michael Scott, of Dale, Ind., who will begin an emergency medicine career at Indiana University in Indianapolis. "My education has been excellent, was great preparation for the USMLE, and positioned me for a great result in the match," he said, adding that he is indebted to the CRS. "I doubt if I would have chosen to attend Vanderbilt if it were not for the financial assistance the CRS provided me, and quite possibly may have been unable to further my career in the way I envisioned. Regardless, my life will be much simpler and happier after graduation without the burden of a mountainous debt."

Scott said he chose emergency medicine because of the broad-based nature of the specialty and its unpredictability. "I also like being the first physician to evaluate a patient," he said.

Danny Chang, originally from Alameda, Calif., is also going into emergency medicine and will begin a residency at the University of Southern California, Los Angeles.

"I enjoy the energy and pace of the work and variety of patient problems that present in the ED," he said, adding that he is eagerly awaiting the start of his residency. "I've developed a strong foundation to build on from my four years at Vanderbilt, and certainly the encouragement and support from the CRS has been a key part of my development. I am very grateful to the CRS for their faith in me as a CRS scholar and will strive to honor their support by practicing medicine at the highest level in the years ahead."

Julie Thwing, of Dallas, Texas, will stay at Vanderbilt for her residency in internal medicine/pediatrics. She said she wanted to serve her residency at Vanderbilt because the medical center's reputation and because it was a "good fit."

"I've made a lot of friends here in the Vanderbilt community," she said. "The physicians here become your friends as well as colleagues," she said.

Thwing said that her career might someday lead her back to Africa, where her parents are missionaries, trained as linguists. Thwing also spent time in Haiti during medical school, conducting research on HIV.

"My heart is in Africa though," she said. "I feel called there. There's a huge need and my HIV research is helping prepare me for that."

Rose Bohan, of Baltimore, Md., is the fourth CRS scholar in the class of 2002. She will serve a residency in psychiatry at the University of Maryland Medical Center in Baltimore. CRS

– NANCY HUMPHREY

DONNA JONES BAILEY

John Royston Long won the Canby Robinson Society's Ideal Physician Award for the Class of 2002. The award is presented to a member of the graduating class whom fellow classmates would most like to have as their personal physician. With Long is Dr. William Stoney, president of the CRS.

Simons supports Discovery Grants program

DANA JOHNSON

Susan Simons, shown here with husband, Luke, will support a Vanderbilt-Ingram Cancer Center project studying weight gain in breast cancer survivors.

Susan Simons wanted to take her experience with breast cancer and turn it into something positive. She just wasn't sure about the right way to do it.

Susan and her husband, Luke, members of the Canby Robinson Society, are both supportive of Vanderbilt University Medical Center and particularly of the Vanderbilt-Ingram Cancer Center.

So when Susan heard about the Vanderbilt-Ingram Cancer Center's Discovery Grants program, she was intrigued. The Discovery Grants program is based on the philosophy that some of the most innovative ideas that occur in the laboratory are frequently spontaneous and unplanned. Unfortunately, scientists are rarely at liberty to fully pursue their keenest instincts, and the boldest ideas in medical research may be stalled for months or even years due to lack of funding. Federal resources, like the National Cancer Institute, award grants based on proven scientific merit. But accumulating and processing evidence to satisfy this requirement is costly in and of itself.

That's why in 1998 Vanderbilt-Ingram launched the Discovery Grants program. Made possible by the generosity of many private donors, Discovery Grants provide seed funding to expedite promising research ideas in breast, prostate, colon, lung and other cancers. Each quarter, a peer-review committee solicits applications from the more than 200 investigators at the Cancer Center. Discovery Grants are only awarded to support research that is urgent, compelling, and likely to leverage subsequent funding from the National Cancer Institute or others.

Discovery Grants are a key part of a 10-year Vanderbilt-Ingram strategic plan and a special fund raising campaign to support it – the Campaign to Imagine a World Without Cancer.

Susan Simons has selected a project that is studying weight gain in breast cancer survivors who have received chemotherapy. The research is being conducted by Janet M. Friedman, Ph.D., research assistant professor of Medicine and Janet Carpenter, Ph.D., assistant professor of Nursing.

She had come to a Vanderbilt-Ingram luncheon where she heard a speech by Dr. Harold L. Moses, director of the Vanderbilt-Ingram Cancer Center, and met Dr. Jennifer A. Pietenpol, associate professor of Biochemistry and associate director for basic science programs.

"The Discovery Grant program seemed to me a wonderful way to take a relatively small amount of money and take it as far as possible," Simons said. "It's a good way to leverage a gift."

Simons said she chose Vanderbilt because it is designated as a Comprehensive Cancer Center by the National Cancer Institute. "Such exciting research is going on at Vanderbilt."

The weight gain research project is one that Simons hopes will help many breast cancer survivors.

"Now that we've actually selected a project, I hope that the results will help breast cancer survivors, that it will enhance the quality of their lives in a major way," Simons said. "As a breast cancer survivor, you're very excited to have the gift of life. On the other hand, you want it to be the best it can be. Aside from the issue of self esteem, the weight gain puts you at risk for other diseases like diabetes and heart disease." CRS

– NANCY HUMPHREY

CRS

Scholarship Progress Notes

The Scholarship Campaign Committee for Vanderbilt University School of Medicine is pleased to recognize the teaching contributions of one of its committee members, Dr. Alice C. Coogan (MD'88) and to describe progress toward our campaign goal.

The course in Pathology at Vanderbilt has been a defining experience for medical students over the last 75 years. From 1925 until the early 1960s, most of the lectures as well as supervision in the laboratory and at autopsies were carried out by Drs. Goodpasture, Dawson, or Shapiro. Dr. James Dawson, also known as "Lean Dog" or "Mad Dog" Dawson, was respected and feared by graduates during the 1940s. He died in 1986, shortly after his granddaughter Alice Clark (Coogan) took Pathology at Vanderbilt. Although rumored to be somewhat chauvinistic, he would have been very proud to know she went into Pathology, joined the Department at Vanderbilt after training at Duke, and assumed responsibility for the Pathology course in 1997. At the last Cadaver Ball, Alice was honored with the Shovel Award, given by the fourth-year class to their most respected teacher. More recently, she was awarded one of the six Excellence in Teaching prizes given to faculty by the medical center. Alice, for the next few years, will be taking a break from her teaching duties to spend more time with her five children. In addition to these duties, we are pleased that Alice will continue to work with the Alumni Committee of the Scholarship Campaign. We are hopeful that she will return to Pathology, and that one or more of her children will follow in her footsteps and those of their great grandfather Dawson.

The scholarship campaign continues

An award-winning case statement brochure, which will be distributed to all alumni over the next few months, was honored as "Best in Show" at the Addy Awards sponsored by the Nashville advertising community and has also received a "Gold" award from the national CASE organization.

Progress is also being made toward our goal of $50 million. Since July of 1999, $2.8 million has been contributed in cash to the scholarship program as well as $9 million in documented bequests. These new funds are in addition to the $25 million of endowed scholarships previously contributed.

If you would like to play an active role in this exciting campaign for scholarship support, please contact the VUSM Scholarship Campaign Office at (615) 343-4399. CRS

– ROBERT D. COLLINS, M.D.

Dr. Alice Coogan shares her 2002 Shovel Award with her five children, Michael, John, Anne, Tom and George.

ANNE RAYNER POLLO

Cake, cont.

Erik Musiek, a second-year CRS scholar, said he chose the M.D./Ph.D program because he wanted to learn how to do research to expand the current arsenal of treatments for certain diseases. "Research lets you contribute to the creation of new therapies that might someday improve far more lives than you could possibly affect in clinical practice," he said.

Musiek, whose wife, Amy, is also a Vanderbilt medical student, said the CRS is helping him achieve his goal. "It alleviates the financial concerns that would likely have driven me away from a research-oriented career. Unfortunately, getting a Ph.D and going into research often pays less than private-practice medicine, but because of the generosity of the CRS, I don't have to abandon research just to pay off medical school debts, which can be enormous."

He hopes to someday hold an academic position at a university medical center and run a research lab as well as seeing patients in clinic. His research interests are neurodegenerative diseases (Parkinson's and Alzheimer's disease) and he may clinically pursue neurology, radiology or internal medicine.

Eshaghian, another second-year scholar in the M.D./Ph.D. program, moved to the United States with his family from Tehran when he was only a few months old. He was born with a heart condition called coarctation of the aorta and aortic stenosis and had corrective surgery as a young child. "I am eternally indebted to the surgeons who saved my life and I enjoy science. Finally I enjoy getting a chance to help others in any way I can. I had opportunities in college, of which I was able to take advantage, and I feel health is the best gift one could give to another. For these reasons I have chosen the medical field."

Eshaghian is pursuing a career in dermatology and will be doing his thesis work in the lab of Dr. James Sligh Jr., assistant professor of Medicine, studying mitochrondrial deletions in non-melanoma skin cancer. CRS – NANCY HUMPHREY

GEORGE W. HOLCOMB JR., M.D.
Executive Director
Medical Alumni Affairs

alumni journal

Medical Alumni Regional Dinners: 2002

Our regional alumni dinners provide the planning highlights for the medical alumni staff during each spring season. This year is no exception as we visited the West Coast with a reception and dinner in Seattle on May 28. Dean Steven G. Gabbe discussed current activities on our campus and future goals for the medical center. We enjoyed seeing local graduates, former residents, fellows and former faculty at these events. The same program was repeated May 29 in San Francisco, May 30 in San Diego and May 31 in Los Angeles. Dr. John E. Chapman joined the visiting staff in welcoming the alumni, many of whom he graduated during his tenure as Dean.

Medical Alumni Reunion 2002: Memories and Gratitude

As Reunion 2002 nears, we recall many fond memories of earlier days at VUSM. Depending on one's particular era of involvement, you may recall the teachings of legends like Drs. Barney Brooks, Hugh Morgan, Amos Christie, and Rudolph Kampmeier. In later years, stalwarts like Drs. Jack Davies, Thomas Brittingham, John Shapiro, Mildred Stahlman, and, currently, Robert Collins, John Tarpley and Corey Slovis, as well as others, are fondly remembered for outstanding teaching abilities. The close personal contact between faculty members and medical students has been a Vanderbilt tradition since 1875.

Medical Alumni Reunion 2002: A Program Overview

October 24-26 is the date for our next medical alumni reunion. In addition to the School of Medicine Reunion events, all alumni and friends are invited to a number of star-studded "extraVUganza" activities throughout the campus including the homecoming parade, tailgate and football game, and for dinner and dancing. Festivities begin Thursday afternoon with a golf outing hosted by Vice Chancellor Harry R. Jacobson at The Legends Club. Later that evening a welcome reception will be held at the new Frist Center for the Visual Arts, a very special addition to Nashville. Those who have not revisited the campus recently will be amazed at the new buildings and current construction activities.

On Friday, several lectures by prominent faculty are scheduled including special reports from the Vice Chancellor and Dean Gabbe. Of particular interest to the Quinqs will be the traditional presentation of 50-year pins and certificates to the graduates of 1952 and 1953. A luncheon follows with presentation of the Distinguished Alumni and Distinguished Service Awards.

Saturday morning the latest advancements in surgery, pediatrics and ob/gyn will be presented during departmental Grand Rounds. Of interest to all will be a description of new construction projects – Medical Research Building III, Monroe Carell Jr. Children's Hospital and the Bill Wilkerson Center for Otolaryngology/ Musculoskeletal Institute.

Social highlights of the weekend will be the all-alumni dinner-dance on Friday evening at Loews Vanderbilt Hotel and the class parties on Saturday evening. These events will surely provide lasting memories for all of us.

Hopefully, each of you in classes that graduated in 1952, 1953 and those ending in 1, 2, 6 and 7, will return for reunion activities. By mid-July, reuniting classes will receive more specific details regarding other attractions, availability of hotel rooms and reservation cards to be returned, so be on the lookout for these packets.

We do hope that you can return for several or all of these events. Please keep in touch and call l-800-288-0266 or 322-6146 for answers to questions regarding Reunion 2002. For additional information you may prefer to visit our Web page at http://www.mc.vanderbilt.edu/alum-affairs or check the reunion schedule at www.vanderbilt.edu/alumni/reunion

Best regards,

George W. Holcomb, Jr., M.D.
Executive Director
Medical Alumni Affairs

Faculty News • Alumni News

Faculty News

Dr. H. Scott Baldwin has joined the Vanderbilt faculty as professor and vice chair for Laboratory Sciences in Pediatrics after more than 10 years with Children's Hospital of Philadelphia, where he was a clinical cardiologist and co-director of cardiovascular research. At CHOP he researched molecular and genetic etiology of congenital heart disease. Baldwin will be focusing on developing and training physician-scientists in pediatric laboratory-based research at VCH. He brings with him three National Institutes of Health (NIH) grants.

Dr. James E. Crowe Jr., associate professor of Pediatrics and assistant professor of Microbiology and Immunology, has been selected as the recipient of the 2002 Judson Daland Prize for Outstanding Achievement in Patient-Oriented Clinical Research by the American Philosophical Society (APS). Crowe received an honorarium and recognition at the APS annual general meeting on April 26.

***Dr. Raymond N. DuBois Jr.**, Mina Cobb Wallace Professor of Medicine and associate director of Cancer Prevention, has been selected to receive the 2002 Richard and Hinda Rosenthal Foundation Cancer Research Award by the American Association of Cancer Research (AACR). The award recognizes translational research that has made or promises to soon make a notable contribution to improved clinical care in the field of cancer research. DuBois is the first Vanderbilt faculty member to be selected for this honor. DuBois also has been named director of the Vanderbilt Digestive Disease Research Center that opens in June.

Dr. Christopher D. Ferris, assistant professor of Medicine, has been named one of four academic physicians in the United States to receive the Charles E. Culpeper Scholarship in Medical Science, a program designed to support the career development of academic physicians. The award, part of the Rockefeller Brothers Fund, a philanthropic organization, is given on behalf of carefully selected physicians of high potential achievement who are committed to careers in academic medicine. Ferris, who joined the faculty in 2000, was nominated by Vanderbilt for his work in the mechanisms responsible for iron transport out of cells. Only one other Vanderbilt faculty member has won the award, **Dr. Katherine T. Murray**, associate professor of Medicine and Pharmacology. She received the scholarship in 1989.

***Dr. Steven G. Gabbe**, dean of Vanderbilt University School of Medicine, received the 2002 Association of Professors of Gynecology and Obstetrics/Wyeth-Ayerst Career Achievement Award. The $10,000 award enables recipients to address the continuing need for research and development in medical education within the specialty of obstetrics and gynecology. Gabbe also received the Joseph Bolivar DeLee Humanitarian Award from the Board of Directors of Chicago Lying-in Hospital in recognition of his outstanding work to study and alleviate complications of pregnancy due to diabetes and has also been elected president of the Society for Gynecologic Investigation.

***Dr. Gerald B. Hickson**, HS'78-80, F'81-'82, professor and vice chair of Pediatrics and director of General Pediatrics, and Amy Casseri, director of Pediatric Services Development, will co-chair the Vanderbilt Child Advocacy Council (VCAC), which includes representation from the Vanderbilt community as well as the Middle Tennessee region. Physicians, community leaders, community child advocates, and legislative experts are among those who make up the council profile.

***Dr. Philip J. Kregor**, MD'88, has been recruited as associate professor and the new Director of Orthopaedic Trauma in the Department of Orthopaedics and Rehabilitation. Kregor assumed the position on Jan. 1.

***Dr. Harold L. Moses**, MD'62, HS'62'64, Benjamin F. Byrd Professor of Oncology and director of the Vanderbilt-Ingram Cancer Center, was recently elected as vice president and president-elect of the Association of American Cancer Institutes. He will serve two years in this role, followed by two years as president of the organization, which includes more than 80 centers.

Lillian B. Nanney, Ph.D., professor of Plastic Surgery and Cell and Developmental Biology, has been appointed to serve on the surgery, anesthesiology and trauma study section at the Center for Scientific Review at the National Institutes of Health. Her term, which began the first of January, ends June 30, 2004. Study sections review NIH grant applications, make recommendations on these applications to the appropriate NIH advisory council and survey the status of research in their fields of science.

Jennifer A. Pietenpol, Ph.D., has been named to senior leadership of the Vanderbilt-Ingram Cancer Center as associate director for basic science programs. An associate professor of Biochemistry, Pietenpol has been a member of the Vanderbilt faculty since 1994. **Scott Hiebert, Ph.D.,** professor of Biochemistry, has been appointed to succeed Pietenpol as leader of Vanderbilt-Ingram's Research Program in Signal Transduction and Cell Proliferation, which she led for the past two years. Pietenpol succeeds **Lawrence J. Marnett, Ph.D.,** who has served as associate director for basic science programs since the Vanderbilt-Ingram Cancer Center was established in 1993. Marnett remains as Mary Geddes Stahlman Professor of Cancer Research and director of the A.B. Hancock Jr. Research Laboratory.

Dr. Margaret Rhea Seddon, assistant chief medical officer of the Vanderbilt Medical Group, has been selected to serve as a member of the Institute of Medicine's Committee on Aerospace Medicine and Medicine in Extreme Environments. She will hold the committee appointment until September 2003.

Dr. Jeffrey A. Sosman has joined the Vanderbilt-Ingram Cancer Center to lead its program in treating melanoma, the most deadly form of skin cancer. Sosman joined the faculty Dec. 1 as professor of Medicine in the division of Hematology-Oncology. He will also lead a program in tumor immunology and serve as medical director of Vanderbilt-Ingram's Clinical Trials Office.

Dr. C. Michael Stein, associate professor of Medicine and Pharmacology, has been named editor of *Clinical Pharmacology and Therapeutics* (CP&T).

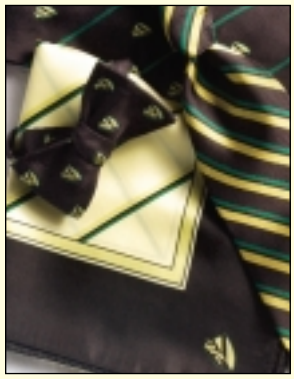
***Dr. Yi-Wei Tang**, associate professor of Medicine, and director of Molecular Infectious Disease Laboratory, has been elected as an editor of the *Journal* of *Clinical Microbiology*.

Susan R. Wente, Ph.D., has been named professor and chair of Cell and Developmental Biology at Vanderbilt University Medical Center. Currently a member of the department of Cell Biology & Physiology at Washington University School of Medicine, she will assume her new post July 1, 2002.

***Dr. Keith D. Wrenn**, program director of the Department of Emergency Medicine, has been selected as one of 10 outstanding program directors in the nation to receive the Accreditation Council for Graduate Medical Education (ACGME) Parker J. Palmer "Courage to Teach" Award. He was among 90 other program directors to be nominated for the award.

** Indicates CRS member*

Tie one on!



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'47

Dr. Robert E. Nesbitt Jr., MD'47, was awarded the Wisdom Award of Honor in 2001 for the advancement of knowledge, learning and research in education. Nesbitt became the first academic chairman of the Department of Obstetrics and Gynecology at Upstate Medical University in Syracuse, N.Y. He served as chair for 20 years. In 1981 he was named emeritus and moved to Florida where he served as professor of Ob/Gyn at the University of Tampa and also as medical director of the VA Hospital of Tampa. He now resides in Martinez, Ga. and writes scientific articles and poetry.

'60

Dr. Elbert A. White III, MD'60, HS'60-'61, '63-'65, '76-'78, retired Dec. 31, 2001 from the practice of ophthalmology in Corinth, Miss. He has practiced ophthalmology since 1970. He previously practiced pediatrics (1966-1975).

'61

***Dr. Richard B. Johnston Jr.**, MD'61, HS'61-'62, has been named associate dean for research development in school of medicine at University of Colorado Health Sciences Center. Previously, Johnston was medical director of March of Dimes and conducted laboratory research and served as chief of pediatric immunology at Yale University. His son, **Richard B. Johnston III, MD'89**, was voted one of three best sports medicine orthopaedic surgeons of 2001 by *Atlanta Magazine*.

'68

Dr. Robert B. Shearin, HS'68-70, was professor of Pediatrics at Georgetown University until 1990 doing specialty training in infectious diseases and adolescent medicine. He is now in full-time private practice in the greater Washington D.C. area.

'71

Dr. Albert Thomas Indresano, HS'71-'73, has been named chair of the Department of Oral and Maxillofacial Surgery at the University of the Pacific School of Dentistry. He is also program director and chief of UOP's new Oral and Maxillofacial Surgery Residency Training Program with Alameda County Medical Center, Highland Hospital.

'72

***Dr. Ralph E. Wesley**, MD'72, HS'72, FA'80-83, CF'83, is an oculoplastic surgeon and clinical Professor of Ophthalmology at Vanderbilt University Medical Center. He serves as president of the National Academy of Medicine and also the American Society of Ophthalmic Plastic and Reconstructive Surgery.

'77

Dr. Ronald Bronitsky, MD'77, HS'77-'80, is in private practice as a pulmonary/critical care specialist with Southwest Pulmonary Specialists in Albuquerque, N.M. He currently serves as the director of the Presbyterian Hospital Intensive Care Units. He also recently had the opportunity to portray one of the leads (Ben Stone) in Sondheim's musical, "Follies" with Musical Theater Southwest and most recently was onstage as one of the Jordanaires in the musical revue "A Closer Walk With Patsy Cline."

'80

Dr. Fred Gorstein, FA''80-94, former professor and chairman of the Department of Pathology at VUMC, is now Director of Laboratories and Director of the Pathology Training Program at Thomas Jefferson University Medical Center in Philadelphia. He has received the "Distinguished Service Award of the Association of Pathology Chairs" and has been editor-in-chief of *Human Pathology* for 16 years.

'81

Dr. Joseph C. Thompson, MD'81, is directing a blood donor center and clinical laboratory in Los Angeles. He is also enjoying traveling – 70 countries so far – with an emphasis on scuba diving and bird watching and camping.

Dr. Ann D. Thor, MD'81, HS'81-'84, has accepted the chair position at the University of Oklahoma Department of Pathology. She is the Lloyd E. Rader Professor and Chair of Pathology.

'94

Dr. Daniel W. Lin, MD'94, has completed a urologic oncology fellowship at Memorial Sloan-Kettering Cancer Center and has accepted a position at the University of Washington. He is also a new father. His first child, Steven Richard Lin, was born in November 2001.

Dr. Elizabeth Stephens, MD'94, has taken a new position at Oregon Health Sciences University as the Associate Director of the Diabetes Center. She is also engaged to be married in 2003 to Dr. Peter Mortola.

'97

Dr. Keri Rae DeSoto, MD'97, has joined the physicians' staff at the Evelyn Frederick Health Center in Millersburg, Pa. She completed her residency in internal medicine at Maine Medical Center in Portland, Maine in June 2001.

Dr. Dan Viner, MD'97, and his wife, Jessica, had twin girls, Gabrielle and Rebecca, in October 2001. They reside in Shaker Heights, Ohio.

Dr. Michael J. Wells, HS'97, has been appointed an assistant professor at Texas Tech University's Department of Dermatology. He is also a pharmacy editor for the E-Medicine's Dermatology section. He and his wife, Kim, have a new baby girl named Sydney.

DANA JOHNSON

GOODPASTURE BOOK SIGNING

Dr. Robert Collins signs copies of his biography *Ernest William Goodpasture: Scientist, Scholar, Gentleman*. The book is available at Vanderbilt and Davis-Kidd bookstores in Nashville and through the Province House Publishers, 1-800-321-5692.

In Memoriam

Dr. James Sumpter Anderson Jr., MD'53, died Dec. 11, 2001. He was 72. Anderson practiced as an anesthesiologist in Nashville from 1956 to 1978.

Dr. Willard D. Bennett, MD' 40, died on Jan. 11. He was 86. He practiced anesthesiology in Louisville for seven years, then moved to Montgomery in 1956 where he practiced anesthesiology at Baptist Hospital until his retirement in 1985. He is survived by his wife, Martha, a son, James, and two grandchildren.

Dr. Thomas M. Blake, MD'44, HS'47-'48, F'50-51, professor emeritus at the University of Mississippi Medical Center, died March 10, 2002. He was 81. He set up the heart catheterization laboratory at UMC and organized a course in physical diagnosis, the "introduction to clinical medicine" course, for more than 30 years. He is the author of five editions of the medical textbook, *The Practice of Electrocardiography* and an atlas on electrocardiography that was published in 2000. He officially retired in 1990 but still consulted on EKG interpretation.

Dr. Josh Daniel Davis, MD'48, died Nov. 24, 2001 in Florida. He was in the private practice of psychiatry in Gainesville for 16 years and completed his career with a combination of positions in psychiatry and medical administration in Alabama and Florida, including a faculty appointment at the University of Alabama College of Community Health, Chief of Psychiatry at the VA Medical Center in Tuscaloosa and director of the Post Traumatic Stress Disorder Program at the Gainesville VA Hospital. He retired in 1992. He is survived by his wife, Carol, two daughters, four sons and six grandchildren.

Dr. Floyd W. Denny, MD'46, HS'46-'47, FA'53-'55, died on Oct. 27, 2001. He was 78. Denny was a distinguished professor of pediatrics at the University of North Carolina School of Medicine where for many years he headed the Department of Pediatrics and guided infectious research. With his long-time colleague Dr. Wallace Clyde, he identified Mycoplasm pneumoniae as the most frequent cause of pneumonia in older children and young adults. He was awarded the VUSM Distinguished Alumnus Award in 1985.

Dr. Arthur M. Freeman Jr., MD'40, died on Nov. 44, 2001. He was 84. While maintaining his own gastroenterology practice for 50 years, he served as professor of Medicine at the University of Alabama-Birmingham from 1949 to 1988 and chaired the department of medicine at the South Highlands Hospital (now Health South) from 1966 until 1988. He is survived by his wife, Mary Katherine, daughter, Katherine, son, Dr. Arthur M. Freeman III, MD'67, and four grandchildren.

Dr. Sidney C. Garrison, MD, '43, died Nov. 9, 2001. He practiced medicine in Murfreesboro from 1949 until 1986 and for years was the city's only internal medicine specialist. He co-founded the Murfreesboro Medical Clinic. He is survived by his wife, Eska Sessoms Garrison, and two daughters, Joyce and Susan, seven grandchildren and four great-grandchildren.

Dr. Paul U. Gerber, MD'58, died Oct. 2, 2001 in Miami. From 1964 until his retirement in December 2000, he practiced general surgery at area hospitals including North Shore Medical Center, Mercy Hospital, Doctor's Hospital and Parkway Regional Medical Center. He is survived by his wife, Linda.

Dr. B. Leslie (Les) Huffman, MD'54, died Aug. 28 in Toledo. He was 72. He maintained a practice of 4,000 to 5,000 patients and from the 1960s to the 1980s was president of groups such as the American Academy of Family Physicians and the American Board of Family Practice. He is survived by his wife, Carol, daughter, Debi, sons, Les and Jim, five grandchildren and a great grandchild.

Dr. James R. Glassner, MD'81, died Dec. 16, 2001 in Montgomery, Ala. He was 46. Glassner practiced with Montgomery Eye Physicians since 1985. He was killed in a bicycle accident near Union Springs, Ala. He is survived by his wife, Rebecca, and daughters Kristen and Sarah.

Dr. Robert A. Goodwin, HS'46, CF'47-'61, FA'61-01, died on Dec. 9 at his home in Nashville. He was 87. Considered one of the world's leading authorities on histoplasmosis, Goodwin had taught at Vanderbilt since 1947 and worked at the Veteran's Administration Hospital. He was professor emeritus at Vanderbilt at the time of his death. He is survived by Jean, his wife of 57 years, two daughters, a son, and three grandchildren.

Dr. Charles T. Henderson, HS'46-'47, died July 15, 2000. He began his general surgery practice in Marietta in 1954 and never officially retired. He is survived by his wife, Joyce, five children and six grandchildren.

Dr. Leonard J. Koenig, HS'44,'47, CF'70-'89, died April 10. He was 81. Koenig was a pediatrician for more than 40 years who taught at Vanderbilt and served as chief of Pediatrics at Baptist Hospital. He is survived by his wife, Wilma, three sons, Stephen, Nathaniel and Joel, and eight grandchildren.

Dr. Aubrey B. Lee, MD'32, died Sept. 21. He was 94. He practiced medicine in Opp, Ala. since 1950. He is survived by a daughter, Mindel, and three granddaughters.

Dr. Earl C. Lowry, MD'33, died on March 28. He was 94. During service in World War II, he commanded the 195th General Hospital in France and received the prestigious "Legion of Merit Award" for his contribution in Washington, D.C. as the assistant executive director of the Office for Dependents Medical Care, a program used as the model for Medicare. He is survived by his wife, Olivia, two daughters, five grandchildren and two great-grandchildren.

Dr. James S. Morgan Jr. HS'82-'84, died of cancer on July 22, 2001.

Dr. Peirce M. Ross, MD'48, HS'48-'51, died on Jan. 20 in Nashville. He was 88. He is survived by two daughters and three grandsons.

Dr. Ernest Sachs, HS'42, died on Dec. 3, 2001 after a long battle with leukemia. He was 85. He was a prominent neurosurgeon and Emeritus Professor of Medicine at Dartmouth Medical School. A leader in the field of brain and spinal surgery, he was the first physician selected for a Fulbright Senior Fellowship to study medicine. He is survived by his wife, Jeanne, and six children.

Dr. Stephen Schillig, HS'54-'55, F'58-'60, FA';57-01, died Oct. 29, 2001. He was 74. He was a member of the Vanderbilt Department of Medicine from 1961 until his retirement in 1998. He and his daughter, Ruth, died within hours of each other, both of cancer. He is survived by his wife, Mary.

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For more information, contact Sarah Reynolds, Director of Development, at (615) 343-4399.

Dana (left) and Justin Piasecki took a year's leave of absence during their second year of medical school to pursue a dream, training to make the kayaking team for the 2000 Olympics in Sydney, Australia. They were unsuccessful in their attempt, but grateful to Vanderbilt for supporting the experience.

Sarah Page Hammond receives the School of Medicine Founder's Medal from Dr. Steven Gabbe.

2002 Vanderbilt University Medical School Graduation

PHOTOS BY DANA JOHNSON

Robert "Sandy" Neblett embraces his father Dr. Wallace W. Neblett, MD'71, HS '71-'72, '75-'77, professor of Pediatric Surgery at VUMC.

Julie Thwing is all smiles at the post-graduation celebration.

Drs. Steven Gabbe and Harry Jacobson were among the speakers at the medical school recognition ceremony.

Vanderbilt Medicine

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