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Lens

A New Way of Looking at **Science**

NEW WAYS TO REFILL THE MEDICINE CHEST

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Lens –
A New Way of Looking
at **Science**

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EDITOR
Bill Snyder

CONTRIBUTING WRITERS
Lisa DuBois
Leigh MacMillan
Melissa Marino
Bill Snyder

PHOTOGRAPHY/ILLUSTRATION
Don Button
Christopher J. Cannistraci
Dean Dixon
Dominic Doyle
David Johnson
Sam Kittner
Casey McKee
William Oldham
Anne Rayner
Antonello Silverini

DESIGN
Diana Duren/Corporate Design, Nashville

DIRECTOR OF PUBLICATIONS
MEDICAL CENTER NEWS AND PUBLIC AFFAIRS
Wayne Wood

EDITORIAL OFFICE
Office of News and Public Affairs
CCC-3312 Medical Center North
Vanderbilt University
Nashville, Tennessee 37232-2390
615-322-4747
E-mail address: william.snyder@vanderbilt.edu

Cover: Mysteries within the medicine chest

Photo illustration by Dean Dixon

They are ill discoverers that think there is no land, when they can see nothing but sea.

–SIR FRANCIS BACON

Lens **is published three times a year by Vanderbilt University Medical Center in cooperation with the VUMC Office of News and Public Affairs and the Office of Research. *Lens*® is a registered mark of Vanderbilt University.**

Our goal: to explore the frontiers of biomedical research, and the social and ethical dimensions of the revolution that is occurring in our understanding of health and disease. Through our *Lens*, we hope to provide for our readers – scientists and those who watch science alike – different perspectives on the course of discovery, and a greater appreciation of the technological, economic, political and social forces that guide it.

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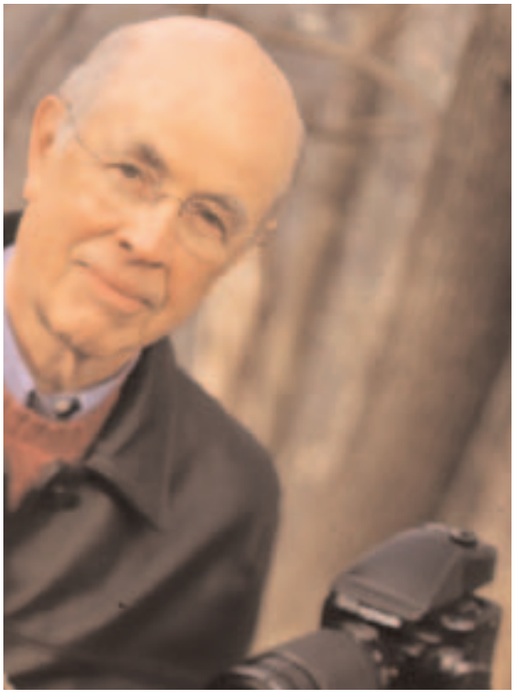

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John Oates, M.D., sees beauty in complexity – whether he's examining the magnified petals of a wildflower or the intricacies of drug metabolism. The founder of Vanderbilt's Division of Clinical Pharmacology is best known for discoveries that shaped the field of prostaglandin biology. Equally valuable to his far-flung colleagues and friends: his vision, commitment to science and insatiable curiosity.

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Doctors are on the front line when it comes to detecting adverse drug reactions and side effects. It's a hit-or-miss system, and efforts to improve post-marketing surveillance of approved pharmaceuticals have had only limited success. The creation of an independent drug safety board may help, but nothing can replace the vigilance, imagination and persistence of our "medical sleuths."

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For decades, scientists had searched unsuccessfully for a way to treat severe sepsis, a complication of bloodstream bacterial infections that kills 250,000 American adults every year. Then, in 1994, Vanderbilt sepsis researcher Gordon R. Bernard, M.D., was asked to lead a "long-shot" clinical trial of a promising drug. How a partnership with industry led to a "common good."

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Steven M. Paul, M.D., president of Lilly Research Laboratories, and Vanderbilt's Alastair J.J. Wood, M.B., Ch.B., who chaired the recent FDA advisory panel on COX-2 inhibitors, tackle some of the economic and legal challenges facing the nation's pharmaceutical industry. Among their suggestions: improved patent protection and other incentives to encourage the development of "the drugs that we need."

32 THE PATIENT'S RESPONSIBILITY

No amount of work by the Food and Drug Administration can ensure the safety of the nation's drug supply if doctors and patients don't prescribe or take medication responsibly. But while medical and consumer education may improve drug safety, costs will probably continue to rise – and that may not be such a bad thing.

Drug discovery in the 21st Century

A sea change in knowledge, technology … and collaboration

By P. Jeffrey Conn, Ph.D.

Professor and Director
Program in Translational Neuropharmacology
Vanderbilt Department of Pharmacology

Director, Program in Drug Discovery
Vanderbilt Institute of Chemical Biology

DEAN DIXON

Over the past decade, we have witnessed unparalleled advances in our understanding of basic biological processes that contribute to a host of human disorders. The highly celebrated elucidation of the sequence of the human genome and other technological gains have allowed identification of a broad range of regulatory proteins and complex signaling systems that play critical roles in a variety of normal physiological processes as well as pathological conditions in virtually all major organ systems.

Today we have an understanding of the mechanisms underlying complex human disorders such as Alzheimer's disease, diabetes, multiple cancers, schizophrenia, and many others. These key new insights may provide paths to fundamental advances in care or even cures for patients suffering from these disorders.

Translation of this new knowledge into practical gains in health care has moved more slowly, despite the recent doubling of the National Institutes of Health budget, and a 16-fold increase in research-and-development spending by pharmaceutical companies between 1980 and 2002. Many of the drugs currently available were developed before the 1950s, prior to the recent expansion in our understanding of the basic biology underlying human disorders.

Recent years have seen a steady decline in the number of new drugs approved for clinical use, and many of the recent approvals represent subtle changes

Translation of the extraordinary progress of recent years into fundamental advances in human health and patient care is a major challenge facing today's biomedical research community.

to existing medications, providing incremental rather than fundamental advances in therapeutic strategies. The decrease in introduction of fundamentally new drugs into clinical practice during a time of increased knowledge and increased research spending stems in part from a fundamental shift in the basic paradigms used for drug discovery.

In the early drug discovery era, novel therapeutic agents were derived from known compounds, often plant extracts, which had medicinal properties. The major goal was to isolate the therapeutic component of the plant and refine it by making relatively modest chemical modifications.

Investment was often made with no understanding of the basic mechanism of the drug's action, although there was existing knowledge that the compound had properties that allowed it to reach the target organ and have clinical efficacy. Also, there was some level of understanding of the potential toxicity based on clinical experience with the plants from which the compound was derived. Because of this, the risk that a drug discovery program would fail was relatively low.

Today the properties of known medicinal plants have been largely realized. We rarely have the luxury of embarking on a drug discovery program with this level of confidence in our ultimate success. Instead, we begin with knowledge of a biological system and identification of a potential drug target found among the many potential targets known from our new understanding of the human genome.

Instead of knowing that a drug interacting with this target will have clinical efficacy, we make a hypothesis based on our still limited and imperfect understanding of complex biological systems.

Typically, there are no existing drugs that interact with that target, forcing a search for a novel compound that has the desired effect and then engineering the properties required for a useful drug. This process is expensive and inherently high risk – we may reach the end of a project that cost hundreds of millions of dollars only to find that our original hypothesis was incorrect and the drug has no clinical efficacy or has unforeseen toxicity.

Translation of the extraordinary progress of recent years into fundamental advances in human health and patient care is a major challenge facing today's biomedical research community. The complexity of this task requires the combined efforts of outstanding scientists, engineers and clinicians with strong expertise in a broad range of disciplines.

Traditionally, the NIH and academic institutions have supported basic biomedical research, while industry has supported commercial development of medicines and medical products. While scientists in academic and other basic science settings have made significant progress in furthering our understanding in biology, chemistry and related disciplines, they often fail to make the critical link that allows this information to be useful in an industry setting.

Likewise, fiscal pressures that govern research efforts in industry make it increasingly difficult for companies to invest significant resources in exploratory projects and basic research that capitalize on translating the most exciting discoveries of basic science into marketable products.

The most innovative and high-impact advances in therapeutics will likely come from aggressive efforts to provide a bridge that allows translation of advances in basic science to novel therapeutic agents. While this translation is clearly the mission of pharmaceutical and biotech companies, it is critical that scientists at NIH-funded institutions focus increasing attention on their role in contributing to the therapeutic discovery process.

In addition to the advances in basic biology, we have realized tremendous advances in combinatorial chemistry, development of large libraries of small molecules, and other approaches to high-throughput synthetic chemistry. These libraries are now widely available to the research community, and new high-throughput screening technologies have been developed that allow more widespread mining of the libraries.

The combination of high-throughput screening and synthetic chemistry provides an unprecedented opportunity for NIH-funded investigators to engage in discovery and development of small molecule probes of biological pathways.

These probes could provide the tools needed to directly test whether drug-like molecules can be developed that interact with a novel target of interest and have the effects that were predicted in studies using molecular and genetic approaches. Such advances could provide a major step in the discovery of novel therapeutic agents by identifying the most viable approaches for further investment in an industry setting.

In addition, academic investigators are increasingly engaged in tackling other critical issues inherent in modern drug discovery paradigms, such as, how do we predict at an earlier stage whether a drug will have clinical efficacy or toxicity? Rather than gaining answers to these questions at the end of a billion-dollar program, basic and clinical scientists can contribute to the design and execution of early proof-of-concept clinical studies that predict ultimate efficacy, and which may lead to the development of biomarkers that predict later toxicity.

Multiple changes in science, business and society are forcing a fundamental shift in traditional approaches to drug discovery. Realizing the exciting promise of recent advances in the face of fiscal constraints presents a challenging but exciting opportunity.

Individuals across the spectrum of biomedical research and discovery share a common optimism that we are at the beginning of the most exciting era yet in changing the face of human disease. It is critical, however, that different players in this arena find new models to leverage our collective resources and talents.

This issue of *Lens* highlights one approach for bridging the gap to new therapeutics. **LENS**

Pictured left:
Tomorrow's medicine chest? Three-dimensional model of a heterotrimeric G protein, pursued as a possible target for drug therapy.

Photo illustration by Dean Dixon

[THE PUSH TO IMPROVE THE PIPELINE]

BY BILL SNYDER

Last year only 23 truly new drugs, called "new molecular entities," were approved in the United States.

That's less than half of the number approved in 1996, even though annual research-and-development spending by the pharmaceutical industry more than doubled – to nearly $40 billion – during the same eight-year period.

With the sequencing of the human genome has come a plethora of new technologies to mine it. Yet this new wealth of biological understanding, coupled with the growing demand for drugs that can treat and prevent chronic disease, has raised the bar for proving safety and efficacy to unprecedented heights. Consequently the search for new drugs has become more complicated – and much more expensive.

Depending on the calculations, the journey of a single pill through the convoluted development pipeline can take 15 years and cost more than $1 billion. That's before any money is spent on marketing.

Much has been written lately about the perceived excesses of drug marketing and inadequate efforts to ensure drug safety. This issue of *Lens* begins with a look at the top of the pipeline, and how academic medical centers are partnering with industry and the federal government to replenish the shelves of society's medicine cabinet.

"Drug companies realize the need to cover a broader range of biology. They just can't do it all and never have," says Lawrence J. Marnett, Ph.D., director of the Vanderbilt Institute of Chemical Biology (VICB). "… And so partnerships with universities, with academic health centers, especially, make a lot of sense."

The three-year-old institute exemplifies the growth of "translational" research programs at universities around the country. Aided and encouraged by the federal government, these efforts are designed to develop the tools and the knowledge base needed to meet today's drug-development challenges.

"Our goal … is to take those very early stage discoveries around drug targets and lead compounds, and go another step toward handing that information off to biotechnology and pharmaceutical companies and other organizations that can hopefully translate our discoveries into new drugs for patients," says Jeffrey R. Balser, M.D., Ph.D., associate vice chancellor for Research at Vanderbilt University Medical Center.

Toward that end, the VICB recently opened a high-throughput screening facility to help search for small molecules (a class of organic chemicals) with drug-like activity. Vanderbilt also has signed a "master research agreement" with biotechnology giant Amgen to conduct an array of collaborative research projects.

The intent of these efforts is to encourage Vanderbilt researchers to pursue the therapeutic potential of their discoveries.

Discovering a potential drug target is not enough, explains P. Jeffrey Conn, Ph.D., who directs VICB's drug discovery efforts. If academic scientists took the next steps – identifying a compound that acted on the target, and conducting the laboratory and animal tests necessary to validate its therapeutic potential – "you can then justify a company really locking into a full-scale drug discovery program," he contends.

"It's going to be difficult to bridge that gap," cautions Jason Morrow, M.D., director of the Division of Clinical Pharmacology at Vanderbilt, because the cultures of academic science and industry are so different. "Drug companies want the proprietary rights to a particular agent," he says. "A partnership tends to be a more risky business."

DEAN DIXON

"There are real benefits … to the scientists doing the research. Even if only 10 percent of these compounds were picked up by industry, the scientific programs would benefit from having potent new tools to probe the biology in cells and even in animals more deeply, leading to new discoveries."

Heidi Hamm, Ph.D., Earl W. Sutherland Jr. Professor and Chair of the Department of Pharmacology at Vanderbilt

Jennifer Washburn, author of University, Inc., is more than skeptical. In the February issue of *The American Prospect* magazine, she wrote: "Instead of honoring their traditional commitment to teaching, disinterested research, and the broad dissemination of knowledge, universities are aggressively striving to become research arms of private industry."

Gordon R. Bernard, M.D., assistant vice chancellor for Research and Melinda Owen Bass Professor of Medicine at Vanderbilt, disputes that contention.

While collaborations with industry can result in conflicts of interest, many universities, including Vanderbilt, have implemented procedural and contractual safeguards to identify and manage such conflicts. These safeguards protect the academic mission while permitting opportunities to transfer new information and technologies for the benefit of society, Bernard says.

Marnett agrees. "We are not going to be drug companies … But we can advance the field," he says. "We can identify new therapeutic concepts, new drug-design concepts. That's what we should be doing."

Turn up the light

Where will the new drugs come from?

One area to watch: G protein-coupled receptors (GPCRs).

GPCRs are embedded in the membranes of nearly every cell and are the most common conduit for signaling pathways found in nature.

Two-thirds of all drugs target these receptors. The beta-blocker drug propranolol lowers blood pressure by preventing adrenaline from binding to its GPCR. Drugs that are given to relieve symptoms of Parkinson's disease act through a GPCR that binds dopamine.

Parkinson's disease illustrates the complexity of the signaling pathways that utilize GPCRs. Characterized by tremors, difficulty walking and muscle weakness, the disease is caused by the progressive loss of dopamine-producing nerve cells and the resulting lack of dopamine, a neurotransmitter involved in the coordination of muscle movement.

Current dopamine replacement therapy squelches the tremors and improves coordination, but prolonged use of the drugs can cause significant side effects, including involuntary muscle movements and hallucinations, and the medications become less effective as the disease progresses.

Because loss of dopamine disrupts a complex web of signaling pathways in the brain, it may be possible to restore this balance by "tweaking" pathways involving other neurotransmitters.

While at Merck Research Laboratories, where he was head of neuroscience, Conn and his colleagues found that activating a particular GPCR that binds the neurotransmitter glutamate – mGluR4 – relieved symptoms of Parkinson's disease in animals. However, they could not find a compound that binds only to mGluR4, and does not activate other glutamate receptors elsewhere in the brain.

Allosteric modulation might solve the problem.

This tongue twister refers to the ability of some compounds to bind to a secondary site on a receptor in a way that "modulates" its activation by a primary "ligand" such as a neurotransmitter or hormone. Primary ligands fit into the receptor's main binding site like a key fitting a lock, and "turn it on."

The modulator, on the other hand, acts like the dimmer switch in an electrical circuit, adjusting the intensity of the receptor's activation. The anti-anxiety drugs Valium, Xanax, Librium and Ativan, for example, "potentiate" or turn up the activity of the benzodiazepine receptor when it binds to its primary ligand, the neurotransmitter gamma-aminobutyric acid (GABA).

Conn wondered whether he could find an allosteric potentiator that was specific

for mGluR4. However, "my department could only handle a maximum of three programs at any given time," he says. "And to take a kind of half-baked idea … and decide we're going to really pull the trigger on a drug discovery program was such a high risk."

Then, in 2003, he saw an opportunity to pursue his idea at Vanderbilt.

A generation ago, Conn might have spent his entire career searching for a compound that could modulate mGluR4 activity. Now, thanks to the recent installation of a high-throughput screening facility at Vanderbilt, he and his colleagues can test tens of thousands of small molecules for drug-like activity in a single day.

Ultra low volume liquid handlers squirt nanoliter amounts of the compounds into 384-well "microplates" containing their target. Reactions are detected via fluorescence or luminescence as the plates are maneuvered by articulated robots through the screening system.

Compounds that bind to the allosteric site on mGluR4 will be tested in animal models of Parkinson's disease to see if they actually relieve muscle rigidity and restore coordination.

Conn admits that there is considerable skepticism among his colleagues in industry about "whether we can really pull it off … it's very high risk." That hasn't discouraged universities across the country from developing similar capabilities for screening compounds.

"This is where we fill the gap," he explains. "I think we are at a turning point in the whole drug discovery industry … We are at a point where different players in the whole therapeutic discovery arena can start to bring a lot more to bear to this process …

"I see it as a really challenging time. But mostly I see it as a very exciting time."

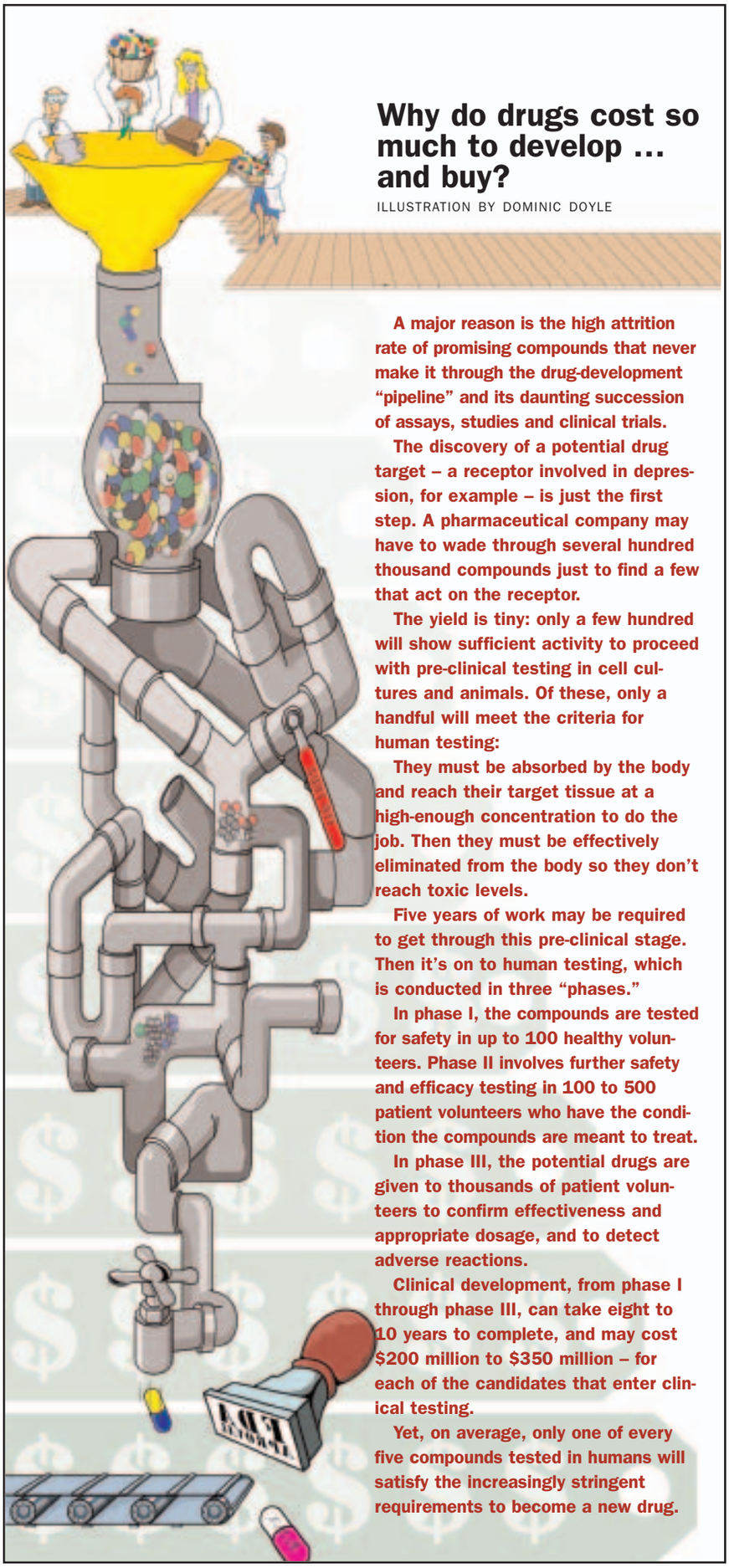
Pie in the sky

Another potential source of new drugs: compounds that interact with G-proteins.

G-proteins are intracellular molecular switches, involved in nearly every physiological – and presumably, pathological – process. They translate and transmit signals from the receptor to the "response machinery" deep inside the cell.

Here's how they work:

When a neurotransmitter or hormone binds to its G protein-coupled receptor on the surface of a cell, the receptor, in turn, activates G proteins that bind to it inside the cell. The proteins actually split into two active parts – alpha subunits and



Why do drugs cost so much to develop … and buy?

ILLUSTRATION BY DOMINIC DOYLE

A major reason is the high attrition rate of promising compounds that never make it through the drug-development "pipeline" and its daunting succession of assays, studies and clinical trials.

The discovery of a potential drug target – a receptor involved in depression, for example – is just the first step. A pharmaceutical company may have to wade through several hundred thousand compounds just to find a few that act on the receptor.

The yield is tiny: only a few hundred will show sufficient activity to proceed with pre-clinical testing in cell cultures and animals. Of these, only a handful will meet the criteria for human testing:

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

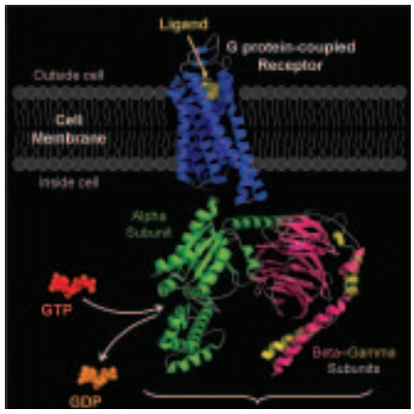
Five years of work may be required to get through this pre-clinical stage. Then it's on to human testing, which is conducted in three "phases."

In phase I, the compounds are tested for safety in up to 100 healthy volunteers. Phase II involves further safety and efficacy testing in 100 to 500 patient volunteers who have the condition the compounds are meant to treat.

In phase III, the potential drugs are given to thousands of patient volunteers to confirm effectiveness and appropriate dosage, and to detect adverse reactions.

Clinical development, from phase I through phase III, can take eight to 10 years to complete, and may cost $200 million to $350 million – for each of the candidates that enter clinical testing.

Yet, on average, only one of every five compounds tested in humans will satisfy the increasingly stringent requirements to become a new drug.



Pictured left: Three-dimensional crystal structure of a G protein coupled receptor (GPCR) embedded in a cell membrane, with its loosely attached heterotrimeric G protein, consisting of alpha, beta and gamma subunits, inside the cell. When a ligand, such as a neurotransmitter or hormone, binds to its GPCR, the receptor changes shape in a way that catalyzes the release of guanosine diphosphate (GDP) from the alpha subunit. GDP, an organic molecule involved in intracellular energy exchange, is replaced by the higher-energy guanine triphosphate (GTP). That, in turn, causes the alpha subunit to break apart from the beta and gamma subunits. The subunits then interact with other intracellular proteins to transmit signals down two independent pathways. Within a few seconds, GTP is converted back to GDP, the subunits recombine, and the signals are "turned off."

Illustration by William Oldham

beta/gamma subunits – both of which can stimulate independent signaling pathways.

Drugs that target GPCRs are rather blunt instruments; they can trigger far-ranging side effects. Is it possible to develop drugs that can be delivered – with "nano-surgical" precision – to the G protein of a specific receptor inside a particular type of cell? Could that achieve the therapeutic manipulation of a unique signaling pathway without affecting physiology anywhere else?

That prospect has tantalized Heidi Hamm, Ph.D., for more than two decades. But until recently the idea was, as Hamm puts it, "total pie in the sky."

In 1993, Hamm helped solve the structure of the alpha subunit with the late Paul B. Sigler, M.D., Ph.D., and his colleagues at Yale.

More recently, she and colleagues at the University of Illinois at Chicago and the University of Wisconsin-Madison showed how the beta-gamma subunit of an inhibitory G protein controls the release of neurotransmitters and hormones. It prevents vesicles containing these chemical messengers from fusing to the cell membrane and spilling their contents outside the cell.

The discovery, reported this spring in the journal *Nature Neuroscience*, could lead to new ways to treat conditions as diverse as pain and diabetes.

Hamm admits that G protein "therapy" is unlikely to attract major drug company investment – at least not yet. So five years ago, about the time she was moving from Northwestern University to Vanderbilt, she and her colleagues formed their own drug discovery company in Evanston, called cue BIOtech.

They chose to study a receptor embedded in the membrane of clot-forming platelets that binds the coagulation factor thrombin.

Blood clotting is essential for wound healing, but too much thrombin in the wrong place can trigger a heart attack. Blood-thinning drugs like Coumadin can prevent platelets from forming clots, but – unless the dose is carefully monitored – they can cause uncontrollable bleeding.

It has been difficult to block thrombin, which actually is an enzyme that activates its receptor by chopping it in half. So Hamm and her colleagues are trying to tackle the problem from inside the cell, by blocking receptor action instead of receptor binding.

So far, they've been able to make "very potent" small molecules that prevent the thrombin receptor from binding to or activating its G protein. "In cells – we haven't gotten to animals yet – they do exactly what we want them to do," she says. "They're inhibitors of platelet aggregation."

Drug companies are still skeptical, but now at least Hamm's idea doesn't seem so pie in the sky.

The role of government

The onerously high cost of making new drugs has not escaped the attention of federal health officials.

Last year in a report entitled "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products," the U.S. Food and Drug Administration called for increased public-private collaboration to boost drug development through the application of new technologies.

"We must modernize the critical development path that leads from scientific discovery to the patient," the report urged.

Developing new tools to aid drug discovery also is the goal of the Molecular Libraries Screening Center Network, established last year by the National Institutes of Health as part of its Roadmap initiative to help translate new scientific knowledge into "tangible benefits for people."

The aim is to harvest the fruits of the genomic revolution, make them available to scientists in universities and industry alike, and encourage them to work together as never before, explains Christopher P. Austin, M.D., senior advisor for translational research at the National Human Genome Research Institute.

"What we hope to do … is the high-capital investment … take the assay, do the robotic screening on a big library, do some initial chemistry, and give (scientists) back a small molecule compound which allows them to query the function of that gene or pathway – to test a hypothesis," Austin says.

The federal efforts have their share of skeptics, including Steven M. Paul, M.D., president of Lilly Research Laboratories. "I am worried that obtaining the kind of molecular probes required for even *in vivo* testing may prove to be too time-consuming and expensive," Paul says, "and may divert precious NIH funds away from basic or clinical biomedical research."

The federal initiatives in no way are meant to diminish government's role in supporting fundamental discovery, Austin responds. Tools developed by the public sector, however, can help establish the therapeutic potential of new compounds, and encourage industry to push them through the pipeline.

"As long as … we're all aware of what we can do and can't do, I think we'll be fine," he says. **LENS**

Thinking outside the cell

BY MELISSA MARINO

While most researchers plumb the depths of the cell to find drug targets for modern-day ailments, Billy Hudson, Ph.D, advances into the great expanse beyond the cells' margins to uncover drug targets hidden in this extracellular netherworld.

All cells exist in a sea of amorphous protein called the extracellular matrix. Composed primarily of insoluble collagens and proteoglycans, the matrix is more than just filler. It shapes tissues and supports and influences a multitude of cellular processes.

"Matrix components are specifically involved in the etiology and pathogenesis of disease, making the matrix a valuable drug target," says Hudson, director of the Vanderbilt Center for Matrix Biology.

Changes within the matrix underlie several of the complications of diabetes, particularly those involving the kidney. When glucose concentrations remain high for long periods, matrix proteins can be altered by glucose reacting with the amino groups of the proteins.

This process, called glycation, results in large, cross-linked molecules that inhibit normal cell function. In the kidney, glycation can limit the organ's filtering function and lead to kidney failure.

After several years of studying matrix changes involved in diseases of the kidney, Hudson was challenged to "do something" to stop the process by a former postdoctoral fellow at the University of Kansas, J. Wesley Fox, Ph.D.

"We were making strides in understanding the process, when Wes Fox says, 'Why don't you develop a drug to prevent that?'" Hudson recalls. "I said, 'That sounds good, but I don't really have the money to do that.'" Fox replied that he would find the money if Hudson worked on the drug.

With a unique combination of scientific expertise and a sharp business sense, Fox found investors to support Hudson's new line of inquiry. In 1994, Fox, Hudson and colleagues at the Karolinska Institute in Sweden founded BioStratum, a biotech company dedicated to pursuing the matrix as a drug target.

Efforts to pharmacologically arrest glycation-related pathology had shown some progress, but the most promising drug candidate, aminoguanidine, had proven too toxic in clinical studies. Drawing on his studies of the extracellular matrix, where diabetes-induced glycation is very active, Hudson found an effective compound that inhibited multiple pathways of glycation-related pathology, but was entirely natural in the body.

Hudson answered Fox's challenge with the compound pyridoxamine (brand name Pyridorin), a vitamin B6 derivative. Both *in vitro* studies and animal models showed that pyridoxamine prevented the glycation-related pathology that contributes to diabetic kidney disease.

Phase II clinical trials, completed last year, showed that Pyridorin was safe and effectively slowed the progression to kidney failure. Phase III trials are set to begin this year.

From this unconventional thinking, a new approach to drug development was born, bringing together academic researchers and the biotech industry to chase down the next generation of pharmaceutics.

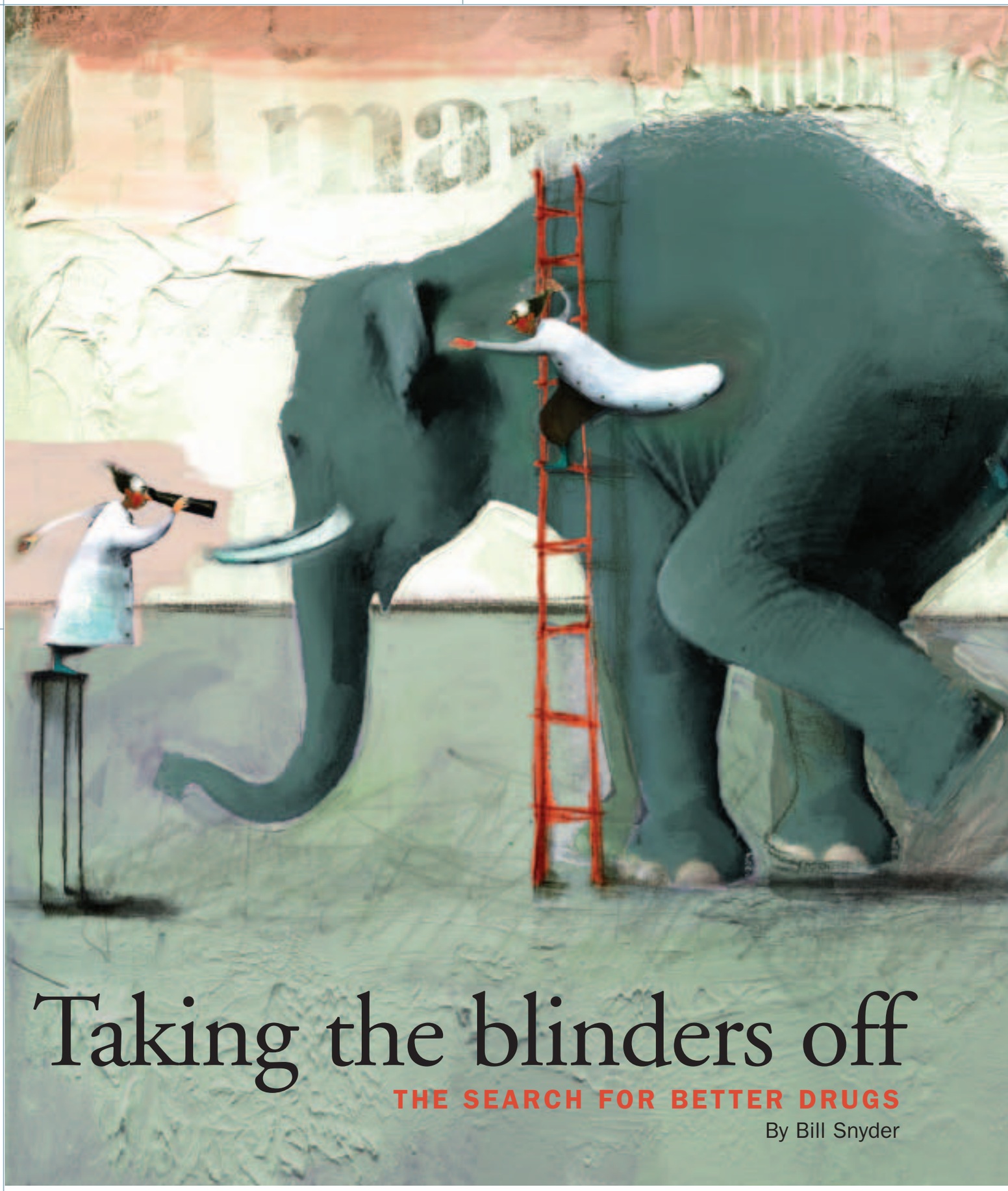
In contrast with pharmaceutical companies taking over drug development, this approach allows universities to continue to participate in the drug discovery and development process and to reap some of the financial benefits: the university and researcher can maintain the patent on a therapy and license its use.

Fox has gone on to become president and CEO of another biotechnology company, NephroGenex, Inc., which was co-founded by Hudson. In Hudson's case, the foray into biotech has had a beneficial impact on his more basic research interests as well.

"I now have two additional grants based on that drug (Pyridorin) to explore basic mechanisms – not to develop a drug – and others have been awarded NIH grants to explore the actions of Pyridorin," Hudson says. "So there is a positive feedback into basic science that can come from this approach."

Billy Hudson, Ph.D., (left) discusses a research project with graduate student Roberto Vanacore.

ANNE RAYNER



Taking the blinders off

THE SEARCH FOR BETTER DRUGS

By Bill Snyder

Illustration by Antonello Silverini

The recent withdrawal of the blockbuster painkillers Vioxx and Bextra from the market underscores an urgent need to upgrade the tools and science of drug discovery, say academic and government scientists. ✳ "We are truly a blind man and the elephant," says Christopher P. Austin, M.D., of the National Human Genome Research Institute.

The human genome may encode a million distinct protein targets, yet only about 500 of them have been "hit" by small-molecule drugs. Scientists are only beginning to understand how drugs aimed at a single target may affect diverse physiological pathways and systems.

"If you pull one lever, it's going to have an effect on another lever, which is connected to two other levers," Austin says. "Before you know it, you've pulled the tail of the elephant and activated the elephant's brain, which makes the elephant pick up its foot—which you didn't know exists—and stomp on you ...

"You can see the leg coming up in the air, but you say, 'Is that really a leg coming up in the air? I didn't know *that* was there.' You don't know until it lands on you," he says.

That's what happened with the selective COX-2 inhibitors Vioxx and Bextra, Austin says.

The drugs were developed to relieve arthritis pain and inflammation without the gastrointestinal side effects of traditional anti-inflammatory drugs, which block both cyclooxygenase (COX) enzymes. Only after millions of people had taken the drugs for years did it become apparent that they increased the risk of heart attack and stroke.

"What we still really lack in the whole drug discovery/drug development pipeline is good enough predictive toxicology," says Daniel C. Liebler, Ph.D., director of the Proteomics Laboratory at Vanderbilt.

"We can certainly give a very toxic drug to a rat or a mouse or a dog, and observe classic signs of toxicity (such as) changes in liver and kidney function tests," Liebler says. "But what we lack are good biomarkers for more subtle dysfunctions that will ultimately manifest themselves after the person's taken a drug for six months … like with Vioxx."

Proteomics, the study of the proteins, is one avenue toward that goal.

In the last few years, through such technologies as mass spectrometry, scientists have identified protein markers that seem to correlate with the emergence or progression of certain diseases, and with the response of disease to treatment.


ANNE RAYNER

"What we found was a genetic polymorphism which is much more common in African-Americans than in Caucasians … This was a completely unexpected finding … When you propose these genetic studies, people will say, 'Well, you're going on a fishing expedition.' And I say, 'Yeah, but this time we caught a whale.'"

David W. Haas, M.D., principal investigator, AIDS Clinical Trials Unit at Vanderbilt

In a mouse model of breast cancer, for example, Vanderbilt researchers recently showed that the level of several proteins plummeted within 12 hours after administration of Tarceva, a cancer drug that blocks the receptor for epidermal growth factor. This suggests that the proteins may be "biomarkers" for tumor growth.

"You could see these changes … way before any surgical or MRI (magnetic resonance images) will show tumor shrinkage," says Richard M. Caprioli, Ph.D., director of the Mass Spectrometry Research Center, who participated in the research.

More study is needed to determine whether a drop in the concentration of these proteins can be reliably correlated with tumor shrinkage in response to Tarceva. With the help of proteomics in the future, however, "we might be able to predict if a drug is going to be effective in a patient – even after the first dose," Caprioli says.

Watching drugs work

Imaging technologies offer another avenue for predicting the effectiveness of drug therapy.

Researchers in the Vanderbilt University Institute of Imaging Science are exploring dynamic contrast imaging, an MRI method that can create a three-dimensional image of angiogenesis, new blood vessel formation. When standardized, this method may provide a way to determine the effectiveness of anti-angiogenic agents, says institute director John C. Gore, Ph.D.

Vanderbilt recently purchased a 7-Tesla magnet, 140,000 times the strength of the Earth's magnetic field, which will allow institute researchers to conduct magnetic resonance spectroscopy.

Using this technique, researchers can measure very precisely the levels of neurotransmitters in the brain. "We think that's an important area," Gore says, "not only for certain brain disorders such as addiction, but also for looking at the effects of drugs."

Positron emission tomography or PET is another imaging technology that is being harnessed for drug discovery. By tacking a radioisotope of fluoride or carbon onto a drug, for example, researchers can use PET to detect the radiation emitted by the labeled drug, and create an image of where it goes in the body.

Fluorescence imaging techniques, such as two-photon excitation microscopy, potentially provide a way to look into the living cell and watch what happens when a drug hits its target. This not only may aid drug discovery; it may salvage a promising class of cancer drugs called MMP inhibitors that were largely abandoned by drug companies after several clinical trials failed to show any survival benefit in patients with advanced disease.

MMP stands for matrix metalloproteinases, enzymes that are thought to contribute to the growth and spread of cancer, by helping to increase the tumor's blood supply and means of escape to other parts of the body.

Vanderbilt cancer researchers have developed a "proteolytic beacon" that can detect and measure MMP activity. The beacon is a fluorescent probe that releases a flash of fluorescence when split by the enzyme.

When an MMP inhibitor is given to block the enzyme, the beacon doesn't flash as brightly. In this way, the researchers hope to determine the dose of drug necessary to inhibit these enzymes, as well as

In the future, with the help of proteomics, "we might be able to predict if a drug is going to be effective in a patient – even after the first dose."

which patients are most likely to respond to therapy.

"We're talking about cellular-based screening, high-content screening," says David W. Piston, Ph.D., professor of Molecular Physiology and Biophysics who is participating in the research. "If you're doing front-line screening in the cell, you're two steps closer to the patient."

Eventually, data from these studies will be integrated with data from genomic and proteomic studies to build "3-D models" that more accurately predict drug activity. "You're going to find a lot fewer things that take you down the wrong path," Piston predicts.

Sidelining the side effects

One of the biggest barriers to the successful launch of a drug is the adverse drug effect or unexpected side effect that may not become apparent until late in clinical testing or after marketing.

While the adverse effect may occur in only a tiny minority of patients, it may be serious enough that the drug company has no choice but to flush the entire effort – perhaps 12 years of work and up to a billion dollar investment – down the drain.

Advances in genetic research may come to the rescue.

In the late 1970s and early 1980s, Vanderbilt scientists led by Grant R. Wilkinson, Ph.D., D.Sc., for example, identified some of the first polymorphisms, or genetic variations, in a group of liver enzymes called cytochrome P450s that metabolize or break down drugs in the body. Drugs are more likely to reach toxic levels in people whose enzymes do a poor job breaking them down.

More recently, Wilkinson and his colleagues, including Richard B. Kim, M.D., and David W. Haas, M.D., discovered that a polymorphism in a drug-metabolizing enzyme gene impairs the ability to metabolize the AIDS drug efavirenz. This polymorphism is about six times more common in African-Americans than in Caucasians, which may explain why efavirenz blood levels are generally higher in African-Americans.

Individuals with this genetic variant tend to accumulate higher levels of the drug in their blood, and as a result they may experience mental confusion, strange dreams and other central nervous system disturbances, says Haas, principal investigator of the Vanderbilt AIDS Clinical Trials Unit. The side effects can be so disturbing that patients stop taking their medication.

Pharmacogenetics – the study of how genetic differences affect drug

Viagra
and the value of serendipity

Jackie Corbin, Ph.D., didn't set out to develop a drug. He just wanted to do good science and understand how the body works.

He couldn't have known at the outset of his career that his work would lay the foundation for the blockbuster drugs for erectile dysfunction: Viagra and related compounds.

It's hard to pinpoint the first step down the road that led to Viagra, but Corbin, professor of Molecular Physiology and Biophysics at Vanderbilt, has forged ahead on this path since the 1960s.

"We never had any thoughts about developing any pills when we started our research," said Corbin. "When my research first started, we were trying to figure out how cyclic nucleotides (cyclic AMP and cyclic GMP) worked in the body. That was a very basic physiological question."

Cyclic GMP and cyclic AMP are second messengers, molecules that carry signals from the cell surface to proteins within the cell. Earl Sutherland, M.D., the late Nobel laureate and Vanderbilt professor, discovered cyclic AMP in the 1950s while studying the cellular action of hormones. Cyclic GMP was discovered later.

Sutherland's work also suggested the existence of enzymes called phosphodiesterases, or PDEs, which degrade cyclic nucleotides.

In the early 1970s, scientists knew that cyclic AMP and cyclic GMP bind to and activate intracellular protein kinases, enzymes that regulate the activity of other cellular proteins. It was believed that these were the only cyclic nucleotide-binding proteins present in mammals.

In 1976, Corbin and his postdoctoral student Tom Lincoln, Ph.D., identified a novel protein that bound to cyclic GMP. Corbin, Lincoln and their colleague Sharron Francis, Ph.D., currently professor of Molecular Physiology and Biophysics, eventually purified and characterized the newly recognized protein, determining that it was a phosphodiesterase that degrades cyclic GMP. It was later named PDE5.

Around the same time, other groups showed that increased intracellular cyclic GMP levels promote the relaxation of smooth muscle, while PDEs that degrade cyclic GMP counter this action. These findings suggested that blocking the enzymes could relax the musculature of blood vessels, and consequently lower blood pressure.

At that point, drug companies took interest.

"In the mid-'80s, drug companies would come to us and ask us for our enzyme and for our consultation to work to develop inhibitors to block (it)," Corbin said.

Pfizer Pharmaceutical developed and began testing one compound, but an interesting side effect shifted the company's attention – away from blood pressure.

"Sharron and I were at a meeting in the early '90s, and had dinner with some of the Pfizer people. We knew they'd been working on these inhibitors, so we asked if they had any good ones. They said '…we've got one where its effect on blood pressure is not that great, but some male patients have noticed it causes penile erection.'"

Pfizer began clinical trials of their compound, sildenafil (Viagra), on men with erectile dysfunction. The drug proved highly effective and had few side effects. Viagra hit the market in 1998 and soon became one of the best-selling drugs in history.

Today, Viagra and related PDE5 inhibitors tadalafil (Cialis) and vardenafil (Levitra) are some of the most financially successful drugs on the market. The drugs are now being studied in other conditions including pulmonary hypertension, Raynaud's Syndrome (a circulatory disorder), recovery from stroke, cystic fibrosis, and as possible preventives for erectile dysfunction and heart disease.

"So we kind of accidentally entered the Viagra field by working on cyclic AMP and cyclic GMP, which just happened to be crucial mediators (of erectile dysfunction)," says Corbin, whose lab continues to investigate PDE5. "But we think that Viagra wouldn't have been possible if we had not laid the groundwork and discovered the enzyme and the mechanism.

"Our work involved some logic, some prediction, some direction, but a lot of serendipity. I like to think that's the way basic science ought to be."

– MELISSA MARINO

ANNE RAYNER

"What the human genome is teaching us is that there is tremendous variability among individuals at the genetic level … and that it ought to be possible to understand how that variability … in a whole set of genes might perturb responses in an individual or in a group of people to drugs."

Dan M. Roden, M.D., director of the John A. Oates Institute for Experimental Therapeutics at Vanderbilt

response – may lead to more "rational" drug development and prescribing. "It may be possible in the not-too-distant future to screen a person's genome for polymorphisms that have clinical implications and then choose an appropriate regimen or an appropriate drug dose based on knowing their genetic background," Haas says.

Haas says the polymorphism that affects the metabolism of the AIDS drug could not have been discovered without the help of a national DNA "repository" established by the Adult AIDS Clinical Trials Group, a federally funded group of 34 centers in the United States, including Vanderbilt, which evaluates new AIDS treatments.

DNA on deposit

Vanderbilt recently joined forces with the U.S. Food and Drug Administration, the pharmaceutical giant GlaxoSmithKline and First Genetic Trust, a Chicago-based company that has pioneered DNA banking, to advance genetic-based medicines and diagnostics.

The goal: to expand the collection of DNA samples from patients who suffer a rare adverse drug event called long QT syndrome. The syndrome can lead to potentially fatal arrhythmias, abnormal heart rhythms.

When physicians anywhere in the country report drug-induced long QT syndrome to the FDA, the agency will refer them and their patients to Vanderbilt for participation in the study.

"We've been interested in this rare adverse drug effect for many years, with the idea that it is genetically determined," says Dan M. Roden, M.D., director of the John A. Oates Institute for Experimental Therapeutics at Vanderbilt and a principal investigator in the collaboration.

"The key first step in searching for genetic variants that may increase susceptibility is finding enough patients who have suffered this unusual event," Roden says. If genetic variants are found, it may be possible to develop diagnostic tests that can be used to identify, in advance, people at high risk for this side effect if they take certain drugs.

Genetic testing is not an easy sell, however. "There are drugs for which there are potentially very effective genetic tests that can predict, with a high degree of probability, side effects," Haas says. "But the companies that make those drugs are not pushing for genetic testing because they think … they will lose market share.

"Suppose there are three drugs for providers to choose from, and one of them shows that a genetic test will help you prescribe it better," he explains. "Most clinicians right now would rather just write the prescription for the other drugs and avoid genetic testing.

"Genetics is not going to be used to guide prescribing just because it makes sense. It will only happen if accomplished, forward-thinking investigators, in partnership with the community, really push this forward and make it a reality."

> "Genetics is not going to … guide prescribing just because it makes sense. It will only happen if … investigators (and) the community really push this forward."

In 2000, Haas and his colleagues began developing a process for obtaining informed consent to collect an extra blood sample for DNA studies from patients participating in AIDS clinical trials. Since then, the repository, which is housed at Vanderbilt, has collected nearly 8,000 samples from different individuals.

So far, about 10 genetic studies have been undertaken using the DNA samples. Information from these studies is being used to help develop a vaccine against the AIDS-causing human immunodeficiency virus (HIV), and to develop treatments that can rebuild or "reconstitute" the immune systems of patients that have been damaged by HIV infection.

"It's really just a glorious explosion of discovery," Haas says.

William E. Evans, Pharm.D., director and chief executive officer of St. Jude Children's Research Hospital in Memphis, agrees. Evans and his colleagues pioneered the use of genetic testing to improve treatment of childhood cancers.

"The burden is on us at academic medical centers to begin to not only provide … evidence that these genetic polymorphisms are influencing significantly the drug response," Evans said during a recent lecture at Vanderbilt, "but to begin to incorporate that into treatment plans and protocols and to show … that it actually makes a difference." **LENS**

Why targeted cancer therapies have not hit the 'bull's-eye'

BY MELISSA MARINO

Mace Rothenberg, M.D.

ANNE RAYNER

An informal search of medical news Web sites on any given day will typically return dozens of reports on the discovery of a new cancer-related gene, yet only five new agents have been approved for the treatment of cancer since 2000.

With so many new molecular and genetic targets being identified, why is the pace of cancer drug development so slow?

Leading researchers believe current design and analysis of clinical trials may contribute.

In a 2003 review in *Nature Reviews Cancer*, Vanderbilt cancer researchers Mace Rothenberg, M.D., David Carbone, M.D., Ph.D., and David Johnson, M.D., identified factors that may be prematurely sending some potentially useful cancer drugs to an early grave.

From a large volume of preclinical studies, compounds that inhibited angiogenesis, the formation of new blood vessels, appeared to be the "dawn of a new era" in cancer therapy, describes Rothenberg, professor of Medicine and Ingram Professor of Cancer Research.

Laboratory studies suggested that angiogenesis inhibitors alone could be used to cure cancer. Because blood vessel formation was one of the decisive factors in tumor growth, researchers thought that inhibiting this process would kill tumors by robbing them of their blood supply. Also, angiogenesis inhibitors were thought to be much less toxic than standard chemotherapeutics.

When the first angiogenesis inhibitor trials began, an ensuing hysteria – in the form of enrollment "lotteries" and patients traveling cross-country to participate – followed. The frenzied expectation surrounding these drugs soon diminished as the evidence began coming in from the clinical trials. When used alone, the first generation of angiogenesis inhibitors were not clinically effective.

These "failures" forced scientists to rethink their strategy. The tide shifted to testing angiogenesis inhibitors as an adjunct to conventional cytotoxic therapies and to developing better angiogenesis inhibitors. This strategy proved much more effective, leading to the approval of the first angiogenesis inhibitor, Avastin, last year.

"Animal/preclinical models have been very useful in helping us explore the biology of cancer, but we have very few useful models that have been developed that recapitulate the complexity of human cancers in the clinical setting," Rothenberg explains.

"I think the mistake has been in assuming that these results will accurately predict clinical effect. They do not."

In the 1990s, researchers optimistically predicted that targeted therapies – drugs designed to act only on a single cellular component – would be more effective and would eventually replace conventional cytotoxic therapies. Since targeted therapies would only affect cells that harbored the specific target, the drugs also would be safer and cause less damage to normal tissues.

This hypothesis was based largely on trials of Herceptin, the first growth factor targeted monoclonal antibody approved to treat breast cancer. It prevents epidermal growth factor (EGF) from binding to a receptor known as Her2.

"At a very crucial time in its development, it was recognized that only those tumors that had significantly high levels of expression of the receptor Her2 would likely respond," Rothenberg says. Because of this, the clinical trials were limited to patients whose tumors overexpressed Her2, and quickly showed that it was a beneficial agent to incorporate into therapy.

However, when the same strategy was tried with another receptor that binds EGF, Her1, "Lo and behold, this didn't carry over," he says.

Her1-targeted drugs such as Iressa, Tarceva and Erbitux showed a similar activity in all patients, whether their tumors expressed low, intermediate or high levels of the receptor. Even patients whose tumors don't express Her1 benefited from Erbitux.

Then, last year, scientists discovered that patients were more likely to respond to Iressa or Tarceva if they had a mutation in the Her1 receptor.

"So that taught us an important lesson," Rothenberg says. "Even though we talk about targeted therapies, different targets may have different rules of engagement. We can't make a sweeping assumption that what is true in one is true in all."

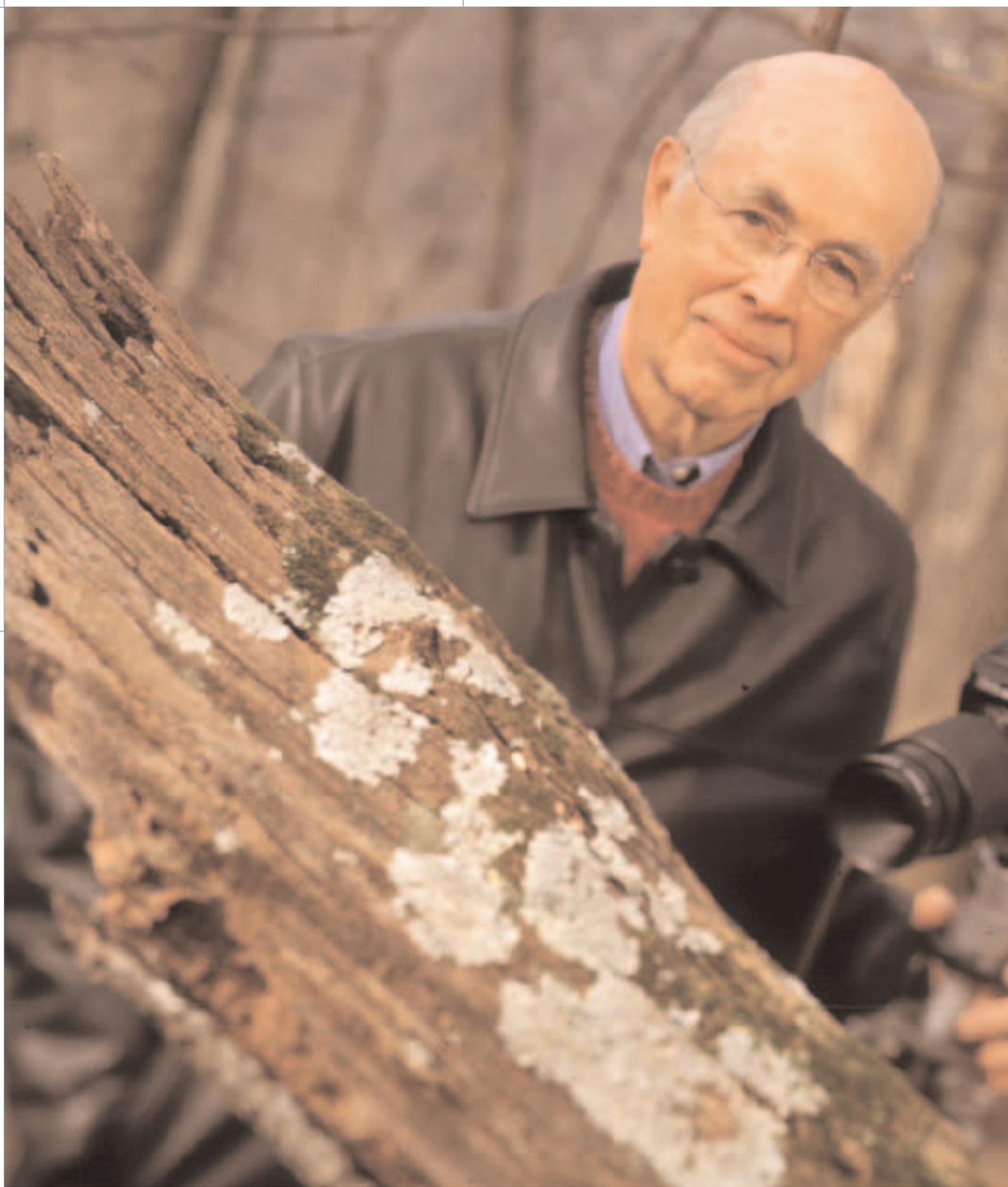
Underlying the unpredictability is a significant amount of crosstalk between numerous cell-signaling pathways.

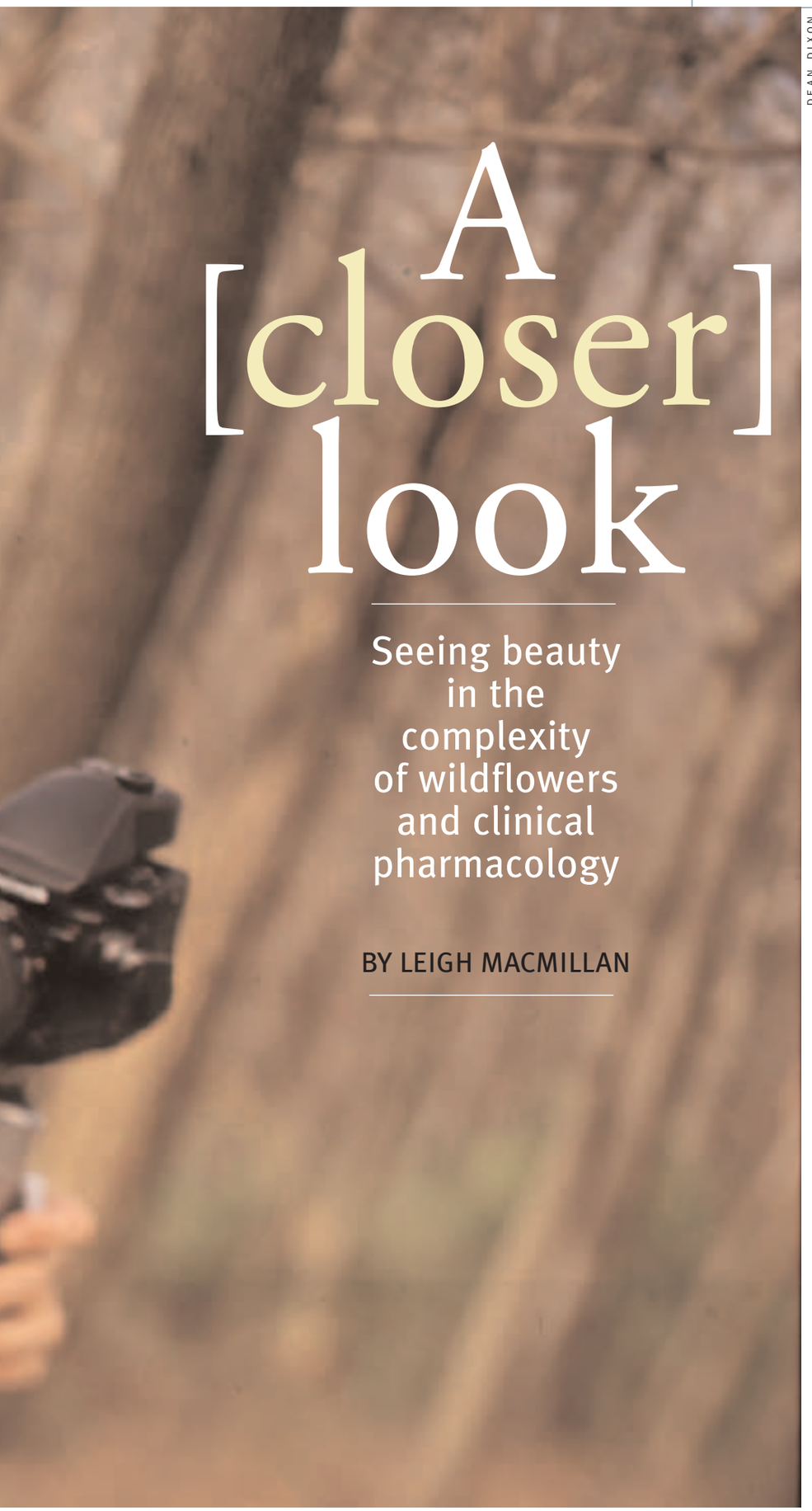
"Shutting down one pathway doesn't necessarily lead to death of the cancer," he says. "Other regulatory pathways may be abnormally functioning in these cells. Therefore, our approach currently is to target complementary pathways, so that we can more completely shut down those growth factor signaling pathways that are driving the cancer cell."

Rothenberg and colleagues also are using pharmacogenomic profiling to define the biology that drives the clinical activity of drugs, both the antitumor activity and toxicity.

"To relate this information about drug response to genomic or proteomic profile of the tumor will give us hopefully more useful and predictive information about what drugs might be useful in what doses and in what setting," he says.

"We are at an unprecedented time of opportunity in the field of drug development," Rothenberg concludes. "The gap that has existed for many years – between what we understand about the science of cancer and the way we treat cancer – is narrowing."





DEAN DIXON

A [closer] look

Seeing beauty in the complexity of wildflowers and clinical pharmacology

BY LEIGH MACMILLAN

Looking through a camera lens was nothing new for John A. Oates, M.D., but this time the view was different. As he trained his new macro lens on a Spring Beauty, an ordinary pink and white wildflower that graces woody hillsides and uncultivated front lawns, he was struck by the extraordinary beauty of the magnified flower.

The experience 15-odd years ago sparked him to enroll in a photography course and to add wildflower hunts to his global travels.

"It is certainly true that I've had a fascination with the intimate detail of wildflowers – details that elude the view from a distance," he says during a recent conversation in his office at Vanderbilt University Medical Center. He's silent for a long moment before launching into a quote from Henry David Thoreau's *Walden*, slowly at first, then with growing confidence.

"The scenery of Walden is on a humble scale, and, though very beautiful, does not approach to grandeur, nor can it much concern one who has not long frequented it or lived by its shore …"

Leaning back in his chair, he's careful to note that Thoreau's comment didn't inspire him, but that it fits.

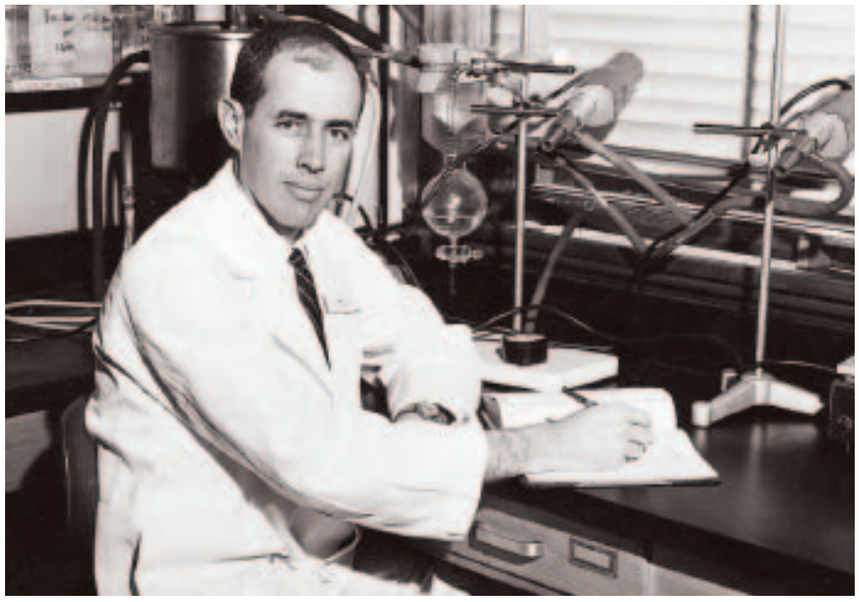
"What he's saying is that the beauty isn't something you spot while driving by – like the Rocky Mountains – it's only apparent to the people who frequent the shores … to those who become intimately acquainted with it," Oates says.

Oates frequents the shores – of wildflowers, of biological signaling pathways, of the discipline of clinical pharmacology. He looks closely and sees deeply.

His dossier is thick with achievements: discoveries that shaped the field of research related to biologically active molecules called prostaglandins; activities that built the foundations for the discipline of clinical pharmacology and made its principles central to drug development.

"I think he's one of the greats of Pharmacology and of American medicine," says Garret A. FitzGerald, M.D., chair of Pharmacology at the University of Pennsylvania School of Medicine.

At 73, Oates, the Thomas F. Frist Sr. Professor of Medicine at Vanderbilt, could easily choose to relax his intense gaze. But there are too many biological complexities yet to understand, too many wildflowers yet to behold.



Pictured here, from top: John Oates, M.D., in his Vanderbilt laboratory in the 1960s; during a family whitewater rafting trip on the Nantahala River in North Carolina in 1991 (Oates is front right); and with his research nurse, Sheilah Winn, R.N., who has worked with him since 1989. At bottom, the Oates family on vacation in the mid-1990s. From left, Meredith, Oates' wife of 49 years, John Oates, daughter-in-law Jennifer, youngest son Jim, daughter Larkin, granddaughter Caroline, daughter-in-law Jane, and oldest son David. Of their grandchildren, who now number six, Meredith Oates says they think their grandfather is "the best playmate."

Photos courtesy of the Oates family

Oates and his team recently received a three-year award to study the link between the cyclooxygenase (COX) enzymes – which produce prostaglandins and other products – and Alzheimer's disease. The group has ongoing studies to understand how acetaminophen and aspirin interact with the COX enzymes to block activity, and why those drugs are more effective in some cell types. He is in conversation with division colleagues about using acetaminophen to combat diseases as varied as rhabdomyalysis and malaria.

He continues to be active in the Division of Clinical Pharmacology he founded more than 40 years ago, and is watching with interest the establishment of the John A. Oates Institute for Experimental Therapeutics at Vanderbilt.

A broad grin creeps across his face when he is asked how long he'll keep all this up. "As long as I've got ideas," he chuckles.

[Sowing the seeds]

The ideas started coming early. As a young medical student at the Bowman Gray School of Medicine of Wake Forest College, Oates had the option of writing a paper or doing a research project for the physiology course.

"A group of my friends and I decided to test whether or not peritoneal dialysis would be beneficial for kidney failure," he recalls. "At the time, that idea hadn't been introduced clinically."

The group had only limited access to laboratory equipment, but the physiology department had an excess of electrocardiogram machines. The bright medical students reasoned that they could use the EKG to look for effects of elevated potassium – one way that kidney failure leads to a fatal outcome.

Their experiments in dogs showed that peritoneal dialysis prevented elevated potassium following renal failure. The taste of research whetted Oates' appetite, and he went looking for more.

What prompts a medical student to seek opportunities to study potassium and the heart?

"I guess I was always curious," Oates says, recalling his eastern North Carolina childhood spent exploring, camping, sailing and reading adventure novels.

Colleagues agree.

"I think he's much more curious than most," says Robert A. Branch, M.D., director of Clinical Pharmacology at the University of Pittsburgh, who worked closely with Oates for 20 years. "He's logical; he's well-informed; but primarily I think his driving force is curiosity."

Pictured here: John Oates, M.D., (center) featured on the cover of the May 3, 1971, issue of *Modern Medicine* with (from left) research fellows Russ McAllister, M.D., Barton Grooms, M.D., and Cliff Cleveland, M.D.

"He has an inquisitive mind – a *very, very* inquisitive mind," says L. Jackson Roberts II, M.D., professor of Pharmacology and Medicine at Vanderbilt.

When in 1955 Oates approached one of the cardiologists at Wake Forest about studying the effects of potassium in the heart, he was directed to the chair of the Biochemistry department, Camillo Artom, M.D., Ph.D.

"I was a naïve student who thought I could do anything," Oates says.

Artom listened politely, told Oates his ideas were interesting, and then advised him instead to work on the main research area in the Artom laboratory: phospholipids – the fatty molecules that constitute the cell's membrane and are the starting materials for the production of many signaling molecules.

The seeds were sown. Both cardiovascular biology and lipid biology would become recurring themes in Oates' research career.

His time in the Artom laboratory was likely responsible for his success in obtaining an internship position at Cornell Medical Center, Oates says. "I wasn't the top student in my class ... and that was a great institution."

At Cornell, Oates was introduced to the idea of joining another great institution, the National Institutes of Health. The "Doctor Draft" implemented at the start of the Korean War was still in place, and Oates was prepared to enter the Air Force when he learned that a fellow resident was going to the NIH instead of into the Army.

He applied and was offered a clinical associate position at the NIH.

"I think I was fortunate that I was in a house staff program where there were bright people who were interested in research and one of them put me onto this opportunity at the NIH," Oates says.

The move to Bethesda proved to be a key one.

[The thrill of discovery]

One night in 1959, Oates headed back into the lab at the National Heart Institute – now the National Heart, Lung, and Blood Institute – with the sense that he and his team were onto something big. The graph he charted from the day's data didn't let him down. He called one of his colleagues at home at 11 p.m. to relate the news: the drug they were studying appeared to lower blood pressure.

It was the first time Oates remembers feeling the thrill of discovery, and he was hooked.

"It's incredibly exciting, to be working on something for a long time, and then all of a sudden – bang! – it's there, something new that nobody has ever seen before," he says. "In this case, it's fair to say that we all had hoped the drug might have an effect on blood pressure in humans, but there was no precedent for it in prior animal studies."

The drug was methyldopa. At the time of Oates' discovery, there were no effective drugs for treating patients with severe hypertension – the subset of hypertensive patients who are most susceptible to stroke, heart attack and kidney failure. Methyldopa, developed and marketed as Aldomet by Merck, became the first.

The NIH group, headed by Albert Sjoerdsma, M.D., Ph.D., and Sidney Udenfriend, Ph.D., had not set out to discover methyldopa's usefulness as an antihypertensive drug. The drug from Merck was simply an experimental tool, part of ongoing efforts to understand the biochemistry – synthesis and metabolism – of aromatic amines like norepinephrine and serotonin, as a way to gain information about hypertension and its treatment.

"The pharmacologists at Merck had completed toxicology studies and commented to us that they had given rabbits doses of up to 1 gram per kilogram without lowering blood pressure or having any adverse effect," he recalls, a mischievous twinkle in his eye. "They said it can't possibly be pharmacologically active."

Aldomet was one of the major treatments for severe hypertension for about 15 years, Oates says. It was replaced by a newer generation of antihypertensive agents, but is still used for certain indications, including high blood pressure in pregnancy.

Oates' experience in the Sjoerdsma-Udenfriend unit set his career trajectory, he says.

"I think one of the most important things you can do as a young person entering science is to work with the right mentor – somebody who's successful and having fun with it. Science is like most things in life: you win some and you lose some. In order to sustain through the ups and downs, you have to have tasted success in science and had the thrill of a discovery, or two, or three ...

"At the NIH there were a lot of young scientists my age who were really having a ball doing research, and it was because of the senior leaders who were creative, energetic, had good ideas, and were committed to clinical research. I was fortunate for having landed in a group like that," Oates says.

It was in this dynamic and uniquely productive environment – where discoveries and approaches from the laboratory were applied to clinical research – that Oates' vision for clinical pharmacology germinated. His ideas sprouted and took form in the Division of Clinical Pharmacology at Vanderbilt, the division Oates founded in 1963 and directed for 25 years.

[Growing a discipline]

Oates was not alone in embracing the notion of a discipline that would bridge

Pictured here: Two examples of Oates' extensive collection of wildflower photos: Indian Paintbrush (left) and Michigan Lilies. The lilies were found on the Middle Tennessee farm of Vanderbilt colleague Mildred Stahlman, M.D., but have now disappeared, Oates says.

laboratory research and clinical investigation. He and a handful of other young scientists, some of them his peers from the NIH, began to call themselves clinical pharmacologists and form units around the country in the early 1960s.

"Clinical pharmacology became what those five or so investigators took it to be," says David Robertson, M.D., director of Vanderbilt's General Clinical Research Center. "They all knew each other, and they met and called themselves the 'non-society of clinical pharmacology.'

"They were each great scientists in their own fields, and they insisted on carefully controlled studies. I think if John had an ideology with which he approached research, it was that measuring things carefully and thinking properly about study design was the way to make discoveries."

At Vanderbilt, Oates found a confluence of the right ingredients for a successful program, including a pharmacology chairman, Allan D. Bass, M.D., who was committed to the idea, and a thriving clinical research center, one of the first NIH-funded centers in the country.

"Allan Bass had a vision that the scope of pharmacology ought to include clinical investigation and human pharmacology," Oates recalls, "and that was unique at the time."

So with Bass' enthusiastic support and an early award from the Burroughs Wellcome Fund, Oates set about building a world-class clinical pharmacology program – a division of the Department of Medicine with strong connections to the basic scientists in the Department of Pharmacology. His efforts met with stunning success.

"I think John's extraordinary talents have been in having a vision for the field of clinical pharmacology and in recruiting and retaining people who have very complementary skills and creating an environment in which they flourish," says FitzGerald, who served as the second director of Clinical Pharmacology at Vanderbilt.

"Those talents have been why, under John's leadership, this model of what we call translational research now really flourished at Vanderbilt in a way that I don't think it did anywhere else, and that's really his great gift to that institution and to the country."

Branch, who was a faculty member in Vanderbilt's Clinical Pharmacology division for 16 years, borrowed from Oates' model when he set up the division at Pittsburgh.

"The most important thing was the atmosphere of getting enterprising people to be enterprising," Branch says. "He didn't tell people what to do. He had foresight in putting together infrastructures, like the mass spectrometry resource. He understood the mechanics of networking and cooperative multidisciplinary research way before it became popular and a buzzword at the NIH.

"In the first generation of clinical pharmacology centers, as the leaders retired, the centers fell apart. John's is the only one, that when he moved on to become chairman of Medicine, continued to grow. And it's *the* most substantial clinical pharmacology unit anywhere."

From the vantage of this influential division, Oates shaped clinical pharmacology's impact. He has served as a scientific adviser over the years to various pharmaceutical and biotechnology companies, including Merck.

"He understood what was required to work out how well drugs worked, and why they worked, and who they worked in," says David Shand, M.D., Ph.D., a retired pharmaceutical company executive who was on the Vanderbilt faculty in the 1970s.

"He has been instrumental in our way of thinking about groups of drugs and drug interactions; it's really a style of thinking that he's contributed to the drug discovery and development process," Branch adds.

[Putting together the pieces]

Clinical pharmacology, perhaps more than other biomedical research disciplines, has an obvious link to the pharmaceutical industry, Oates says.

"To put it simply, you like for your work to be where the action is. And molecules going into human beings for pharmacologic purposes are what we're interested in. Our cooperation with industry has repeatedly been valuable in bringing us investigational tools for discovery."

Methyldopa was one such "tool" that allowed Oates and colleagues to illuminate aspects of blood pressure regulation. The team's research on guanethidine, another blood pressure medication, identified drug interactions as an interesting and important area in clinical pharmacology, Oates says.

Studies of a drug candidate that never made it to market also had a major impact on concepts in drug metabolism.

The drug candidate, code named SU-13197, was being investigated as a potential antiarrhythmic drug when the global chemical company Ciba enlisted Oates' assistance in studying its metabolism and human pharmacology.

"It was just the beginning of the era of realizing that it's important to investigate metabolic fate early in the process of drug development," Oates recalls.

Oates and his colleagues followed the availability of radiolabeled SU-13197, discovering that only a fraction of the unmetabolized drug appeared in the systemic circulation following oral administration compared to intravenous administration. It was the first solid evidence of what came to be known as "first pass metabolism" – the

clearance of an orally delivered drug by the liver and intestinal tract on the drug's "first pass" through these drug-metabolizing organs.

The team also found evidence that drugs with a high first pass metabolism, like SU-13197, had a high degree of inter-individual variation, a concept that continues to shape drug discovery and development now in the genomic era.

Grant R. Wilkinson, Ph.D., who joined the faculty in 1971, and Shand went on to develop what Oates calls "elegant clearance concepts" that describe drug disposition. But that would not have happened were it not for a "very proactive" interaction with industry.

"It's just one example of how our involvement with industry gave us the tools to make discoveries," Oates explains. "Once we had those tools, the opportunities for creativity opened."

Creativity has characterized Oates' distinguished scientific career. Among his many discoveries, those in the field of prostaglandin biology are most noted. When he became interested in these widespread signaling molecules, he traveled on sabbatical to learn firsthand from a leader in the field – the Karolinska Institute's Bengt Samuelsson, M.D., Ph.D., who went on to win the Nobel Prize for his work.

Oates has been "a trailblazer" in the development of new methodologies that contributed to the teasing apart of the components of prostaglandin physiology, Branch says.

Prostaglandins are members of a large family of molecules called eicosanoids that are derived from fatty acids, predominantly arachidonic acid, and which have varied and profound physiological and pathophysiological effects. The eicosanoid field started with the discovery of two compounds, and now boasts over 2,000 family members, Roberts says.

"His group would develop a new method that would allow that area to be developed, and then they would develop another new method and so on. It was painstaking work, and they put a lot of pieces of the jigsaw puzzle into the prostaglandin-eicosanoid story," Branch says.

The Oates team defined the role of prostaglandins in renin release by the kidney, demonstrating the importance of prostaglandins as a pathway parallel to the adrenergic nervous system in controlling renin release and regulating blood pressure.

The group also discovered that the prostaglandin PGD2 is the principal prostaglandin mediator in human mast cells. That finding is being explored in drug development for allergic rhinitis and asthma, Oates says.

As for his current research projects, he says they're at a "speculative stage," adding, with a sly chuckle, that "these are exciting times."

[A lasting legacy]

Oates' contributions have been honored many times over. He is a member of the prestigious Institute of Medicine of the National Academies of Science, the adviser to the nation on matters of biomedical science, medicine and health. He is a Fellow of the American Association for the Advancement of Science.

He singles out two awards as most meaningful to him: one from early in his career, the American Society for Pharmacology and Experimental Therapeutics Award for "Outstanding Basic Pharmacologic Investigations in Man;" and one from just last year, an Award of Excellence in Clinical Research from the General Clinical Research Centers Program of the NIH. These awards applaud the hypothesis-driven clinical research that has distinguished his career.

Central to such research is the patient, and Oates has never lost sight of his calling as a physician.

"He's in clinic every Monday; his patients love him," says Jason D. Morrow, M.D., current director of Clinical Pharmacology.

"He has been, first and foremost, a great physician," agrees Robertson. "He never let his people stop being clinicians."

Robertson is one of the more than 300 fellows who have trained in the Division of Clinical Pharmacology at Vanderbilt. About a third of them have gone on to leadership positions in either academia or industry related to drug discovery and development.

"If I had to pick the most influential person in clinical pharmacology in the United States over the past three decades, it's John," says Morrow, who also was a fellow in Clinical Pharmacology at Vanderbilt.

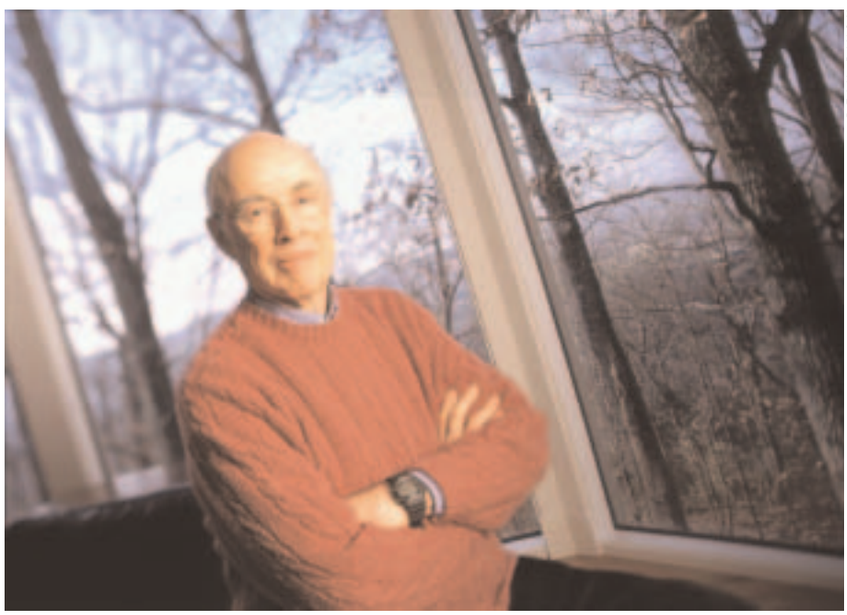
This legacy of success will be extended in the John A. Oates Institute for Experimental Therapeutics, launched last fall.

"This new institute recognizes Vanderbilt's commitment to growing the kind of science that John made famous here – understanding how drugs work in the body, why not everyone responds to drugs the same way, and how we can use that information to make better use of the drugs we have and to develop new drugs," says Dan M. Roden, M.D., director of the Oates Institute and former director of Clinical Pharmacology.

As the new institute blooms and begins to flourish, Oates will be watching.

Closely. **LENS**

"If I had to pick the most influential person in clinical pharmacology in the United States over the past three decades, it's John."



DEAN DIXON

First, DO NO HARM

PHYSICIANS AND DRUG SAFETY

By Lisa A. DuBois

At first, Nancy J. Brown, M.D., wasn't certain whether or not she was seeing a pattern among her patients.

It was 1992, and the young clinical pharmacologist at Vanderbilt University Medical Center noticed that some of her patients seemed to have an allergic-type reaction to ACE-inhibitors, medications used to treat hypertension and reduce the risk of heart disease and kidney failure.

Not commonly, but often enough to notice, some of them were coming in with symptoms of angioedema – swelling of the lips, face, tongue and throat. Even more disconcerting, it struck her that an inordinate number of patients with side effects were African-American.

Brown decided to pursue her hunch. First, she called various drug companies, but few had readily available data on adverse reactions. Next she spoke with Marie R. Griffin, M.D., MPH, a Vanderbilt pharmacoepidemiologist, who contacted colleagues at the U.S. Food and Drug Administration to see if there had been any similar reports.

As it turned out, a company had just submitted an application to the FDA for a new ACE-inhibitor drug, and had reported seeing higher rates of angioedema than anticipated. That company had included more African-Americans in its trials than previous studies had done.

Like sleuths, Griffin and Brown then examined the Tennessee Medicaid database, comparing rates of angioedema among both black and white patients on ACE-inhibitors with patients on calcium channel blockers, a different class of medication for reducing blood pressure.

"When we controlled for (type of medication) we found that blacks (on ACE-inhibitors) were four-and-a-half times more likely to have angioedema than whites," says Brown, now a professor of Medicine and Pharmacology. "The other thing we noticed was that there were a number of people who'd had episodes of angioedema who'd been left on their ACE-inhibitor."

In other words, even when patients presented with angioedema, many physicians hadn't made the connection that the medication was the underlying cause.

Part of the reason was because angioedema, even among blacks, is a rare event. But also, while some people took only a pill or two and quickly experienced dramatic swelling of their tongue or lips, other patients had been taking the medicine for months or even years before the side effect kicked in. Still others never experienced bad reactions.

Brown, who has earned national recognition for her research on blood pressure regulation, now has a grant to try to weed out the biologic mechanisms for angioedema induced by ACE-inhibitors. One of her concerns, she says, is, "How do you study something that is still a pretty rare side effect?"

Nancy J. Brown, M.D.: Always vigilant for the rare adverse side effect

Photo by Anne Rayner

At first glance, it would seem that if a drug has gone through the rigors of discovery and development, through clinical trials and FDA approval, any adverse side effects should have already been observed and noted. After all, isn't it the responsibility of the FDA to ensure that only safe drugs are put on the market?

The answer is yes – if only it were that easy.

Deadly elixir

Of late, scientists and regulators have been anxiously grappling with the problems posed by post-marketing surveillance of approved pharmaceuticals. What may seem like a miracle cure in controlled clinical trials, several thousand people strong, may become a totally different animal once it is released to the open market and prescribed by tens of thousands of physicians to millions of patients.

Ignoring strict warning labels, many patients take medicine off-label, meaning they take it for illnesses for which it hasn't been approved. They also take combinations of drugs that counteract each other's beneficial effects, under-dose to save money or take more than the recommended dose to try to get quicker relief.

Even more confounding is the fact that two patients with the exact same disease can follow the exact same treatment plan – and the drug works beautifully for one, but doesn't help the other patient at all.

All of these challenges have served to usher in a new era of pharmacoepidemiology – the study of pharmaceuticals among populations of patients. According to Wayne A. Ray, Ph.D., director of the Division of Pharmacoepidemiology at Vanderbilt, the field first emerged in the aftermath of two therapeutic disasters.

In 1937, a Tennessee drug company began selling Elixir Sulfanilamide, a sulfa drug used to treat streptococcal infections. More than 100 people, many of them children, died after taking the medication, which was dissolved in diethylene glycol, a toxic chemical normally used as antifreeze. In response, Congress passed the Pure Food, Drugs and Cosmetics Act of 1938, requiring products to be rudimentarily tested for safety before they reached consumers.

The second disaster involved the drug thalidomide, marketed in the 1950s and early '60s as a sleeping pill and a cure for morning sickness in pregnant women. Thalidomide caused profound birth defects in more than 10,000 children in 46 countries before it was pulled from the worldwide market.

Although a pharmacologist at the FDA, Frances Oldham Kelsey, M.D., Ph.D., prevented thalidomide from being marketed in the United States, the side effects were so catastrophic that in 1962 the United States began requiring that drugs undergo well-controlled studies demonstrating efficacy before they can be sold to consumers.

The problem in our present day and age, says Ray, is that the rather cumbersome guidelines for ensuring safety and efficacy of drugs slowed down the process of getting drugs to market, and in the 1980s consumers and pharmaceutical companies alike began pushing for quicker approval.

The upshot, he says, is that "… to get drugs to market in a reasonable amount of time, we put them through phase I, II and III trials, but we still don't know much about them. We know enough about a drug so that people can begin using it, but not enough about its long-term effects. So we have to keep studying it."

Unfortunately, that is where the existing system falls short. "Following a drug once it's on the market is a free-for-all," he says.

Reporting the signal

The system the FDA uses for conducting post-marketing surveillance of drugs, MedWatch, relies on doctors, nurses and pharmacists to report safety concerns, based on suspected serious adverse reactions they have observed. There are two instances in which this type of reporting system works well – if a problem arises that is extreme or unusual, or if a problem appears within a large proportion of consumers.

In the first instance, a drug may produce such an unusual, distinctive form of toxicity that physicians immediately take notice, such as the idiosyncratic birth defects among pregnant users of thalidomide.

Another example is the drug-induced arrhythmias discovered in consumers of the antihistamine Seldane.

"Seldane was given to millions of patients before the potential for severe drug reactions causing life-threatening arrhythmias was recognized," says Dan M. Roden, M.D., who directs the John A. Oates Institute for Experimental Therapeutics at Vanderbilt. "Most of the adverse effects only occurred in patients who were using Seldane in combination with other drugs."

Although the arrhythmias caused by Seldane toxicity were so rare that they were hard to detect, their uniquely abnormal patterns enabled physicians to eventually track similar peculiar rhythms among patients and trace them back to use of the

DEAN DIXON

Once in a lifetime

Finding a way to short-circuit sepsis

BY LISA A. DUBOIS

Gordon R. Bernard, M.D.

They said it couldn't be done.

Despite decades of research, scientists had been unable to find a treatment for severe sepsis, a life-threatening complication of bacterial infection, usually of the bloodstream, that kills at least 250,000 adults in the United States each year. During the previous 25 years, more than 30 compounds had been tested to treat severe sepsis. All of them had failed.

"Researchers were getting discouraged. They were saying that this disease is too severe and too complex," says Gordon R. Bernard, M.D., an internationally known sepsis researcher and assistant vice chancellor for Research at Vanderbilt University Medical Center.

Frustrated, some scientists argued that the U.S. Food and Drug Administration had set impossibly high standards for treating near-death patients in the intensive care unit. The FDA deemed an ICU drug efficacious only if the patient was still alive after 28 days. Despite the criticism, the agency stuck to its "28-day, all-cause mortality endpoint" required for approval.

Then in 1994, Bernard received a phone call from investigators at Eli Lilly & Co. in Indianapolis. They had patented a recombinant human activated protein C (APC) as a potential heart drug, but had decided not to pursue if for that use.

APC has anti-coagulant and anti-inflammatory properties. It can become depleted during an infection and as a result, clots can form indiscriminately throughout the body, cutting off the blood supply to vital organs. In this way, the initial infection can set off a chain of reactions, leading to multi-organ system failure and death.

Searching for another use for their compound, Lilly scientists noticed that in previous studies in baboons, APC had shown some efficacy in severe sepsis. They asked Bernard, chief of the Division of Allergy, Pulmonary and Critical Care Medicine at Vanderbilt, to design a small study of about 100 to 150 people to see if their protein could produce effects in humans with severe sepsis that might warrant further investigation.

After treating 131 patients, Bernard reported back to Lilly in 1996 that their compound, later named Xigris, may have saved the lives of some critically ill patients. Also, it clearly replenished the body's supply of protein C that had been sapped by infection and improved the coagulopathy, or coagulation disorders, caused by sepsis.

Lilly opted to continue development. Bernard was appointed principal investigator of an international phase III trial, known as PROWESS, which tested Xigris against a placebo in 1,690 patients worldwide who were in imminent danger of dying from severe sepsis.

Beginning in 1998, Bernard's team of investigators fielded calls from critical care physicians in 160 centers around the globe to determine, in split-second decisions, if a patient could be included in the trial. To qualify, all of the patients had to be dying of sepsis and not from a primary disease such as cancer or heart disease.

Within two years, it became apparent that Xigris was having a significant impact on survival: among the sickest patients the mortality rate for those who took the drug was 13 percent lower than the rate among those on placebo. An independent board of advisors stopped the PROWESS trial in 2000, because it was no longer ethical to give the placebo.

"It was a huge day," says William Macias, M.D., Ph.D., medical director of the Xigris Product Team at Lilly. "First there was a brief moment of disbelief. We knew it was a long shot for the overall trial to be successful, but to stop early was even bigger. This was a once-in-a-lifetime experience."

The PROWESS team had met what had been considered an unattainable benchmark – for every eight patients treated with Xigris, one life was saved. "There are very few drugs for which such a sweeping statement can be made," says Bernard.

"The company realized the risk of creating and testing biological products," Macias says. "You have to invest very heavily before you ever know if you have a drug that will be worth the investment."

Vanderbilt's involvement was crucial, adds Mark Williams, M.D., medical advisor to the Xigris Product Development Team. "One of the main reasons that PROWESS was successful was because Vanderbilt served as the coordinating center," he says, "a triage center under very difficult circumstances."

Williams estimates that 7,500 lives have been saved since 2001, when the FDA approved Xigris. With increasing use, as many as 40,000 lives could be saved each year, he says. Because it can cause bleeding, however, not all severe sepsis patients are candidates for the drug.

"The mortality rate (from severe sepsis) is still too high," says Bernard. "But to make inroads into something this horrific is wonderful. It says we need to keep plugging away at scientific intervention and drug development."

Which is exactly what is happening. Williams is currently running a large clinical trial in 110 sites around the world, testing the efficacy of Xigris in critically ill children. He also is examining the drug's effectiveness in certain cancer patients, with the cautious expectation that treating severe sepsis in this patient cohort may lead to a drop in the overall cancer mortality rate.

The success of Xigris, says Williams, demonstrates how a partnership between university scientists, industry and the FDA can bring a life-saving product to fruition. "Each party has different expertise and strengths," he says, "and when they work together for the common good, we all see the benefit." **LENS**

"The agency (FDA) has only a nuclear bomb (withdrawal) that they can bring to bear...or a powder puff, the powder puff being a change of label, which nobody reads and is totally ineffective."

drug. Seldane was withdrawn from the market in 1997.

A much more difficult problem to identify, says Roden, is drug toxicity that leads to an increase in a common event, such as heart attack or stroke among the elderly. The situation becomes even more complex if patients have been taking a medication for weeks, months or years before they suddenly have adverse reactions. Physicians may have no reason to suspect the drug.

"Suppose a drug increases colon cancer by 20 percent. Unless they do a prospective clinical trial, we will never know, especially if the risk is only present in some patients," Roden says. "My personal bias is that these kinds of unrecognized drug actions are all around us."

A key to determining both the benefits and detriments of a particular drug is finding the first "signal"– the indication of some unanticipated side effect – and reporting that signal to the FDA.

Many epidemiologists and pharmacologists in the field claim that this mode of communication is inherently flawed. "It's hit or miss," admits Vanderbilt's Griffin, professor of Preventive Medicine.

Currently, MedWatch has little authority to affect change even if officials receive information warranting further investigation of adverse events. They can demand that a company conduct post-marketing surveillance on drugs, but they have no power to force a company to do so.

In effect, the FDA has only two options: demand a change of label, or withdraw the drug from the market.

"The agency (FDA) has only a nuclear bomb (withdrawal) that they can bring to bear…or a powder puff, the powder puff being a change of label, which nobody reads and is totally ineffective," says Raymond L. Woosley, M.D., Ph.D., a former Vanderbilt clinical pharmacologist whose work on Seldane led to the discovery of a safer antihistamine now marketed as Allegra.

Beyond that, even if a drug is found to cause a dangerous side effect in rare cases, there is no standardized mechanism for determining what happens next or what should be deemed "acceptable risk."

"Should we deprive 1,000 people of ACE-inhibitors to prevent one episode of angioedema?" asks Griffin. "That's a difficult question."

Search for safety

In the past, drugs were usually given in limited courses of days or weeks to address an acute medical problem. Many of today's medicines are administered to enhance quality of life and to prevent disease from occurring, and can be taken for years on end.

"When you're giving drugs to generally healthy people, the standards have to be higher," Griffin continues. "If a drug is not saving your life, it better not be killing you."

Seeking to advance the "optimal use" of drugs, medical devices and biological products, the federal government in 1999 launched the Centers for Education and Research on Therapeutics (CERTs) initiative.

Seven centers, including one at Vanderbilt, conduct a wide range of research on drug use and safety. Their reach is limited, however.

"When you try to take research into practice, there's a lot that's lost in translation," explains Ray, who heads up the Vanderbilt CERT. "We address drug safety, but also the problem of clinicians using interventions appropriately. For example, it doesn't help if beta blockers prevent deaths if nobody prescribes them."

Meanwhile, aggressive marketing, including direct-to-consumer advertising, has created a demand for new drugs, even among patients for whom the compounds may not be effective and may even be dangerous.

The ticket to better post-marketing surveillance might have to come from a complete redesign of the FDA's framework.

Currently, all the years it takes a drug to go through clinical trials and approval counts against its 20-year patent life. When the patent expires, competitive generic compounds can join the pool.

Vanderbilt clinical pharmacologist Alastair J.J. Wood, M.B., Ch.B., proposes that the FDA reward pharmaceutical companies that conduct post-marketing studies of their products by lengthening their period of exclusivity – postponing the right of generic knockoffs to compete against them.

Wood, Woosley and others also have called for the establishment of an independent agency to monitor drugs once they hit the market.

This February, in response to ballyhoo by physicians, legislators and consumer watch groups, the Department of Health and Human Services announced that the FDA will indeed create a new independent Drug Safety Oversight Board.

Its purpose, according to a press release, will be to promote a culture of openness and to provide emerging information to patients and doctors about the risks and benefits of medications. The board will be composed of FDA employees and various government employees, in consultation with medical experts and patient and consumer groups.

While this is a step in the right direction, Ray says, "the board itself, from what we know, does not appear sufficiently independent nor does it appear to have the authority and resources necessary to do the job."

"Society takes a calculated risk every time we release a new drug onto the market," he continues. "There needs to be someone, some independent authority, in place to make hard decisions." **LENS**

COX-2 inhibitors
A STATUS REPORT

By Bill Snyder

In February, an advisory panel to the U.S. Food and Drug Administration considered whether the cardiovascular risk associated with long-term use of a class of blockbuster arthritis drugs known as COX-2 inhibitors outweighed their benefits.

One of the drugs, Vioxx, had previously been pulled from the market after patients who took the drug in a long-term study were found to have an increased risk of heart attack and stroke.

After three days of testimony from scientists, drug company executives and members of the public, a narrow majority of panelists recommended keeping two other COX-2 blockers, Bextra and Celebrex, on the market – as long as the drug labels included stringent "black box" warnings.

In April, however, the FDA called for the withdrawal of Bextra after concluding that the drug's overall risk-benefit profile was "unfavorable." Celebrex was allowed to stay on the market, but with a black box warning that the agency also required for prescription non-steroidal anti-inflammatory drugs (NSAIDs).

Alastair J.J. Wood, M.B., Ch.B., professor of Pharmacology and Medicine at Vanderbilt who chaired the advisory panel, warned that the FDA's actions did not solve the problem of how to improve drug safety.

"The increased risk of a common problem like a heart attack will not be picked up from our current reporting system," he told the *Los Angeles Times.*

Pictured here: At top, accompanied by her attorney Browne Greene and son Travis, Joan Brierton Johnson of Topanga, Calif., reads testimony on behalf of her 7-year-old daughter Sabrina (in hat), who was blinded by an allergic reaction to an over-the-counter children's pain medicine. In her statement, Sabrina asked that warning labels be required for the products. Panel chairman Alastair J.J. Wood, M.B., Ch.B., of Vanderbilt (middle photo) listens intently. Opposite, Merck & Co. executives hear testimony about their company's product, Vioxx. Other audience members (bottom photos) reflect the tense atmosphere.

Photos by Sam Kittner

Q & A

GETTING THE DRUGS WE NEED

A drug company executive and a university professor tackle the cost, safety and future of pharmaceuticals

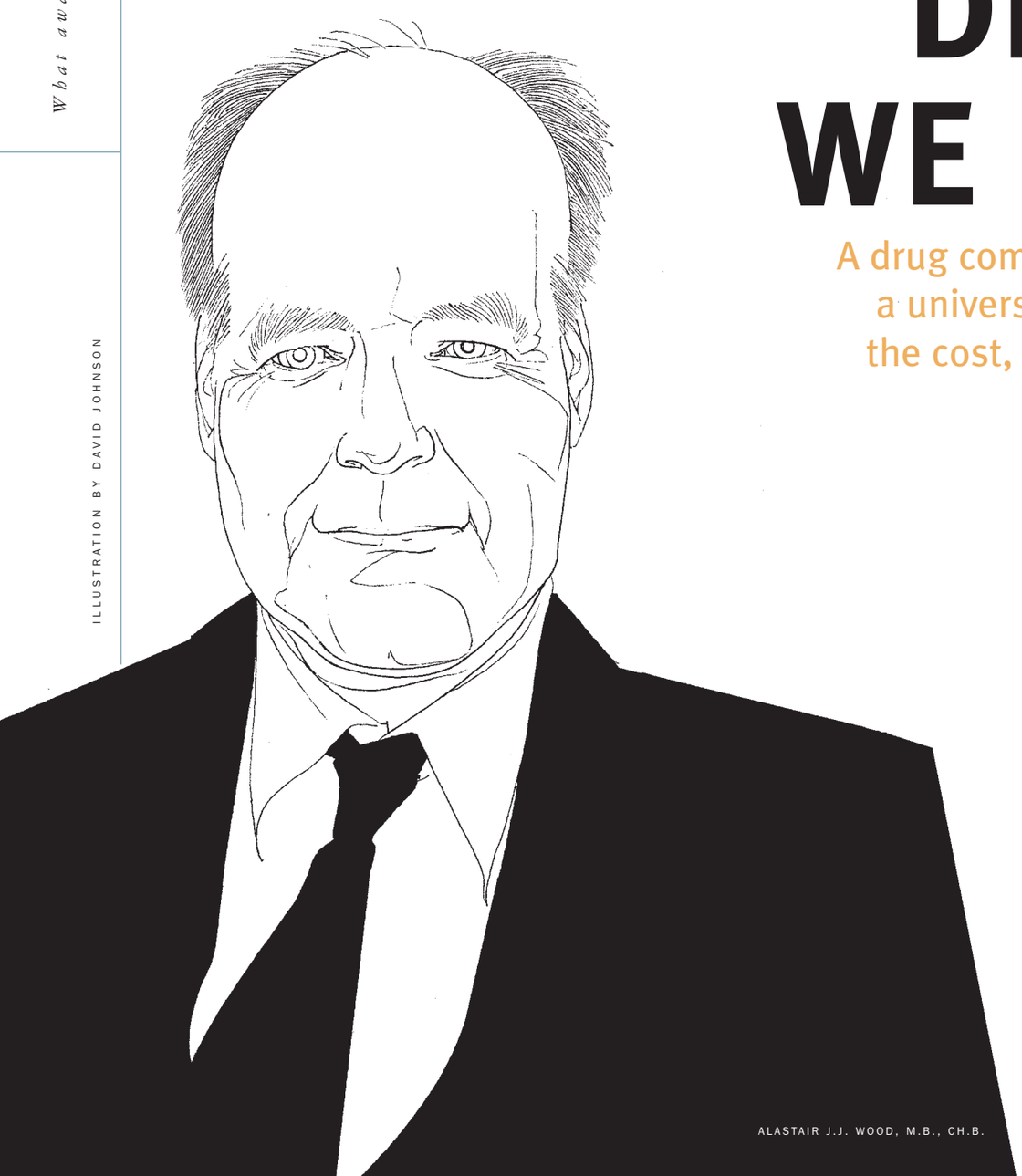


ILLUSTRATION BY DAVID JOHNSON

ALASTAIR J.J. WOOD, M.B., CH.B.

In a recent interview with *Lens* editor Bill Snyder, Steven M. Paul, M.D., president of Lilly Research Laboratories, and Alastair J.J. Wood, M.B., Ch.B., professor of Medicine and Pharmacology at Vanderbilt University Medical Center, traded opinions about the challenges facing the nation's pharmaceutical industry.

Wood, a member of the editorial board of the *New England Journal of Medicine* (and of this magazine), is a former candidate for FDA commissioner. Paul is former scientific director and chief of the clinical neuroscience branch at the National Institute of Mental Health. Their points of agreement – and disagreement – may surprise you.

There is concern that fewer novel drugs appear to be coming to market. What's causing this, and what can be done to solve the problem?

Paul – (For) virtually every disease that we are working on right now, the science is incredibly rich. The number of novel, potentially disease-modifying drug targets that have been discovered as a result of the revolutionary advances in biomedical research over the past two decades is truly remarkable.

(But) if you look at the costs to discover and develop a new drug, from the inception of a discovery project to its launch into the marketplace, we now believe that the number as of 2005 is well over $1 billion. It's been rising almost exponentially over the last 20 years ...

The cost of discovering and developing a new medicine, of course, includes all of the compounds that never make it through the various phases of discovery and development – indeed the attrition rate for drug discovery and development has actually increased somewhat over the past few years despite the incredible science we have at our disposal.

We've got on the one hand this enormous scientific and medical opportunity that we must take advantage of, and on the other hand this enormous challenge of cost.

One of my major concerns is that with all of the political and economic issues that the industry is now facing, we could literally "throw the baby out with the bath water." We might literally need to re-invent a new industry. My worst fear is that the pharmaceutical industry may go the way of the steel industry or the automobile industry or, God forbid, the airline industry.

This would be most unfortunate.

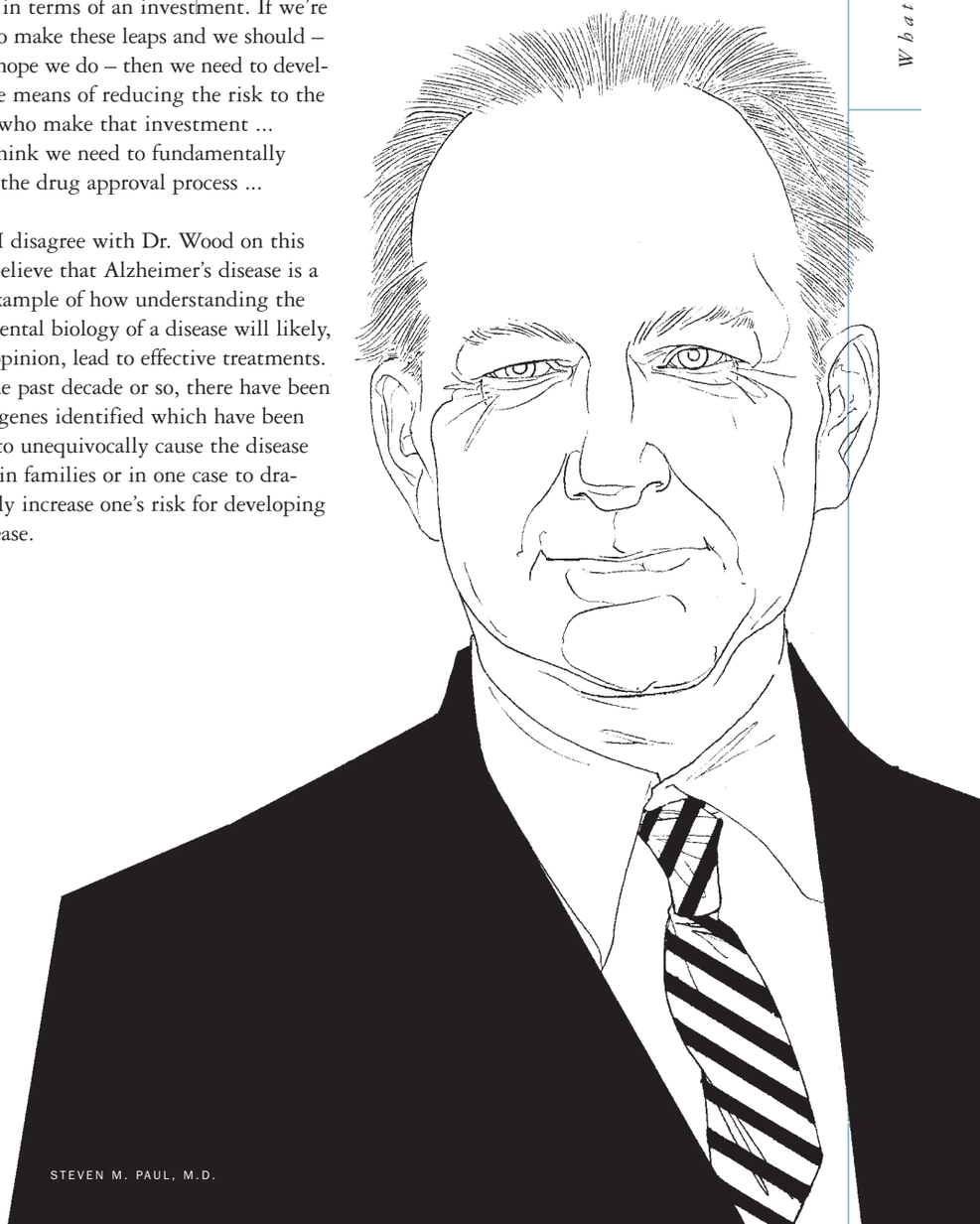
Wood – Whatever that number is, I don't think that's sustainable into the future, at least to develop the kind of high-risk drugs that we need ...

Just to pick Alzheimer's, we don't have terrific data on the fundamental biology right now, so developing drugs to prevent Alzheimer's rather than to treat patients' symptoms is in some ways a leap in the dark, at least in terms of an investment. If we're going to make these leaps and we should – God, I hope we do – then we need to develop some means of reducing the risk to the people who make that investment ...

I think we need to fundamentally change the drug approval process ...

Paul – I disagree with Dr. Wood on this one. I believe that Alzheimer's disease is a great example of how understanding the fundamental biology of a disease will likely, in my opinion, lead to effective treatments. Over the past decade or so, there have been several genes identified which have been shown to unequivocally cause the disease in certain families or in one case to dramatically increase one's risk for developing the disease.

By understanding how these genes influence disease pathogenesis, several novel approaches to treatment have emerged. We now have three or four different types of "anti-amyloid" drugs that are in early clinical development – that I believe for the first time gives us a reasonably good chance of modifying the disease process itself …



STEVEN M. PAUL, M.D.

Unfortunately, most of us believe that the best way to treat Alzheimer's disease is to prevent it from occurring in the first place (but) the current drug development process – including the current limits on intellectual property protection – provides such incredible disincentives for discovering "preventative" agents that very few companies would even approach this at the present time.

Wood – We're talking about Alzheimer's, but you could talk in the same way about other diseases of aging like osteoarthritis, for example, which is going to be a huge problem for my generation. We need to be prepared to develop drugs that lower amyloid deposition (in the brain) or that slow the deterioration of the loss of your cartilage in your hip joints, without the confidence, other than a hope, that that will affect the ultimate endpoint.

I don't think at this stage … that we know with any degree of certainty that lowering amyloid deposition pharmacologically in the brains of humans will necessarily prevent Alzheimer's ... but I think that we need to be prepared to approve drugs based on imaging techniques or whatever … that show a reduction in some surrogates ...

I think we should give limited (patent) exclusivity on the basis of that, and give an extended exclusivity when people demonstrate a hard endpoint … We need to develop regulatory approaches that … encourage the taking of risk. And of course that's going to have to make some fundamental changes in attitude at the FDA itself.

Paul – I absolutely agree. The (intellectual property) challenges right now are formidable. The effective patent life for a new drug today is probably averaging only 10 years or so in the U.S. If it takes 15 years to both discover and develop a drug, five or even 10 years may be too little time to recoup the investments required.

We must be assured that once a drug reaches the market we have a sufficient period of time of patent exclusivity to recoup our investments. Right now with the current patent laws there are also huge incentives for generic companies … to come in and challenge patents in a way that is like winning the lottery ...

By the way, I believe that generic drugs are one important way to reduce prescription drug prices in this country. Prescription drug costs in the U.S. could be reduced by 10 to 15 percent overnight if physicians would prescribe generic drugs when they should. But there will be no more generic drugs if there are not patent protected drugs in the first place.

Wood – I actually think we should also offer extensions of exclusivity on the basis of certain agreed performance goals. For example, if you were developing (the first) statin today … and you demonstrate that it lowers cholesterol, that's a demonstrable indication for which you would get exclusivity.

But if you come back a few years from now and demonstrate … that you've also reduced cardiovascular mortality or morbidity in a significant way, I think that's not an unreasonable reason to get an extended exclusivity … I'm trying to incentivize the performance of the right studies.

Wouldn't that also encourage pharmaceutical companies to do more post-marketing surveillance?

Wood – It could be done in the same way … I think there's a need for a liability protection for companies where they're either conducting a mandated phase IV (post-marketing surveillance) study, which most of the time they don't conduct, of course. But if they're conducting a safety study, they should get liability protection for that …

There are going to be companies which might even disappear as household names because of just astronomic liability … The numbers are being thrown around of more than $100 billion in terms of the liability risk to Merck (over Vioxx), for example. That's a lot of money.

Paul – Let's not forget that somebody's got to pay for such product liability litigation – justified or not. Because of the tremendous incentives trial lawyers have in litigating such cases, I think the legal system is in need of tort reform. This is not to say that people don't have right to recover damages when they've been injured, but in this country right now, I believe this system is out of whack.

Wood – I think it's unbelievable that an industry that produces things that cure people of diseases that ail them has managed to shoot themselves so frequently in the foot and get themselves into a position where they're now in public opinion polls regarded as somewhere down beside tobacco companies …

Paul – This situation hasn't escaped most of us, and it's a problem that we're trying to quickly correct … For example, I believe industry designs and executes clinical trials as good as anyone in the world … Having said that, we as an industry have been accused – with some justification, in my opinion – of not being as transparent and objective as we should be in presenting and publishing our data. Do we always publish all of the relevant data on a given drug? Do we highlight negative as well as positive results?

Just this past year at Lilly we reiterated a code of conduct called the Principles of Medical Research, which fundamentally says we will publish all data that patients and doctors need to know about our drug, period, including any negative results, and of course all safety data we gather on our medicines.

To help communicate our clinical data, we've established a comprehensive clinical trial registry, which is on our Web site, www.lillytrials.com, so that all data on all marketed products, phase I through phase IV, are going to be on a public accessible database …

How can the government and universities help solve the problem?

Wood – I don't think that public money should be committed to the development of drugs. There is a total failure of any evidence that government resources have been successful in developing drugs, at least in my view.

I have some concerns that … NIH … (is) somehow going to get into drug development … (and that) is going to distract us from the fundamental reform of the licensing system in this country to incentivize the development of the drugs that we need.

Paul – If you go back and look at the top 50 marketed drugs, … almost every one of the top 50 had its origins in some research that somewhere in time was funded in the public sector, like the NIH.

However, virtually none of those drugs, with just a few exceptions, would have ever been discovered and made available to patients without enormous investments and risk on the part of the private sector. Not just in the discovery and validation of the targets that these drugs work on, but all of the screening, chemistry, pharmacology, toxicology/metabolism, safety testing, etc., let alone downstream development activity and manufacturing capabilities … work that's required to bring a drug to market, and that most people don't really know about or appreciate …

It's the entire body of that research that allows us to do what we do, and without that enormous investment by the NIH and other federal agencies, we wouldn't have what I have called the incredible substrate for drug discovery and development that we currently have …

We must preserve this synergistic public-private partnership … but we must find ways to improve it further moving forward. I think that NIH resources are best spent in funding all of the fundamental as well as clinical translational research that will allow us to more definitively address the therapeutic and diagnostic approaches we will take in the future.

I really doubt that precious NIH funds are better diverted to discovering or developing drugs, perhaps with some few exceptions … certain orphan diseases or drugs to combat bioterrorism, and perhaps some infectious diseases as well.

Wood – We have a system that incentivizes the development of symptomatic therapies and/or incentivizes the development of therapies for very short treatments: antibiotics … painkillers, and other symptomatic therapies. We've moved now into a situation in which we're developing drugs to prevent diseases. We're developing drugs to be taken for a lifetime.

And politicians, academics and drug companies have done a very poor job of articulating that for the public … One of the reasons prescription drugs are a much more major part of our health care dollar today is that we don't just take 10 days of an antibiotic …

We need to explain to people that the ideal model of health care would put surgeons and anesthesiologists out of work, and we would treat diseases by pills. You know, (the doctor) on Star Trek didn't do much surgery. He waved things at people and people swallowed things and so on … We're going to have to redesign the model of the '50s, if you will …

And the reason that's important is that whereas in a model where you're treating symptoms or disease in an individual, you can much more easily understand and articulate the risk/benefit ratio for that patient, when you're preventing a disease, you never ever know the patient benefited from the drug, ever. But you always know the patient who developed an adverse event.

Paul – I think it starts with society understanding … what benefit/risk actually means. It's become clearer to me, given my experience in the industry, but I'm not sure it's clear to the average citizen.

All drugs have benefits and risks that manifest differently among patients. It is critical that patients and doctors fully understand these risks – and carefully monitor for side effects or the usually rarer serious adverse events that can occur with virtually all drugs. **LENS**

The critical path

CASEY MCKEE

Raymond L. Woosley, M.D., Ph.D.

During the past 20 years, Raymond L. Woosley, M.D., Ph.D., has contributed to current understanding of antiarrhythmic drugs, helped discover the antihistamine Allegra and promoted post-marketing drug surveillance.

Now the former Vanderbilt and Georgetown researcher has a new position and challenge: serving as president of The Critical Path Institute in Tucson, Ariz. The non-profit institute, a joint effort of the University of Arizona, the U.S. Food and Drug Administration and SRI International, aims to help develop a new "toolkit" that can safely speed up drug development.

"Science has generated a lot of new information … but the process of drug development hasn't advanced," explains Woosley, who until January was vice president of the University of Arizona Health Sciences Center. "Companies have tried to take the path that's been trod before and they're afraid to innovate because they're afraid the FDA might not accept the change."

Yet in last year's "Critical Path" report, the FDA called for exactly that: "powerful new scientific and technical methods such as animal- or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques … to improve predictability and efficiency along the path from laboratory concept to commercial product."

The types of adverse reactions that force drugs off the market occur in less than one in 10,000 patients, Woosley wrote in the Winter 2005 issue of *Issues in Science and Technology*. To have any hope of detecting these relatively rare events before marketing, phase III trials would have to be increased by more than tenfold, to include more than 30,000 patients. That would "only further delay development and increase the price of drugs," he wrote.

Instead, Woosley recommends a "staged" approval process, which would allow rapid approval for a carefully defined patient population, and then gradual expansion to other patient groups as long-term safety and efficacy is established. "This approach is similar to the way in which several AIDS drugs, such as the protease inhibitors, were developed and translated into clinical practice in two to four years," he wrote.

There are other issues. The FDA needs more money to monitor drugs already on the market. Industry must invest more in drug safety. And, says Woosley, university scientists should play a greater role as industry watchdogs and helpful partners.

"We need to be there to keep their feet to the fire, but also to share our expertise and make sure that the drugs are developed in the very best way," he says.

– BILL SNYDER

Advice for consumers: "Kick the tires" before taking new medication

Photo illustration by Don Button

The patient's responsibility

By Bill Snyder

Today's scientists are hurtling into the future, discovering new targets for drugs, new compounds with drug-like activity and new tools with which to test them.

Will their efforts lead to improved drug safety and lower costs? Perhaps … but a lot will depend on us – as patients and physicians.

There is growing concern, for example, that Americans are overmedicated. As a result, we may suffer inordinately from adverse drug reactions.

"And that's why safe drugs have to be taken off the market, not because they're unsafe but because their use is unsafe," says Raymond L. Woosley, M.D., Ph.D., a nationally known clinical pharmacologist and president of the Critical Path Institute in Tucson, Ariz.

Some observers point their fingers at direct-to-consumer advertising, but banning the practice alone won't solve the problem. After all, physicians prescribe drugs, and – Woosley believes – many prescribe inappropriately.

"Every school has a six-hour or one-semester course in pharmacology that talks about the actions of drugs, but how to use those safely and how to address drug interactions and how to use drugs in the proper way is not taught in 90 percent of the medical schools in this country," he says. "Medical education has to take a major responsibility for the failures of pharmaceuticals."

Patient education is equally important, says Peter J. Neumann, Sc.D., associate professor of Policy and Decision Sciences at the Harvard School of Public Health.

"We hear a lot about the cost of drugs. But it's the wrong question, really. It should be about the value," says Neumann, whose cost-benefit evaluations have included drug treatments for asthma, lung cancer and other diseases.

"When you go out and buy a car, you get information about the value of the car and the attributes that you care about – the safety, the way it looks, the zero-to-60 power of the engine and so forth.

"When you buy a drug, you might get information about different attributes of value –how convenient is it to take, what are the side effects, what are the benefits, and so forth, and what's the price."

Consumer Reports provides that kind of information through its CRBestBuy Drugs.org Web site, which compares prescription drugs on price, effectiveness and safety, Neumann notes.

But while better education of physicians and patients may help improve drug safety, "at the end of the day, we're probably going to be paying more for our health care," he cautions.

"That's probably not a bad thing … research shows in a very general sense we're getting more health – we're living longer, we're alleviating symptoms, we have less disability, and we're paying more for that ...

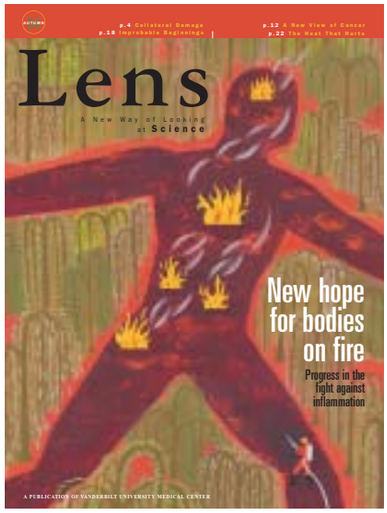
"I'd much rather live today with today's medicine," Neumann says, "even with today's prices, than 30 years ago with 1970s medicine and 1970s prices."

The key is getting the rules right. "You can swing the pendulum too far either direction," he says. Too much regulation stifles innovation. "On the other hand, if you had no scrutiny or too little, then you'd have too many bad outcomes.

"So what's the right mix? I don't know, but I think that's the right question." **LENS**

Through our Lens

LETTERS TO THE EDITOR



Bridging the gap

I've just finished reading the fall 2004 issue of *Lens.*

I suspect that most of us whose lives were spent in the practice of clinical medicine, even academic physicians, have come to realize the huge and widening gap between the basics that we learned in school and the science underlying the modern practice of medicine.

The papers in general medical journals such as the *Journal of the American Medical Association* and the *New England Journal of Medicine* now routinely contain jargon and numerous acronyms for all sorts of molecules such as EGF, IL-6, TNF, CD-4, etc., that at least a general appreciation of developments in molecular biology, genomics and immunology are needed for the reader to understand them.

This issue on inflammation was, as they say, "right on." You have tied enough history and biography to the articles to make them interesting reading, and you have kept the concepts broad and simple so that those of us outside of the research areas can grasp them.

So much for praise of the content. The style, the photography, the art work – altogether – make *Lens* an extraordinary periodical. I have not seen its equal. The work of you and your co-workers significantly enhances the image of Vanderbilt University Medical Center.

OSCAR C. BEASLEY, M.D.
Iowa City, Iowa
Vanderbilt University School of Medicine, Class of '52

Over-the-top imprint

I am an alumnus of Vanderbilt having earned a Ph.D. in Molecular Physiology and Biophysics. I am currently teaching biology at a high school in Michigan.

I thoroughly enjoy the *Lens* magazine and share it with the other science teachers. We often show pictures to our students from the magazines because the illustrations are often better and easier to follow than those in our texts.

I think it is simply terrific and it keeps me up-to-date with Vanderbilt research and current events in science and medicine, not to mention it has the over-the-top imprint of one of my favorite Vanderbilt mentors, Dr. Lee Limbird.

TIM KNITTLE, PH.D.
Brighton, Michigan
Vanderbilt University Graduate School Class of '95

Lens is going global

Later this summer, we plan to launch the first *Lens* Web site, an online version of the magazine with links to the Web pages of scientists at Vanderbilt University Medical Center and around the country.

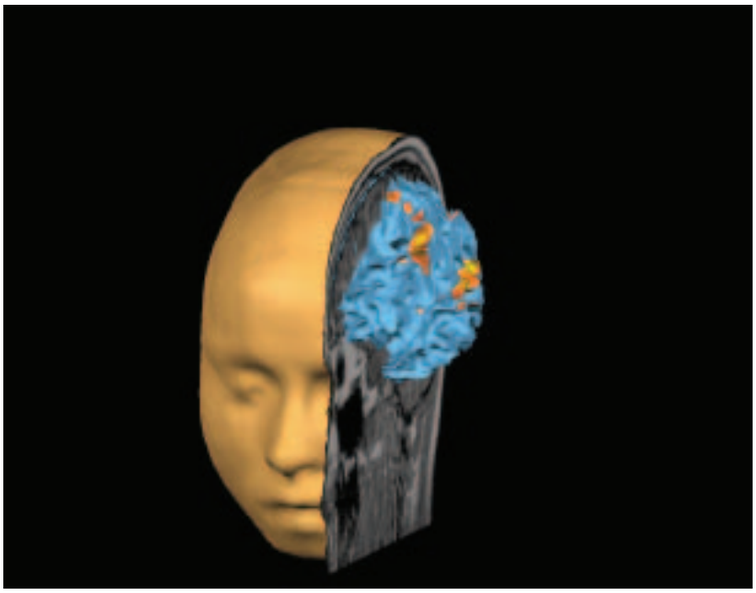
The Web site will archive back issues and include a survey for you to register your opinion about how well we're doing.

For more information, or to be notified when the Web site is launched, contact the editor, Bill Snyder, at (615) 322-4747 or via e-mail: william.snyder@vanderbilt.edu.

Letters to the editor may be mailed to:
Bill Snyder
Vanderbilt University Medical Center
CCC-3312 Medical Center North
Nashville, TN 37232-2390
Or faxed to (615) 343-3890

Functional magnetic resonance imaging (fMRI) data shows brain activity during a mathematical processing task. The image is overlaid on a surface rendering of the cortex to illustrate its spatial orientation.

Illustration by Christopher J. Cannistraci
Courtesy of the Vanderbilt University Institute of Imaging Science



IN THE NEXT ISSUE:

Waves, rays and fireflies
Advances in imaging technologies are generating startling new pictures of the body – down to individual molecules.

Revealing the brain's secrets
New "pictures" may help scientists solve the mysteries of addiction, autism and Alzheimer's disease.

Putting a beam on cancer
Fluorescent probes are being studied for their potential to pinpoint – and destroy – previously hidden cancers.

Lens

Vanderbilt University Medical Center
CCC-3312 Medical Center North
Nashville, TN 37232

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