

07
AUTUMN

p.4 The heart's healing superpowers
p.10 Genetics of sudden death

p.16 Eugene Braunwald: grand maestro
p.28 Cholesterol conundrum

Lens

A New Way of Looking
at **Science**



How to
build a
stronger
heart

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

AUTUMN 2007

VOLUME 5, NUMBER 2

EDITOR

Bill Snyder

CONTRIBUTING WRITERS

Stephen Doster
Lisa DuBois
Liz Haldeman
Leigh MacMillan, Ph.D.
Melissa Marino, Ph.D.
Jessica Pasley
Bill Snyder
Erin Tillman, Ph.D.

PHOTOGRAPHY/ILLUSTRATION

J.P. Cartailier, Ph.D.
Dean Dixon
Dominic Doyle
Dynamic Duo Studio/Images.com
David Johnson
Asia Kepka
Anne Rayner
Photo researchers
Susan Urmy

DESIGN

Diana Duren

**MEDICAL CENTER NEWS AND PUBLIC
AFFAIRS AND DIRECTOR OF PUBLICATIONS**

Wayne Wood

COPY EDITOR

Nancy Humphrey

EDITORIAL OFFICE

Office of News and Public Affairs
D-3237A MCN
Vanderbilt University Medical Center
Nashville, Tennessee 37232-2390
615-322-4747
E-mail address: william.snyder@vanderbilt.edu

Cover: Photo by Anne Rayner, tattoo by Dominic Doyle, and bicep by Mark Davis, assistant strength and conditioning coach at Vanderbilt University.

Where there is no vision, there is
no hope.

– GEORGE WASHINGTON CARVER

Lens is published twice 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.

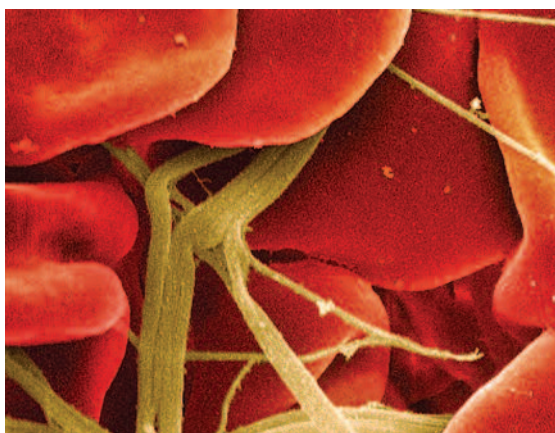
© 2007 by Vanderbilt University



page 10 When the heart stops beating



page 16 Opera in the cardiology suite



page 22 The yin and yang of clotting

2 POISED FOR THE FUTURE

Cross-disciplinary collaborations are revolutionizing heart disease treatment and prevention around the world.

4 CARDIAC REGENERATION

Damaged hearts one day may be renewed, thanks to an experimental “regenerative medicine” technique that uses stem cells harvested from the patient’s bone marrow. The goal is to get the right cells to the right place, and get them to do the right thing – turn into new heart muscle.

10 OFF TEMPO

Nearly every minute of every day, an American is killed by sudden cardiac death. With the help of genetic screening and pharmacogenomics, scientists are finding ways to identify – and prevent – the errant heartbeat before it takes another life.

13 BABIES AT RISK

Abnormal heart rhythms may underlie some cases of sudden infant death syndrome. Now the question is: How should doctors look for them?

16 MAESTRO OF AMERICAN CARDIOLOGY

Perhaps more than any other academic physician, Eugene Braunwald, M.D., has made a huge imprint on current understanding and treatment of heart disease. But his true genius may be the ability to embrace the symphony of tones, harmonies and processes that are the beating heart.

22 TOO MUCH CLOT

People with obesity and diabetes are more likely than others to die of heart attacks and strokes. The culprit is thrombosis – their blood tends to clot more easily. Racing before the rising tide of these twin epidemics, Vanderbilt scientists are trying to find out why.

28 THE CHOLESTEROL CONUNDRUM

Cholesterol is either “bad” or “good” depending upon the company it keeps; what’s transporting it around the body. Here’s the latest on efforts to keep it – and you – out of harm’s way.

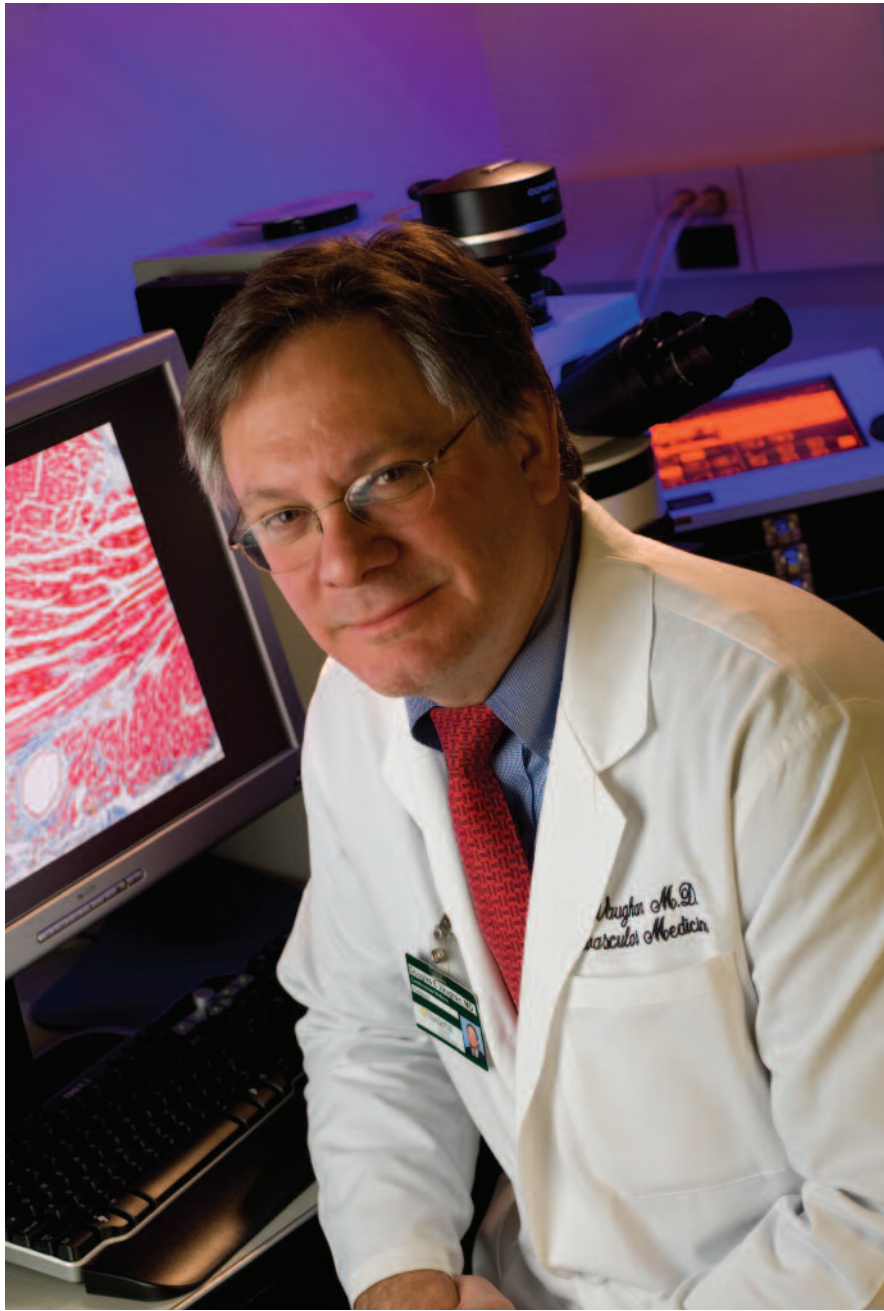
32 THE PEOPLE’S AGENDA

Elizabeth Nabel, M.D., director of the National Heart, Lung, and Blood Institute, and Rose Marie Robertson, M.D., chief science officer of the American Heart Association and professor of Medicine at Vanderbilt, discuss how public-private partnerships can advance the fight against heart disease and stroke.

36 FROM AUTO PARTS TO CELL PARTS

Jackson “Jack” Roberts, M.D., internationally known for his research on free radicals, wasn’t supposed to become a scientist. After college, he planned to run the family auto parts businesses. But then he took physiology from “Doc” Rogers, and the course of his life was changed forever.

DEAN DIXON



Poised for the future

By Douglas E. Vaughan, M.D.

Director, Vanderbilt Division of Cardiovascular Medicine
C. Sidney Burwell Professor of Medicine
Professor of Pharmacology

More rapidly, perhaps, than has any other field of medicine, the treatment of heart disease has been transformed by extraordinary advances in basic and clinical science.

One of the best examples of the impact of research is in the management and treatment of patients with acute MI (myocardial infarction, or heart attack).

The evidence for many of the standard treatments that we routinely apply today, including beta-blockers, acute reperfusion therapy, statins and angiotensin-converting enzyme (ACE) inhibitors can be attributed to the investigative efforts and leadership of Eugene Braunwald, M.D., who is profiled in this issue of *Lens*.

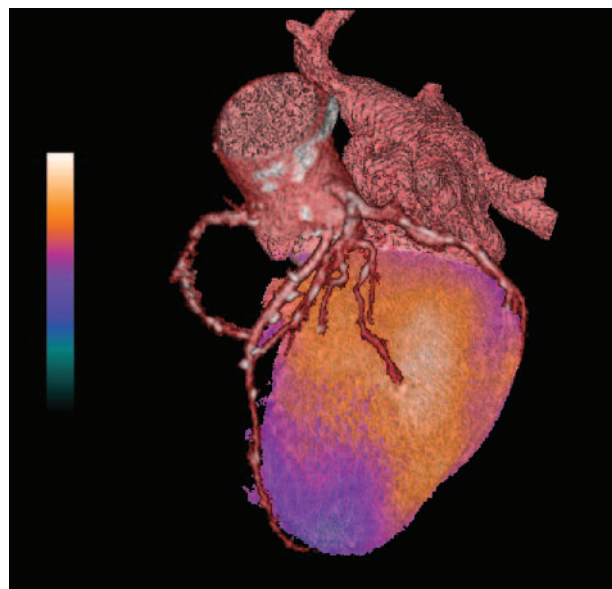
This issue also will examine two other areas of active research that have been conceptually informed and motivated by Braunwald's ground-breaking work – mechanisms of coronary thrombosis (clotting in the coronary arteries), and new treatments to improve cardiac function after a heart attack.

These advances are examined from the perspective of researchers at Vanderbilt University Medical Center, a microcosm of the breadth and depth of research and cross-disciplinary collaborations that are revolutionizing heart disease treatment and prevention around the world.

Investigators at Vanderbilt, for example, have pioneered numerous advances in cardiovascular research, including fundamental insights into the metabolism of prostaglandins and other eicosanoids, the molecular biology of blood pressure regulation, and the molecular mechanisms of cardiac arrhythmias.

Pictured at right: Fusion of two images of the heart – a computerized tomographic (CT) angiograph and a myocardial perfusion image (MPI).

Courtesy of Murray Mazer, M.D., associate professor of Radiology and Radiological Sciences, Vanderbilt University Medical Center



Many of these studies have been conducted in the Elliott V. Newman Clinical Research Center, one of the first centers of its kind in the country and also one of the most productive in terms of the volume of CRC-related research papers that are published each year.

Another example is the Vanderbilt Heart and Vascular Institute, which in 2005 joined cardiology, cardiac surgery and vascular surgery under one roof.

The institute provides a new opportunity to improve the ways we interact, and to increase the efficiency and quality of what we do. It achieves a real partnership between the providers, whether they are physicians, nurse practitioners or nurses, and the hospital that was not possible before.

Last year, the National Heart, Lung, and Blood Institute (NHLBI) designated Vanderbilt, along with the Cleveland Clinic and the University of Pennsylvania, as a Specialized Center of Clinically Oriented Research (SCCOR) in Hemostatic and Thrombotic Diseases.

The Vanderbilt SCCOR grant will allow investigators from throughout the Medical Center to investigate why patients with obesity, insulin resistance and type 2 diabetes are at greater risk for arterial thrombosis and premature coronary disease.

It is critical for us to understand the mechanisms of these phenomena if we are to effectively prevent coronary events in these increasingly prevalent populations.

Over the last several years, no area of cardiovascular science has been more exciting or controversial than the area of stem cell biology. Do we have the capacity to regenerate cardiac tissue and function with resident stem cells in the myocardium

(heart muscle) or from cells derived from the blood, bone marrow, or other sources?

As part of the newly formed Cardiac Cell Therapy Research Network, another NHLBI initiative, we recently began testing the efficacy of bone marrow-derived cells for the treatment of patients with acute MI and for patients with chronic left ventricular dysfunction.

Our working group includes basic scientists with expertise in cardiac development and stem cell biology, and a rather remarkable group of physicians from interventional cardiology, bone marrow harvesting and transplantation, cardiovascular imaging, cardiac surgery, electrophysiology and heart failure.

The confluence of technology, pharmacology, surgery and genetics also is being applied to the identification and prevention of abnormal heart rhythms (arrhythmias) that are a frequent cause of sudden cardiac death. At Vanderbilt, for example, Dan Roden, M.D., and his colleagues are scanning the human genome for gene variants that put people at higher risk for fatal heart arrhythmias.

These examples illustrate how hypotheses about disease that emerge from basic science discoveries can be tested in the clinic and, conversely, how clinical observations can lead to entirely new and unexpected hypotheses. With current and anticipated developments at the cellular and molecular level, including knowledge of the human genome, future opportunities for continuing these advances are enormous.

There are numerous challenges to maintaining this momentum, however.

Cardiovascular research is an extremely expensive activity. The diminishing margins

in health care in this country eventually will impact the ability of Vanderbilt and other academic medical centers to invest in research. Federal budget limitations already are affecting cardiovascular research and the training of new investigators.

Here again, Vanderbilt scientists are playing an important role.

Rose Marie Robertson, M.D., the first Vanderbilt faculty member to serve as president of the American Heart Association, has been the association's chief science officer since 2003. She and NHLBI director Elizabeth "Betsy" Nabel, M.D., discuss the current state of research funding, the evolving mission of the institute and the value of public-private partnerships in this issue of *LENS*.

Betsy and I were fellows together at the Brigham and Women's Hospital in Boston. Her vision and leadership have re-invigorated cardiovascular research nationally. She gives us the confidence that critically important areas of investigation will thrive in the years ahead, and that we will be able to continue to make progress in the fight against this nation's leading disease killer. **LENS**



CARDIAC

REGENERATION

CONFERRING HEALING
SUPERPOWERS
TO THE HEART

IF AN UNFORTUNATE RUN-IN WITH A PREDATOR LEAVES A SALAMANDER WITHOUT A LIMB OR ITS TAIL, IN SHORT ORDER, THE CRAFTY AMPHIBIAN CAN **GROW** A PERFECT REPLICA TO REPLACE THE LOST APPENDAGE.

THE TINY FLATWORMS, CALLED PLANARIA, CAN DO ONE BETTER - IF CLEAVED IN TWAIN, THEY CAN **REGENERATE HALF OF THEIR BODY**, RESULTING IN TWO FULLY FUNCTIONAL AND INDEPENDENT WORMS.

NATURE HAS PROVIDED THESE CREATURES WITH ASTOUNDING REGENERATIVE POWERS. UNFORTUNATELY, HUMANS DIDN'T GET SO LUCKY.

OUR REGENERATIVE CAPACITY PALES IN COMPARISON TO THE SUPERHERO-LIKE ABILITIES OF THESE "LOWER" ANIMALS, LIMITED TO ONLY A FEW TISSUES.

BUT RESEARCHERS ARE NOW MAKING PROGRESS USING STEM CELLS TO REPAIR ONE OF THE MOST FREQUENTLY DAMAGED HUMAN ORGANS - **THE HEART**.

BY MELISSA MARINO

ILLUSTRATION BY DYNAMIC STUDIO/IMAGES.COM

HEART ATTACK,

or acute myocardial infarction, inflicts permanent heart damage on approximately 600,000 Americans each year.

During a heart attack, blood flow to the heart is interrupted, starving the tissue of oxygen (ischemia) and damaging or killing the heart muscle cells, the cardiomyocytes. This damaged or dying tissue (the infarction) fails to properly contract and pump blood, leaving heart attack survivors with lasting cardiac failure.

Currently, there is no way to replace or renew damaged heart tissue, but recent progress in regenerative medicine using stem cell therapy is showing promise in healing these “broken” hearts.

“In regenerative medicine, we try to restore some of this lost tissue in order to save lives as well as improve the quality of life,” says Antonis Hatzopoulos, Ph.D., associate professor of Medicine and Cell & Developmental Biology at Vanderbilt University Medical Center.

Only during early embryogenesis does our innate regenerative power rival that of worms and salamanders. As development progresses, the developmental trajectories of embryonic cells become more and more restricted, limiting the regenerative abilities of most human tissues. By adulthood, only a few tissues – skin, blood and the inner lining of the gut – regenerate easily, while in most tissues, regeneration is probably very restricted or nonexistent.

Regenerative capacity is conferred by either resident populations of stem cells that can give rise to new tissue cells when needed (for example, in skin and blood), adult cells that retain the ability to divide and grow (as in the liver), or a combination of the two.

“When it comes to cardiac regeneration, it looks like the heart has none of these mechanisms,” says Hatzopoulos,

who has studied the regenerative capacity of the vasculature for more than a decade.

While recent studies have indicated that the heart may have a very small reserve of stem cells, they have yet to be identified and isolated, he says, so “scientists have turned to other sources of stem cells to see if they would be able to repair damaged heart tissue.”

Bone marrow is an easily accessible and plentiful source of stem cells. The bone marrow produces several different types of stem cells including the hematopoietic stem cells, which produce the circulating blood cells; mesenchymal stem cells, which can differentiate into a variety of cell types; and endothelial progenitor cells, which repair damaged blood vessel walls.

Excitement began to build in the late 1990s, when several laboratories independently reported that circulating stem cells derived from bone marrow could differentiate into many different types of tissue cells, including the endothelial cells that line blood vessels.

Mounting evidence

Recent studies in animals have buoyed the promise of stem cell therapy for heart repair.

In a 2001 study, researchers treated mice with their own bone marrow-derived stem cells following an experimentally induced heart attack. Injection of these cells into the damaged heart tissue improved survival and led to the formation of new cardiomyocytes, vascular endothelium and smooth muscle cells, the investigators found.

“There was also clinical evidence,” says Hatzopoulos, noting earlier clinical observations of tissue regeneration in

people who had previously received bone marrow transplants.

“If you look at a biopsy, you find that some of the cells that are part of the new tissue are coming from the donor (bone marrow) ... indicating that there is a low level of wear and tear and replacement, and that bone marrow stem cells seem to be part of it.”

The mounting evidence triggered a number of clinical trials outside the United States – even while basic scientists were still conducting studies in animal models.

The clinical trials, which have used bone marrow-derived stem cells injected five to eight days after heart attack, have demonstrated that such therapies are safe and may offer a “moderate” improvement in heart function.

Among patients who received the cells, researchers observed an increase in the left ventricular ejection fraction (a measure of how efficiently the heart pumps blood), a reduction in the size of the infarct (indicating that the damaged heart muscle was being repaired), and an improved ability to exercise.

With these promising results, the National Heart, Lung, and Blood Institute in 2006 established a network of clinical centers to investigate this heart repair strategy in a more systematic way. VUMC was among the network’s five founding centers – along with the Texas Heart Institute, the University of Florida, the Cleveland Clinic and the University of Minnesota.

Vanderbilt also recently enrolled its first subjects into a privately-funded study (see “Stem cell pioneer,” page 9).

Despite the promising results from the clinical trials completed to date, the clinical benefit seems modest, suggesting

WHICH IS THE BEST CELL TYPE? HOW DO WE GET THE CELLS TO GO TO THE DESIRED SITE EFFICIENTLY? HOW CAN WE ENHANCE THEIR SURVIVAL IN A HOSTILE ENVIRONMENT? AND HOW DO WE DIRECT THEM INTO BECOMING THE *TISSUE CELLS WE WANT*?

that the therapy has much room for improvement. So researchers are heading back to the bench.

Says Hatzopoulos, "I think the key questions in the field are: which is the best cell type; how do we get the cells to go to the desired site efficiently; how can we enhance their survival in a hostile environment; and how do we direct them into becoming the tissue cells we want?"

While bone marrow is an easily accessible and abundant source of cells, the majority of bone marrow stem cells are ultimately destined to become blood cells. A small percentage of these cells appear to develop into cardiomyocytes, but Hatzopoulos says they may require an extensive "re-education" to produce numbers adequate for significant heart repair.

A major push in the field is to find a stem cell source that is closer to the ultimate goal of generating new heart tissue.

Mesenchymal stem cells, found in the bone marrow and other adult tissues, are known to differentiate into a variety of different cell types in the lab, including fat, cartilage, bone, muscle and nerve cells.

"Mesenchymal cells are closer to becoming heart," says Hatzopoulos, than are other types of stem cells in the bone marrow. This places them at an advantage, but they still require some additional "push" to enhance their therapeutic efficacy.

Super stem cells

At Vanderbilt, Pampee Young, M.D., Ph.D., assistant professor of Pathology and Medicine, and her colleagues are working to identify that push. From a mouse strain that naturally exhibits a high level of regenerative capacity, Young has isolated "super" mesenchymal stem cells.

When injected into mice that have had a heart attack, they secrete factors that



Vanderbilt stem cell expert Antonis Hatzopoulos, Ph.D. In the background, intravascular ultrasound images of the coronary artery, courtesy of Matthew O'Donnell, Ph.D., University of Washington College of Engineering.

DEAN DIXON

increase the proliferation of cardiomyocytes. Their ability to improve heart function after myocardial infarction exceeds that of injections of “normal” mesenchymal stem cells.

One factor that may play a role in their enhanced regenerative capacity is a signaling pathway known to set up the vertebrate body plan early in development, the Wnt pathway.

“We have identified a striking downregulation of the Wnt pathway in the ‘super’ mesenchymal stem cells,” Young says.

Downregulation enhanced mesenchymal stem cell proliferation, she adds, so “modulating the activity in this pathway ... may be an excellent future target for cell based therapies for myocardial injuries.”

A major obstacle is steering the cells to the desired location – the damaged heart tissue.

“In the clinical trials, in the best case scenario, no more than 3 percent to 4 percent of the cells reach the site,” says Hatzopoulos. “Most of them are lost in circulation.”

Hatzopoulos and colleagues have found that, after the ischemic event, there is an active interaction between bone marrow-derived cells and the vascular wall similar to the process seen when inflammatory cells migrate to a site of injury.

“During this process of ischemic injury, there is an upregulation of the inflammatory response,” he says. “Signals go out and mobilize a large number of

cells from bone marrow – including monocytes and lymphocytes – but among them, there are cells that can participate more directly in tissue regeneration.”

The vascular wall also becomes active, or “sticky,” and captures these cells.

“The problem is that this upregulation of the ‘sticky’ vascular wall is a transient event – it happens within the first couple of days after injury and dies off,” Hatzopoulos continues.

It’s impractical to inject the cells that early “because they will be coming into a very hostile environment, so their survival is going to be very limited.” But if they’re injected a week later or a month later, “this area is not going to capture cells.”

One of the challenges, then, “is to find ways to make that homing efficient at the time you want to deliver the cells.”

The biggest hurdle of all may be inducing stem cells to become heart cells instead of blood cells. This will require a deeper knowledge of the cellular factors involved in differentiation.

Hatzopoulos and his colleagues have isolated endothelial progenitor cells from the mouse embryos and have identified about 100 proteins produced by these cells that may have “cardiogenic” properties. They are now examining these proteins in animal models to whittle down the number of factors required for the development of cardiomyocytes from stem cells.

Studying these embryonic stem cells gives researchers a “blueprint” for the differentiation of cardiomyocytes, which they

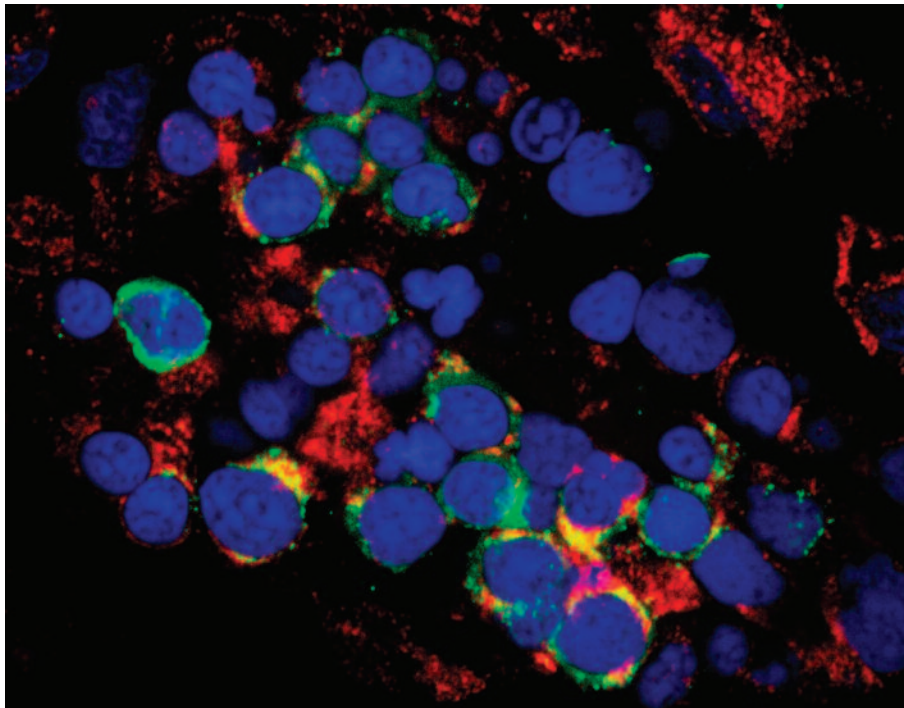
can then apply to other types of stem cells to help guide their differentiation down the desired path.

“We are trying to find factors that will push these cells towards the cardiac lineage in a more effective way,” said Hatzopoulos. “The practical application ... would be that if we put these factors together with stem cells and transplant them in the heart, that they will increase the yield of stem cells that become heart cells.”

If researchers are able to refine this therapy, making it more efficient and effective, stem cell therapy for heart repair could mark a new chapter in regenerative medicine.

“Many diseases – everything from heart disease to bone diseases – are so complicated, that we can’t use genes or drugs (to fix them). We have to have the cell as the building unit. The challenge is to find the right cell, and to make it do what you want it to do,” Hatzopoulos says.

“Cells are the therapeutic unit of the future,” he predicts. “We have only seen the beginning of it.” **LENS**



Confocal microscope image shows muscle cells developing within a cardiac infarct, heart tissue that has died due to lack of oxygen.

Courtesy of Jan Kajstura, Ph.D., and Piero Anversa, M.D., Cardiovascular Research Institute, and the *Proceedings of the National Academy of Sciences*

STEM CELL PIONEER

Earlier this year, John Plummer, Ph.D., a 63-year-old English professor of Vanderbilt University, became the first person in Tennessee to undergo a novel therapy to repair his heart.

About a week after suffering a heart attack, doctors at Vanderbilt University Medical Center siphoned off some of his bone marrow, then shipped the sample off to Amorcyte, Inc., a New Jersey-based biotechnology company that is developing cell therapy products to treat cardiovascular disease.

After processing and enriching the sample to promote the development of stem cells, the company sent the sample back to Vanderbilt, where it was injected into Plummer's coronary artery, from where preliminary studies suggest the cells will diffuse into the his heart muscle.

Plummer, who has taught at Vanderbilt for 36 years, realizes there are no guarantees the procedure will work. But, he says, "it was the prospect of improvement – any improvement – that made it worth it."

Vanderbilt is one of three centers, along with Emory University and the Texas Heart Institute, participating in the Phase 1 clinical trial sponsored by Amorcyte. The trial, which began last year, is testing whether bone marrow stem cells can aid the recovery and

regeneration of heart muscle following a heart attack.

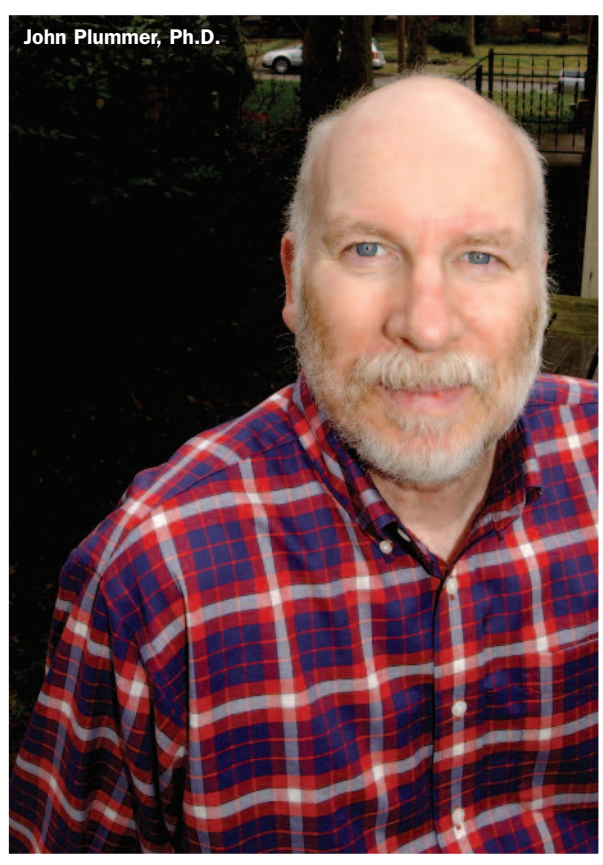
One of the major obstacles in treating patients after a heart attack is the inability to repair the damaged muscle. In about 20 percent of heart attack patients, the muscle loss is permanent, leading to worsening of the heart function and, ultimately, heart failure.

"We can treat a lot of diseases affecting the heart ... (but) we have not made significant strides in the fact that we can do nothing more than treat symptoms in patients with a dying heart," says David Zhao, M.D., director of the Vanderbilt Cardiac Catheterization Laboratory.

"What we hope is to one day be able to treat the entire heart without surgery, and use the bone marrow cells to repair the heart," Zhao says.

"Heart failure has a huge financial impact on our medical system," adds Scott Phillips, M.D., a cardiology fellow who is participating in the Vanderbilt study. "If this proves to be a viable therapy, there would be tremendous benefits, not only for the patient, but in terms of the amount of money a health care system could save. It would be astronomical."

The premise behind cardiac regenerative therapy is this: Bone marrow is rich in endothelial progenitor cells, which circulate in the blood and are thought to facilitate



John Plummer, Ph.D.

SUSAN URMY

the growth of new blood vessels. European scientists for several years have pioneered approaches aimed at using these primitive or "stem" cells to try to repair heart damage.

"This treatment approach looks very promising based on preliminary results already published," says Friedrich Schuening, M.D., chief of the Section of Hematology and Stem Cell Transplant at Vanderbilt.

The Amorcyte trial is enrolling patients with evidence of impaired heart function following a heart attack. Half of the participants in the study will receive a stem cell infusion, while the others will serve as a control, and will receive standard treatment.

They will be followed regularly for up to five years. Assessment tools, aside from a clinical visit, will include echocardiograms (EKGs) and cardiac magnetic resonance

imaging (MRI), which can reveal in detail the ventricular structure and function of the heart.

Within three to six months, investigators expect to see some improvement in heart function.

"This is an exciting opportunity to get into the field of regenerative medicine of the heart," said Douglas Vaughan, M.D., chief of the Division of Cardiovascular Medicine at Vanderbilt and principal investigator of the Amorcyte trial.

"We don't have all the answers about cardiac cell-therapy, but we do know that we have to start doing these trials to start finding the answers to the questions."

– JESSICA PASLEY

BY LEIGH MACMILLAN
PHOTO BY DEAN DIXON

OFF TEMPO

UNDERSTANDING
THE GENETICS
OF DISTURBED HEART
RHYTHMS
AND SUDDEN
CARDIAC DEATH

Hank Gathers. Reggie Lewis. Sergei Grinkov. Young athletes. Unexpected collapse. **Sudden death.**

In March 2006, Davis Nwankwo nearly joined the list.

It was a routine Monday morning practice. The Vanderbilt Commodores were heading to the Southeastern Conference Men's Basketball tournament later in the week. Nwankwo arrived for practice about an hour early, as usual, to visit the trainer and have his ankles iced and taped.

He felt fine.

About 20 minutes into the practice, "my mind went blank and I started to walk away from the drill," recalls Nwankwo, 21, a 6-foot, 10-inch tall senior from College Park, Md. He learned later that he collapsed, stopped breathing, and had no pulse. His heart's normal rhythmic contraction was gone, replaced by rapid, uncoordinated twitching: ventricular fibrillation.

Nwankwo was lucky. Athletic trainer Mike Meyer sent someone racing to get the automated external defibrillator (AED) from the training room. A jolt from the AED and two breaths from Meyer saved Nwankwo's life.

Without these measures, "he would have died on the spot," says Dan Roden, M.D., director of the John A. Oates Institute for Experimental Therapeutics at Vanderbilt University Medical Center and one of the cardiologists who cared for Nwankwo during his hospital stay.



Davis Nwankwo

All in the family

Though the unexpected collapse and death of a young athlete in prime physical condition garners national attention, it is a rare event. But sudden cardiac death in the general population is all too common.

“About 15 percent of all deaths in adults in the United States – almost one death every minute – are sudden cardiac deaths, most due to ventricular fibrillation,” Roden says. “That’s a major public health problem.”

For patients with known heart disease, the “cardiovascular world has gotten very good at projecting risk of sudden cardiac death,” Roden says. Patients who are considered high risk generally undergo surgery to place an implantable cardioverter defibrillator, an electronic watchdog that monitors heart rhythm and delivers a shock in the event of cardiac arrest. Nwankwo had a defibrillator implanted two days after his collapse.

“But very good (at determining risk) is not perfect,” Roden adds. To complicate matters further, fewer than half of all sudden cardiac deaths occur in patients with

known heart disease or conventional markers. That means that for a majority of those who suffer sudden cardiac death, it is the first symptom they experience.

Investigators around the world are turning to genetics to identify patients without “conventional markers” who are at risk for sudden cardiac death. Their efforts are grounded in three large epidemiological studies, the latest of which comes from a group headed by Arthur Wilde, M.D., Ph.D. at the Academic Medical Center in Amsterdam.

Wilde and colleagues performed a case-control study in patients with a defined type of myocardial infarction (ST-elevation MI) who underwent percutaneous coronary intervention (angioplasty or stent placement). The case patients were those who survived ventricular fibrillation that occurred within the first 12 hours of the myocardial infarction. Control patients

were matched for age, gender and infarct size, but did not experience ventricular fibrillation.

“The most intriguing finding of this case-control study ... is that sudden cardiac death among parents and siblings is such a strong predictor of primary ventricular fibrillation,” Wilde and colleagues wrote in their 2006 *Circulation* report. The previous epidemiological studies had also suggested that a family history of sudden cardiac death increases a person’s risk for sudden death.

“What a ‘family history’ means to me,” Roden says, “is that there’s a relatively common genetic variant, or set of variants, in people who have sudden death that is different from people who don’t have sudden death. And that risk shows up when a coronary artery is occluded.”

Roden and Jean-Jacques Schott, Ph.D., of the French INSERM (National

“About 15 percent of all deaths in adults in the United States – almost one death every minute – are sudden cardiac deaths, most due to ventricular fibrillation,” Roden says. “That’s a major public health problem.”

DEAN DIXON



Institute of Health and Medical Research Center) in Nantes, France, are co-coordinators of a five-year, \$6 million initiative funded by the Paris-based Leducq Foundation to search for the genetic variations that increase risk for sudden cardiac death. The network of sites in Europe and the United States aims to generate a genetic risk profile that will make it possible to calculate a patient's risk for sudden cardiac death based on a genetic test.

"For these kinds of genetic screens, you need large, well-characterized patient and control populations, and the resources to do complicated genetic and statistical analyses," Roden says. The network, whose core members include Amsterdam's Wilde, Eduardo Marban, M.D., Ph.D., and Peter Spooner, Ph.D., both of Johns Hopkins University, and Robert Myerburg, M.D., of the University of Miami, plans to carry out its first screen

for genetic variations associated with sudden cardiac death within the next six months.

Rare diseases offer insight

Genetic screening can be done at the single gene or genome-wide level, or somewhere in between. The Leducq-funded investigators will take the middle road, looking for "places in the genes we know and love, so-called candidate genes, where variation might explain susceptibility to arrhythmias and sudden death," Roden says.

Studies of rare inherited cardiac arrhythmias have played a key role in identifying the "candidate" molecules that have roles in powering the rhythmic heart beat. Many of these proteins are ion channels – doughnut-like pores that control

the flow of electrically-charged ions across the cell membrane.

In 1995, Mark Keating, M.D., and colleagues at the University of Utah reported that mutations in two ion channel genes – one encoding a sodium channel, the other a potassium channel – cause congenital long QT syndrome. This disorder, named for the longer than normal time between two points – Q and T – on the electrocardiogram, affects about one in 1,000 individuals in the United States and can cause a potentially fatal arrhythmia called "torsades de pointes." Over the last decade, hundreds of distinct mutations that cause long QT syndrome have been identified in 11 different genes, almost all of them encoding ion channels in the heart.

Likewise, other rare inherited arrhythmias and heart muscle diseases like hypertrophic cardiomyopathy have been linked to mutations in ion channels,

BABIES AT RISK

The genetics of sudden infant death syndrome

Fatal arrhythmias could be the underlying culprits in some cases of sudden infant death syndrome (SIDS). A pair of studies in the Jan. 23, 2007, *Circulation* reported that nearly 10 percent of SIDS victims have mutations or variations in genes associated with potentially lethal heart rhythms.

SIDS is the leading cause of death in infants age 1 month to 1 year in the United States, according to the Centers for Disease Control and Prevention.

The number of SIDS deaths has been declining since the early 1990s – likely due to educational campaigns about the risk of putting infants to sleep on their stomachs and exposing them to cigarette smoke. But despite the drop, SIDS continues to be a leading cause of infant mortality in developed countries, and the underlying basis of the condition remains unclear.

A popular theory proposes that SIDS occurs because of a combination of risks including abnormal physiological state, environmental factors

and developmental vulnerabilities. Genetic factors may also be important.

"SIDS is not one disease," says Alfred L. George Jr., M.D., director of the Division of Genetic Medicine at Vanderbilt. "Multiple conditions can increase the risk of sudden death in an infant. Some have been identified, but many have not."

Anecdotal evidence previously suggested that some SIDS victims carry mutations in genes associated with conditions such as the long QT syndrome that predispose individuals to life-threatening arrhythmias and sudden death. But the proportion of SIDS cases that carry such mutations was not clear.

George's collaborators, Peter Schwartz, M.D., in Italy, and Torleiv Rognum, M.D., Ph.D., in Norway, led the efforts to screen seven arrhythmia-associated genes in 201 SIDS cases from Norway – the largest ever genetic survey of a SIDS cohort. The results published in *Circulation* showed that 9.5 percent of SIDS victims harbored mutations (not seen in controls) in genes

associated with inherited forms of cardiac arrhythmia, such as long QT syndrome.

The researchers identified mutations in several genes, including the gene that encodes the cardiac sodium channel – a protein that regulates the electrical properties of heart cells. George's lab then performed studies to understand the physiological consequences of mutations in the cardiac sodium channel gene, called SCN5A, which has previously been associated with long QT syndrome and several other conditions that cause unstable heart rhythms and sudden death.

"We observed a pattern of SCN5A dysfunction that is reminiscent of what's been observed in long QT syndrome," George says. "That gives us confidence that the mutations observed in SIDS victims are not benign genetic variants – but rather could increase the risk of potentially lethal arrhythmias."

The researchers have similar evidence, to be published separately, demonstrating that

mutations in heart potassium channels are also contributing factors in SIDS.

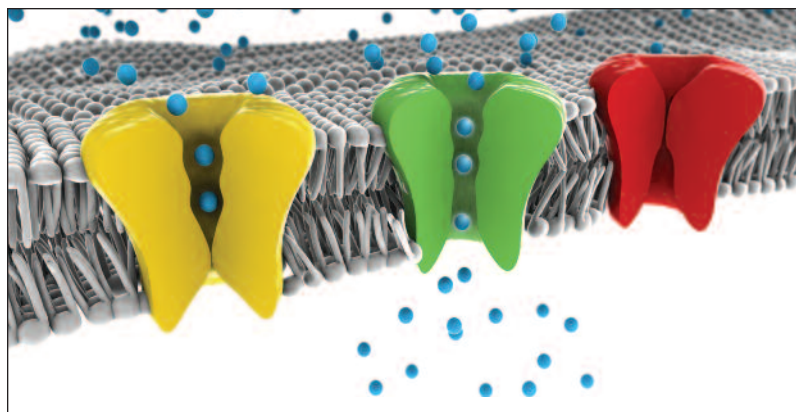
The findings also suggest that there may be strategies to identify whether infants carry one of these mutations before the tragic event of their death, George says.

"We are not recommending that a population-wide genetic screening be done, but there may be simpler, cost-effective measures that should be investigated further, perhaps performing ECG (electrocardiogram) screening of infants, although this idea is controversial."

Inherited arrhythmias are manageable conditions that can be treated with medications or implantable devices, George says.

"There's potentially an infant death every other day in the U.S. due to this problem (arrhythmias)," he says. "Exactly how best to identify this risk and prevent arrhythmia-related death during infancy needs to be determined."

– MELISSA MARINO



Stop, Go and ... Not so fast

Ion channels control the flow of electrically-charged ions across the cell membrane and thus can affect heart rhythm. Red and green figures show closed and open channels. The yellow figure shows a mutation that inhibits ion flow.

Illustration by J.P. Cartailier

calcium-regulating proteins, and components of the muscle cell's contractile apparatus.

The rare cardiac diseases were once only interesting for purposes of "hospital roundsmanship," Roden says, but "their importance now goes well beyond that." They have revealed that the heart is composed of highly interconnected and interdependent systems, and that a defect in just one component of the system can cause a dramatic phenotype.

The rare syndromes have pointed to new components in cardiac physiology. And what's more, variations in the genes implicated by the rare syndromes have turned out to be more common than previously believed and to only sometimes cause disease, a phenomenon called "variable penetrance."

"There's a lot of commonality to these arrhythmia syndromes because the majority of them are caused by ion channel defects," says Dawood Darbar, M.D., Ph.D., "but whether you get the congenital long QT syndrome or Brugada syndrome or atrial fibrillation, no one really knows why that is, and that's something we're trying to understand."

Darbar, assistant professor of Medicine at Vanderbilt, focuses on atrial fibrillation, the most common arrhythmia observed in clinical practice. Atrial fibrillation carries a substantial risk of stroke and affects between 2 million and 3 million

people in the United States, a number that may climb up to 8 million as the population ages. Symptoms range from nothing at one extreme to tremendous disability in terms of shortness of breath on exertion and heart failure on the other.

The fact that atrial fibrillation has a genetic basis has only been recently appreciated. "In the last five years there have been some fairly dramatic findings, and we now believe that up to a third of patients with atrial fibrillation probably have a genetic basis for their disease," Darbar says.

Darbar and colleagues have conducted genetic screens in families with atrial fibrillation, identifying several DNA regions of interest. They also are building a database of clinical information and DNA samples for patients with atrial fibrillation, not just those who are part of large affected families. With more than 900 patients enrolled, this may be the largest such population in the country, he says.

"We're trying to get to the point where we can do a genome-wide screen so that we can look beyond candidate genes to genes that intuitively don't make any sense," Darbar says.

Genotyped prescriptions

Understanding the genetic causes of arrhythmia disorders will ultimately improve treatments, the investigators argue.

Roden: "Knowing what the genetic variants are **will make us smarter** in terms of predicting who is at risk or not, and in terms of tailoring therapy with available drugs or tailoring new therapies."

Antiarrhythmic medications are not terribly effective, Roden says, and are famous for causing a wide range of side effects, including actually worsening the heart rhythm and even creating new abnormal rhythms. And antiarrhythmic drugs are not alone in having these "proarrhythmic" effects. A wide range of non-cardiovascular drugs including antihistamines, antibiotics

DEAN DIXON



Dan Roden, M.D.

and antipsychotics also can create life-threatening abnormal heart rhythms.

It was one of these drug-induced arrhythmias – “torsades de pointes” – that first captivated Roden. What intrigued him, he recalls, was that the same unique pattern on the electrocardiogram occurred in a congenital syndrome (long QT) and a drug-induced arrhythmia. The connection suggested that the genome may hold clues for why drugs elicit this kind of adverse reaction in some individuals but not others.

Roden has pursued the idea that there are genetic contributors to variability in drug response – “pharmacogenomics” – for most of his career, and last year he was named assistant vice chancellor for Personalized Medicine at Vanderbilt. He leads the Pharmacogenomics of Arrhythmia Therapy project, part of the Pharmacogenetics Research Network, a national effort to understand the genetics of drug responses supported by the National Institute of General Medical Sciences. Roden’s arrhythmia-focused team is poised to screen DNA samples from patients who have experienced drug-induced arrhythmias.

“The idea (of personalized medicine) has gone from an intellectual curiosity kind of thing to the notion that it may one day be possible to have generalized genetic profiles of every patient and the informatics infrastructure that will allow you to interrogate that genetic information,” Roden says.

A recent example from Darbar and Roden’s studies demonstrates how genotype might be used to tailor antiarrhythmic therapy. The team found that patients with atrial fibrillation who carry a common variation in the angiotensin-converting enzyme (ACE) gene were more likely to respond to a certain antiarrhythmic medication than patients who did not carry the variant.

“We could predict, based on genotype at one marker, how a patient will respond to the medication,” Darbar says. “This is the first example I know of a pharmacogenetic effect in atrial fibrillation.”

“In all of these spheres – arrhythmia management, drug-induced arrhythmias, sudden death,” Roden says, “the mantra is: knowing what the genetic variants are will make us smarter in terms of predicting who is at risk or not, and in terms of tailoring therapy with available drugs or tailoring new therapies.”

A tall order, perhaps, but one for which these investigators are game. **LENS**

When medication is not enough

The ablation “cure” for arrhythmia

Andrea Boyce’s heart started racing 20 years ago, when she was 17.

“I could ... see my heart beating through my skin,” says Boyce, of Owensboro, Ky. “I would get a headache and start sweating and have a pain down my left arm.”

Boyce eventually was diagnosed with supraventricular tachycardia (SVT), a condition that caused her heart to speed up to 220 beats per minute.

Although her episodes were not frequent, the intensity of her symptoms prompted her doctor to put her on medication, which made her extremely tired and did not prevent the episodes. She continued to have them at least once or twice a year.

“When your heart rate was as fast as mine, all you are thinking about is – am I going to have a stroke or a heart attack? It was very frightening,” she says.

So Boyce asked for ablation, which uses high frequency radio waves to “short-circuit” the abnormal electrical impulses in the heart.

A thin tube or catheter is usually inserted into the femoral vein in the groin and threaded up to a key point in the abnormal circuit in the heart. A burst of radiofrequency energy is delivered to the area to destroy the tissue and prevent the arrhythmia. Patients generally can go home the day after the procedure.

“Catheter ablation therapy has been around for 20 years, but it has only come into prominence in the ‘90s,” says Dawood Darbar, M.D., Ph.D., director of the Arrhythmia Service at Vanderbilt University Medical Center who performed Boyce’s ablation this winter. “It is increasingly becoming the first line of therapy for many forms of arrhythmias.”

“People like Dawood, who perform this procedure, are the only cardiologists who are allowed to use the word cure,” adds Dan Roden, M.D., an internationally known expert on arrhythmia at Vanderbilt. “In many cases the likelihood of a recurrence is very, very low. Everyone else in the field of cardiology just fights back disease.”

“It’s amazing,” says Boyce, who has not had an episode of tachycardia since her procedure. “I was talking to the technician who did my heart ultrasound before the procedure and he was telling me that 15 to 20 years ago it was unheard of to fix electrical parts in the heart unless it was a life-or-death situation.”



Andrea Boyce and Dawood Darbar, M.D., Ph.D.

Another ablation patient who had good results is 65-year-old Bobby Page of Bowling Green, Ky.

Ten years after first heart attack in 1983, Page began experiencing abnormal heart rhythms that increased his risk of sudden cardiac death. Over the next few years, five defibrillators were implanted under the skin of his chest to shock his heart rhythm back to normal.

“You never did know when it was going to hit you,” says Page, a retired truck driver. “They warned me that the shock could throw me to my knees. It never knocked me down, but it has rattled my cage pretty many times. It felt like somebody hitting me in the shoulder blade with a sledge hammer.”

Page, who also has other health concerns including congestive heart failure, poor circulation in his extremities and damage from his heart attack, says he was afraid to leave the house for fear his defibrillator would “go off.”

After the most recent device, implanted in late 2006, gave him a series of shocks to rescue him from abnormal heart rhythms, his doctors at Vanderbilt decided to try ablation therapy. Page said he has not had any trouble since.

There is still a chance that arrhythmias will recur. But for patients like Page and Boyce, the procedure has meant a new lease on life.

“Before having this done, I was very cautious about most of my activity for fear I would trigger the episodes,” Boyce says. “Now I feel much more comfortable trying things.”

– JESSICA PASLEY

Editor’s note: Vanderbilt has long been a regional referral center for ablation treatment of SVT. Recently it opened a comprehensive program to treat atrial fibrillation, the most common arrhythmia in clinical practice.

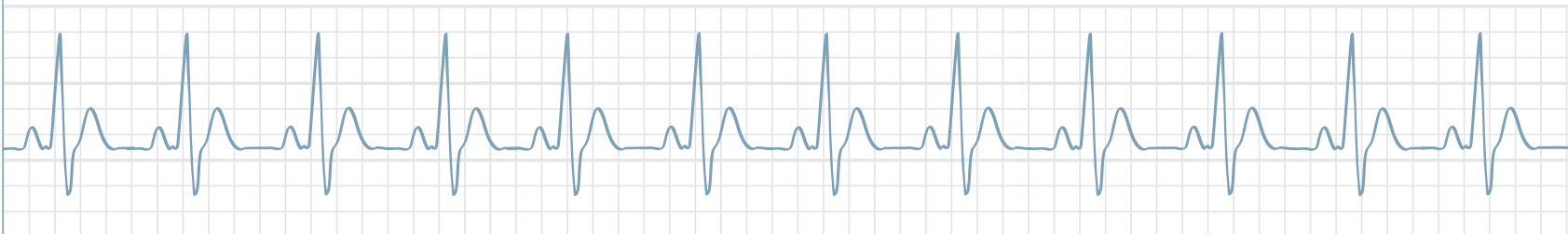
Just as a great symphony is only an elegant idea until it is actually performed, groundbreaking biomedical research is only of potential value until it is actually applied. Perhaps more than any other academic physician, Eugene Braunwald, M.D., has guided the movement of cardiovascular research – recognizing the significance of disparate results and pushing the field forward from bench to bedside. Like a conductor who understands the importance of each note in a symphony, Braunwald is viewed by many as the “grand maestro” of American cardiology.

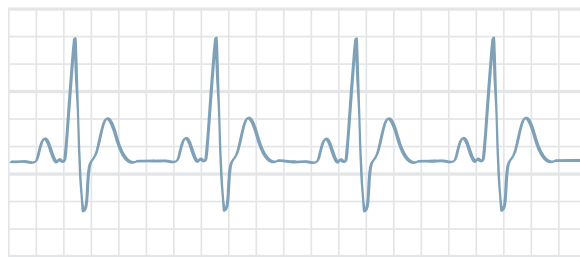
EUGENE BRAUNWALD

MAESTRO OF AMERICAN CARDIOLOGY

BY LISA A. DUBOIS

Photo by Asia Kepka





“He led a series of studies that transformed the face of cardiovascular medicine,”

says Douglas Vaughan, M.D., chief of Cardiovascular Medicine at Vanderbilt University Medical Center. During the past 25 years, in part because of research led by Braunwald, the percentage of people who die within a month of being hospitalized for a heart attack has plunged five-fold, from 20 percent to about 4 percent.

“That is an enormous difference,” says Vaughan, who was part of Braunwald’s research team in the late 1980s. “Every practicing cardiologist has to appreciate the impact of Dr. Braunwald’s insights and research in the mechanisms and treatment of acute myocardial infarction (AMI).”

Braunwald struck his first international chord as the lead author of a 1971 landmark study showing, in an experimental model, that the damage caused by AMI, a heart attack, could be limited by favorably altering the balance between the supply of and demand for oxygen in the heart.

Until that discovery, physicians had believed that once a patient exhibited symptoms of crushing chest pain, little could be done to affect the outcome. When patients with AMIs were rushed to the hospital, they were sedated, put on strict bedrest and, if necessary, defibrillated. If they survived, they were sent home on various medications. During the next year, a quarter of the survivors died, usually of heart failure.

Braunwald was the first to challenge this laissez-faire approach to AMI. In 1967, while visiting the laboratory of Seymour Schwartz, M.D., a surgeon at the University of Rochester, he was shown dogs with experimentally-induced hypertension. Implanted stimulators of the animals’ carotid sinus nerves restored their blood pressures to normal.

At the time, Braunwald, at the ripe old age of 38, had already been chief of cardiology at the National Heart, Lung, and Blood Institute, part of the National Institutes of Health (NIH), for eight years. Immediately, he and his colleagues began implanting stimulators of the carotid sinus nerves in patients, but for a totally different reason – to relieve angina pectoris (chest pain). Although this treatment worked, it was short-lived because of the near simultaneous introduction of coronary bypass surgery, which was a preferable way to correct the imbalance between the heart’s supply and consumption of oxygen.

However, a year later, serendipity came into play. One of Braunwald’s patients with an implanted carotid nerve stimulator was admitted to the hospital with an AMI. Fearing that stimulating the carotid sinus nerves would exacerbate the evolving MI, Braunwald asked the patient to turn off the device. The patient ignored him and continued to press the stimulator to relieve his pain. Eventually, after several “on-off” episodes, Braunwald, in exasperation, removed the stimulator’s battery pack.

Later, when he was reviewing the patient’s electrocardiogram, which had been recorded throughout this period, Braunwald realized that the “patient was a lot smarter than I.” The oxygen deficiency of his patient’s heart actually improved whenever he stimulated his carotid sinus nerves, and worsened when Braunwald turned off the stimulator – the exact opposite of what he had expected. He was thunderstruck.

“That gave me the idea that you might actually be able to modify an MI while it is progressing,” says Braunwald.

SOUND OF MUSIC

Eugene Braunwald was born in Vienna, Austria, on Aug. 15, 1929. He had what he terms an “idyllic childhood” as the firstborn son of a well-to-do Jewish wholesale clothing merchant, William Braunwald, and a homemaker mother, Clara, living in a fine neighborhood, attending an excellent private school, tutored in English and piano, and beginning to partake of the famed cultural offerings of Vienna.

Braunwald’s life took a chilling turn on March 12, 1938, however, when the Nazis occupied Austria. He was immediately expelled from school.

Only a few days later, an SS officer arrived at the Braunwald home (which was attached to the business) and methodically set about liquidating the business holdings, keeping the profits for himself. Two months later, a group of Nazis barged into the home around 3 a.m. and arrested William Braunwald, throwing him into a truck and carting him and other detainees to the train station to be shipped off to a “work” camp.

Clara Braunwald was frantic, but she kept her wits about her. The next morning when the SS officer arrived, she told him that her husband had been arrested, which was unfortunate because the officer had liquidated only half of the business. She pointed out that he could become much wealthier if her husband’s deportation could be delayed until the entire stock was sold.

“You might be right,” the officer mused. He then made a phone call or two, ordering William Braunwald to be returned home.

On July 31, 1938, William and Clara Braunwald packed some lunches and told Eugene and his younger brother Jack that they were going on a picnic. They boarded a trolley, then a taxi, then a train, and eventually crossed into Switzerland. From there they traveled to Paris, and finally wound up in London as wards of a relief agency, in possession of nothing more than the proverbial clothes on their backs.

“It was like the Sound of Music, except there was no music,” Braunwald says, admitting that they barely made it out in time. “Kristallnacht (the wave of pogroms against German and Austrian Jews) came three months later.

“This was a point of no return; Jews were slaughtered on the streets, others were arrested and carted off wholesale to concentration camps. It was the start of the Holocaust. But I was very lucky. I never went hungry and I had no physical injury. So, given the whole scale of things, I feel extremely fortunate.”



Performance of "Aida" at the Metropolitan Opera in the late 1940s or early 1950s, around the time that Eugene Braunwald was paid a dollar a night for his role as a spear carrier.

Courtesy of the Metropolitan Opera Archives

Their fortunes detoured again during the London blitz. Because Austrian refugees were deemed "enemy aliens" in Britain, the Braunwalds had to leave the country or be interned in work camps. They managed to get to New York City, where they had a relative. They arrived the day after Thanksgiving 1939.

Two years later, the United States entered World War II. For young men and women on the home front, the catchword of the day was "engineering." Joining this wave, Braunwald was accepted into the elite Brooklyn Technical High School, in an accelerated program in which both high school and college could be completed in five years.

At New York University, however, Braunwald decided he was more interested in biology than engineering. He wanted to become a physician.

Getting into medical school was much more difficult than it is today. At the time, medical schools had strict quotas limiting the number of Jewish enrollees, and returning war veterans were given first priority. Braunwald was the last student admitted to New York University's medical school class of 1952. (He was also the first out, graduating as the top student in his class).

"My admission to medical school was the most important day of my professional life," he says. "All the pressures were

behind me. I loved every moment of medical school."

Like many financially disadvantaged students of that era, Braunwald, on a full tuition scholarship, lived at home and commuted by subway, toting his microscope, slides, *Gray's Anatomy*, and box of cadaver bones back and forth with him to class every day.

Also, for the first time since he left Vienna, Braunwald took advantage of the outstanding musical performances the city had to offer. He volunteered to be an extra, known informally as "spear carrier," at the Metropolitan Opera, and was paid a dollar a night for his roles in productions of "Aida" and "Tosca." He gave up his "operatic career" once he began his internship.

ELECTRICIANS AND PLUMBERS

Braunwald's instructors at NYU included two Nobel laureates: fellow Austrian exile Otto Loewi, M.D., recognized for seminal discoveries relating to the chemical transmission of nerve impulses; and pioneering molecular biologist Severo Ochoa, M.D.

Braunwald also studied under Colin MacCleod, M.D., who co-authored the pivotal 1944 paper that established DNA as the bearer of hereditary information, and Homer Smith, M.D., a founding father of comparative physiology and nephrology. Medical history, says



Braunwald (right) works with Stanley Sarnoff, M.D., in the animal laboratory at the National Heart Institute (now the National Heart, Lung, and Blood Institute) in 1955.

Photo courtesy Eugene Braunwald, M.D.

Braunwald, "was unfolding all around me. Luckily, I realized what was going on."

In the early '50s, NYU had originated the then novel (and now commonplace) practice of offering a three-month elective to medical students. With the engineering mantra playing in his memory, Braunwald chose for his elective a research rotation in cardiology, studying the hemodynamics of heart failure under the guidance of Ludwig Eichna, M.D., who ran one of the nation's first research cardiac catheterization laboratories.

"Cardiology is in many ways a hybrid between engineering and biology," Braunwald says. "Cardiologists can be divided into electricians and plumbers. Those who deal with rhythm disturbances are the electricians, and those who deal with disturbances of cardiac pumping are the plumbers." Disturbances in the operation of either the rhythm or the pump can cause the heart to fail.

The weekend after graduating from NYU medical school, Braunwald married his college and medical school classmate, Nina Starr Braunwald (1928-1992), who would later achieve pioneer status as a cardiothoracic surgeon. In 1960, she would lead the first team to successfully replace a human heart valve, which she had designed.

After a residency at Mt. Sinai Hospital in New York, Braunwald spent a research fellowship year at Columbia University and Bellevue Hospital, studying under André Cournand, M.D., who would soon win a Nobel Prize for advances in cardiac catheterization.

He completed his medical residency in internal medicine at Johns Hopkins Hospital, where he attended lectures given by cardiovascular giants including Alfred

Blalock, M.D., and Helen Taussig, M.D., who had just developed the “blue baby” operation. Then he went on to the intramural program of the NIH.

In 1967, Braunwald became an editor of *Harrison's Principles of Internal Medicine*, now considered to be the defining medical text for physicians and medical students around the world.

Launched in 1950 by former Vanderbilt professor Tinsley Harrison, M.D., the textbook offered medical students a new way of approaching patients. Instead of describing various diseases, *Harrison's* invited students to understand the biologic basis of signs and symptoms which would lead to correct diagnosis and rational treatment. It was the first textbook to break down the wall between basic science and clinical medicine.

The same year, Braunwald got the chance to apply this new approach to medical education when he was asked to become the founding chairman of Medicine of the new medical school at the University of California at San Diego (UCSD). He seized the opportunity and moved his family, which now included three daughters, to the West Coast.

Braunwald and his colleagues immediately set about bridging the educational divide that existed universally at the time. Surgeons taught anatomy; internal medicine faculty taught physiology and pharmacology. The head of the infectious disease division taught microbiology, as well as clinical infectious diseases. Their approach, which was quite controversial at the time, is now the cornerstone of medical education throughout the country.

Meanwhile, the research in the Braunwald laboratory was going well. His team published key studies on AMI in dogs showing that giving a beta blocker to lower myocardial oxygen demand and reperfusion to increase oxygen supply reduced the size of the MI. This laid the groundwork for a standard of care that was revolutionary at the time, but which still

holds today – namely, that aggressive medical intervention before, during and after a heart attack can reduce myocardial damage and therefore be life saving.

Four years later, after overseeing the graduation of UCSD's charter medical school class, Braunwald was called back to the East Coast, this time to Boston, to chair Harvard University's Department of Medicine at the Peter Bent Brigham Hospital (now Brigham and Women's Hospital). Over time, he held increasingly complex positions, including eight years as Harvard Medical School's Faculty Dean for Academic Programs at Brigham and Women's and Massachusetts General Hospitals.

But his devotion to cardiovascular research never wavered.

THE NEXT FRONTIER

By the end of the 1970s, the injection by catheter of a thrombolytic (clot-busting) agent, streptokinase, into blocked coronary arteries was just beginning to take hold. In 1981, Braunwald's team showed for the first time that when streptokinase was used in this manner to open blocked arteries, myocardial tissue threatened during an AMI could be salvaged by restoring the supply of oxygen-laden blood.

The question then became how to administer these thrombolytic drugs intravenously, so that patients could receive medication as quickly as possible, even away from the hospital – in an ambulance, if possible. Streptokinase worked fine when given through an intracoronary catheter, but it performed poorly as an intravenous therapy.

In the early 1980s, a new class of recombinant-DNA drugs was developed, including the thrombolytic agent, tissue plasminogen activator (tPA), which was effective when delivered intravenously. Braunwald was certain that tPA and the concept of on-site, immediate treatment of evolving AMI was the next frontier, and he prevailed on the NIH to let him set up

a clinical trials network to test this theory.

In 1984, he established the first TIMI (Thrombolysis in Myocardial Infarction) study, which found that intravenous tPA was indeed superior to streptokinase in opening occluded arteries. With more than 800 sites in 46 countries participating in subsequent TIMI studies, today Braunwald is viewed as one of the world's masters of the clinical trial.

“Ask anybody who's ever worked for Dr. Braunwald. The best work you'll ever do is when he is standing behind you, looking over your shoulder,” says Marc Pfeffer, M.D., Ph.D., professor of Medicine at Brigham and Women's Hospital. “He sets high standards, but he lives by those standards, too.”

Pfeffer and his late wife, Janice Pfeffer, Ph.D., came to Boston in the mid-1970s to pursue studies of left ventricular enlargement (also called hypertrophy), associated with systemic hypertension and by AMI with Braunwald.

By the early 1980s, they had established that captopril, an angiotensin converting enzyme (ACE) inhibitor, developed to control hypertension, also reversed hypertrophy and improved cardiac performance and survival in rats with MI. Their findings led to the Survival and Ventricular Enlargement (SAVE) clinical trial, which in 1992 showed that ACE inhibitors improved the left ventricular function and reduced mortality in patients who'd suffered a major heart attack.

Today, ACE inhibition is routinely recommended for patients following an MI, and is given to millions of such patients worldwide each year.

By 1988, doctors knew that patients with elevated low-density lipoprotein (LDL) cholesterol tended to be at risk for recurrent MI. In another study, the Cholesterol and Recurrent Events (CARE) trial, Braunwald and his colleagues studied whether heart attack patients with “average” cholesterol levels (at the time, 210 milligrams per deciliter of blood), also would benefit from taking cholesterol-lowering drugs.

For five “nail-biting” years, Braunwald's team waited for the results, which ultimately showed that patients who took pravastatin to lower serum cholesterol indeed reduced their risk for having another heart attack, stroke, or dying of cardiovascular causes.

More recent TIMI trials have examined the effect of driving cholesterol levels even lower, and have found not only that “lower is better,” but that “much lower is much better.” TIMI investigators are cur-

“CARDIOLOGY IS IN MANY WAYS A HYBRID BETWEEN ENGINEERING AND BIOLOGY. CARDIOLOGISTS CAN BE DIVIDED INTO ELECTRICIANS AND PLUMBERS. THOSE WHO DEAL WITH RHYTHM DISTURBANCES ARE THE ELECTRICIANS, AND THOSE WHO DEAL WITH DISTURBANCES OF CARDIAC PUMPING ARE THE PLUMBERS.”

rently studying the effects of reducing a patient's LDL to a level in the 50s, levels undreamed of 10 years ago.

"We've followed all of these patients extremely carefully, and we don't see any serious side effects with even extreme cholesterol lowering," says Braunwald. "We have not yet reached the (LDL-concentration) floor."

For more than a half century as an academic physician-scientist, Braunwald has been instrumental in numerous discoveries that have saved millions of lives, and, for the record, he has no plans to stop anytime soon.

Now married to his second wife Elaine, formerly a senior hospital administrator, and a grandfather of seven, he is editing *Harrison's* for the 11th time and is leading methods for moving the textbook

into the digital age. He is also piloting new TIMI trials, including several that test the therapeutic potential of novel anti-platelet agents.

He and his team recently began active planning of the 50th TIMI trial, even as he ponders how genetics and information technology will rewrite the score of cardiology.

"The principal task of the cardiologist in 2007 is to diagnose, assess and treat established cardiovascular disease," he says. "As a consequence of the revolution in human genetics, the principal role of the cardiologist by 2027 will be to interpret the patient's genetic information and from this develop a plan personalized for

each patient for the prevention of cardiovascular disease."

Braunwald has left a huge imprint on basic science, translational research, clinical trials and medical education. He has moved easily between the laboratory, the bedside and the classroom. But perhaps his true genius lies in his ability as the "grand maestro" of cardiology to comprehend the big picture, even as he stands in the middle of it – responding to tones, harmonies and nuances in the cavalcade of processes that are unique to the beating heart. **LENS**

NEW VIEWS OF HEART DISEASE

The coming revolution in cardiac imaging

Advances in imaging techniques over the past five years have vastly improved the ability to diagnose and treat cardiac disease, but that's just the beginning.

Constantly improving technologies are on the brink of revolutionizing the way that medicine approaches cardiovascular illness by allowing safer and less invasive methods for current procedures and permitting the detection of pre-clinical disease.

Cardiac catheterization (also known as angiography) has been widely used for more than 30 years to diagnose coronary artery disease. A thin tube, or catheter, is inserted into an artery and is guided to the coronary arteries using X-ray fluoroscopy. A contrast agent injected through the catheter outlines the arteries in X-rays.

The evolution of computed tomography (CT) scanners has increased the speed, spatial resolution and the clarity of the scans, and eliminated the need to insert catheters.

"Coronary CT angiography (CTA) is diminishing the need for arterial catheterizations for a purely diagnostic use, although catheterization is still the mainstay for interventional treatment," says Murray Mazer, M.D., a cardiovascular radiologist at Vanderbilt University Medical Center.

"Coronary CTA at present is

the only non-invasive method with potential to do a good job imaging coronary arteries," he says. It may be especially important for determining the source of chest pain in the emergency room in a more efficient manner than is done today.

CTA is fast (results within one hour) and is 99 percent accurate in determining the absence of significant coronary artery disease. Using CTA in the ER would allow simultaneous evaluation of the pulmonary arteries, while ruling out incidental findings such as lung tumor or perforated esophagus, which also can cause chest pain.

At the same time, says Mazer, "careful control of imaging techniques and X-ray dose modulation software have diminished X-ray dosages by 50 percent to 70 percent, allowing this technique to compare favorably with other cardiac imaging modalities."

Magnetic resonance (MR) is another flourishing imaging modality.

Mark Lawson, M.D., an assistant professor of Medicine and Radiology, heads up Vanderbilt's relatively new cardiovascular MR suite. Using a dedicated cardiology magnet to look for artery blockages, Lawson and his colleagues can perform a heart and whole body angiogram in 45 minutes.

"The image quality for most angiograms is comparable to

CT," says Lawson. Because MR is non-invasive and doesn't require the use of X-rays, patients can have several scans over time to track the progress of their disease.

As stronger magnets are developed, MR will achieve better spatial and temporal resolution, he predicts. Combined with the rapid development of new contrast agents, these advances may lead to the development of coronary MR angiograms, and provide an alternative to CT angiography.

MR technology has several other applications to cardiovascular medicine as well – monitoring bone-marrow derived stem cells used in cardiac regenerative therapy is one example.

At Vanderbilt, for example, Darryl J. Bornhop, Ph.D., and his colleagues in the Department of Chemistry are developing "contrast agents" that could bind to the transplanted stem cells to track their health and survival.

MR eventually may be used to screen high-risk patients for pre-symptomatic signs of cardiovascular disease.

"Once there's a blockage, the horse is out of the barn," says Lawson. With the improved spatial resolution of stronger magnets, "we could see atherosclerotic changes in the wall of the artery before blockage forms."

– LIZ HALDEMAN



Contrast-enhanced whole body magnetic resonance angiogram

Courtesy of Mark Lawson, M.D.



Pictured right: Red blood cells trapped by a web of fibrin threads form a clot.

Illustration by Eye of Science/
Photo Researchers, Inc.

Too Obesity, diabetes and the rising tide of heart disease much clot

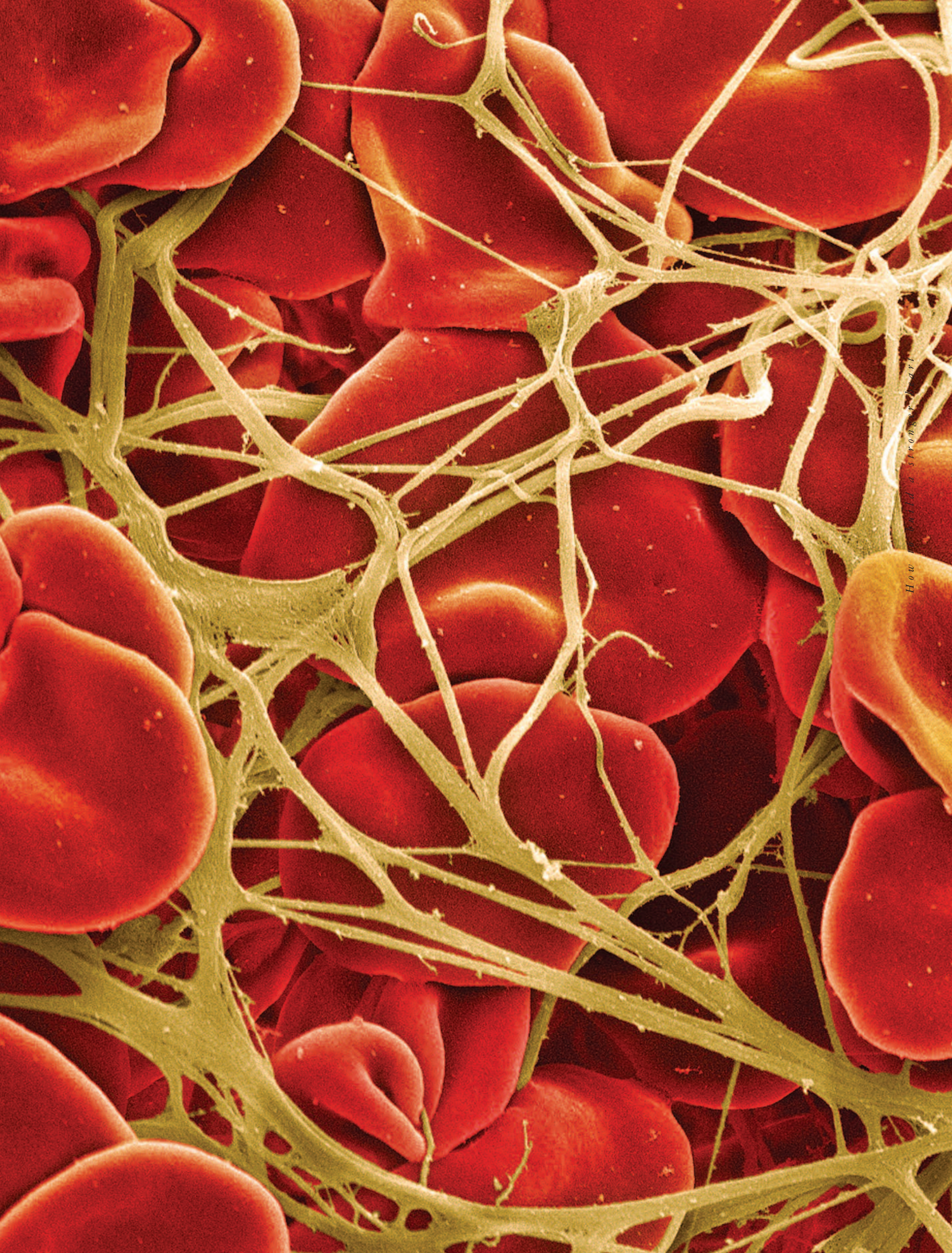
BY BILL SNYDER AND STEPHEN DOSTER

IT MAY START with a fat-rich diet, physical inactivity, smoking or an unfortunate inheritance.

Whatever the cause or causes, the delicate inner lining of an artery is injured – scratched, if you will – revealing the underlying collagen infrastructure. Platelets rush to site to repair the injury and prevent bleeding. They attach themselves to the exposed collagen, and recruit other platelets to join them.

Along comes thrombin to further sound the alarm and “set” the clot. Thrombin, an enzyme, chops up a protein called fibrinogen into short, sturdy strands of fibrin that trap platelets and other blood cells like fish in a net.

Just enough clot can save a life. Too much clot, however, can take it, by blocking an artery and triggering a heart attack or stroke.



How to build a strong plant

“Unless the underlying mechanisms ... (are) identified, there will be an unprecedented number of diabetic patients suffering thrombotic episodes in the next 10 years.”

This may be what's behind the high rates of heart disease among people with type 2 diabetes and obesity.

Currently about 66 million Americans – nearly a third of the adult population – are obese. Most will develop heart disease. “There is no greater threat to American’s cardiovascular health,” warns Douglas Vaughan, M.D., chief of Cardiovascular Medicine at Vanderbilt University Medical Center.

The prevalence of type 2 diabetes also is burgeoning, and is expected to double – to nearly 40 million people – within a decade. At least 85 percent of these people will die from blood clots that stop their hearts or their brains. Women seem to be more vulnerable than men.

“Unless the underlying mechanisms responsible for these events can be identified, there will be an unprecedented number of diabetic patients suffering thrombotic episodes in the next 10 years,” predicts Stephen Davis, M.D., Ph.D., chief of the Vanderbilt Division of Diabetes, Endocrinology and Metabolism.

Davis and Vaughan have joined forces with their colleagues at Vanderbilt to tackle one of the most urgent mysteries of modern medicine – why exactly do obesity and diabetes increase the risk of life-threatening blood clots?

Their inquiry is supported by the National Heart, Lung, and Blood Institute, which last year funded the establishment of a Specialized Center of Clinically Oriented Research (SCCOR) in Hemostatic and Thrombotic Diseases. The University of Pennsylvania and Cleveland Clinic also received SCCOR grants to investigate bleeding and clotting disorders, and to rapidly translate their discoveries into clinical practice.

Certainly, diet and exercise can help people avoid the serious health

consequences of obesity and diabetes. But lifestyle changes are easier said than done. And it is becoming increasingly clear that genetic predispositions influence risk – and the effectiveness of risk-lowering interventions.

“If you have a set of inherited risk factors ..., even modest hypertension (and) modest elevations in lipids ... may have a more deleterious effect on you than they do on another individual with the same numbers but a lower set of genetic risk factors,” says Samuel Santoro, M.D., Ph.D., chair of Pathology at Vanderbilt and a SCCOR participant.

Better understanding of the molecular and genetic contributions to clotting disorders could lead to new therapies that are more effective and have fewer side effects. It also could help doctors identify and manage patients at risk of serious complications during and after heart procedures such as angioplasty.

Another goal of the SCCOR is to help open the door to individualized, preventive medicine. If genetic variations or polymorphisms that increase the risk for thrombosis can be identified, it may be possible to screen patients in advance, and make adjustments in the drugs they are given, the procedures they undergo and the lifestyle changes they make so that they never experience that first heart attack or stroke.

Powerful platelets

In the early 1960s, the landmark epidemiological study conducted in Framingham, Mass., pinpointed high blood pressure, smoking and high cholesterol as major risk factors for cardiovascular disease. Within a decade, coronary care units, angioplasty and open heart surgery had become the standard of care, and drugs

had been developed to lower blood pressure and cholesterol levels.

But while blood pressure drugs and cholesterol-lowering statins remain a pharmaceutical cornerstone in the effort to prevent heart attacks and strokes, “non-traditional” treatments may be equally as important among people with diabetes and obesity. Vaughan believes these people may have “a special environment in their arterial vasculature that promotes cardiovascular complications.

One of the key players is the platelet – the disc-shaped element produced by the bone marrow that promotes blood clotting. While it does not have a nucleus, and therefore is not a cell, it is bristling with receptors, enzymes and other factors that allow it respond to – and powerfully influence – its environment.

Among them:

- + Collagen receptors, notably alpha 2, beta 1 integrin and glycoprotein VI, which enable platelets to attach to exposed collagen at the site of a tear in the blood vessel lining; and
- + Protease activated receptors (PARs), which, when activated by thrombin, trigger the aggregation or clumping of other platelets into the clot.

“When platelets encounter collagen, they don’t just stick to it; they are stimulated to form aggregates,” says Santoro, whose lab at Washington University in St. Louis discovered the alpha 2, beta 1 integrin collagen receptor in 1990. “It is the first component of blood clotting.”

The platelets of patients with type 2 diabetes have been found to “over-express” the integrin receptor. As a result, they may bind more readily to exposed collagen, thereby increasing the clotting risk.

This idea is supported by a mouse model engineered by Santoro, Mary

Zutter, M.D., and their colleagues in 2002, the year before they moved their lab to Vanderbilt. The animals, which lack the integrin gene, exhibit a “profound deficit” in platelet adhesion to collagen.

Zutter, who directs the Vanderbilt Division of Hematopathology, is continuing her efforts to model the mechanism of collagen binding, while Santoro and others in his lab are conducting studies in humans to better understand the genetics of receptor over-expression.

Meanwhile, Heidi Hamm, Ph.D., chair of Pharmacology at Vanderbilt, is trying to understand why the platelets of people with type 2 diabetes seem to be “hypersensitive” to other clotting stimuli, including thrombin. She is focusing on the thrombin receptors, G protein-coupled PAR1 and PAR4.

G-proteins are intracellular molecular “switches” that transmit signals into the cell by attaching to G protein-coupled receptors in the cell membrane. While at the University of Illinois at Chicago in the early 1990s, Hamm and her colleagues solved the G-protein’s three-dimensional structure.

They also showed that a peptide, a piece of protein, could prevent the G-protein from hopping on and off its receptor each time a signal came to the cell. This suggested that the switch for a single pathway, such as the one activated by thrombin, could be disabled by blocking a specific G-protein.

“Maybe PAR signaling is different” in diabetes, Hamm says. “If we find it’s so, could we direct a therapy that could be able to quiet down the platelets?”

Through their collaboration, Hamm and Santoro also have found that the collagen and thrombin receptors influence each other’s activity. That, says Santoro, “suggests some very interesting pharmacological interventions.”

Clot busters

Overactive clotting is not the only problem faced by people with diabetes and obesity. They also seem to have a faulty blood thinning system.

Normally, there’s a whole series of natural anti-coagulants, including protein C and antithrombin III, which circulate through the bloodstream and inhibit clot formation.

Another set of short-lived anti-coagulants generated by the blood vessel lining include nitric oxide and prostacyclin. They inhibit platelet aggregation and dilate blood vessels, thereby improving blood flow.

“Mother Nature must have been very concerned about the possibility that we would form clots inside our blood vessels because we have several different mechanisms that prevent this,” Vaughan says. If the natural anti-coagulants fail to do their job, there’s a “back-up,” called the fibrinolytic (clot-dissolving) system.

The king of the clot-dissolvers is plasmin, an enzyme that hacks apart the fibrin mesh.

Produced in an inactive form, plasminogen, in the liver, it is “liberated” to do its work by other enzymes, called plasminogen activators. These enzymes, in turn, are inhibited by proteins called plasminogen activator inhibitors.

Plasminogen activators like t-PA and their inhibitors, notably PAI-1, thus maintain a balance between too much clotting and not enough. It’s a balance that’s all too easily tipped – in favor of thrombosis.

For example, too much fat in the bloodstream (a characteristic of obesity) and too much glucose (the hallmark of diabetes) can increase levels of PAI-1. So can activation of the renin-angiotensin-aldosterone system (RAAS), which regulates blood pressure.

“For a protein that’s involved in regulating the clot-dissolving system, it’s rather puzzling to see how it’s influenced by a variety of different factors that you would think have nothing to do with clotting or protection from clotting,” says Vaughan, who is internationally known for his research on the fibrinolytic system. “All these things that get messed up in obesity and insulin resistance end up driving PAI-1 production.”

In the 1990s, Vaughan, Nancy Brown, M.D., and their colleagues at Vanderbilt helped identify the critical relationship between the blood-pressure regulating and clot-dissolving systems.

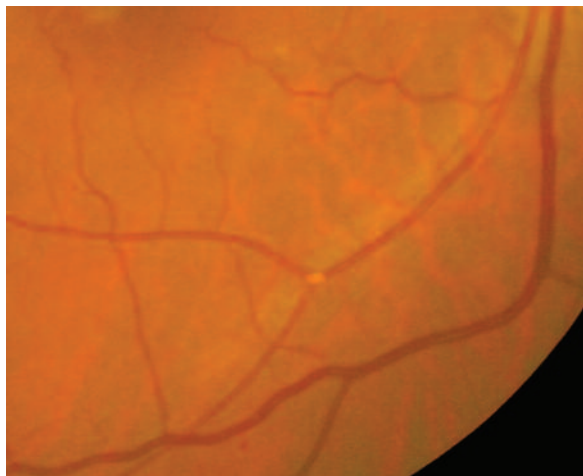
Key players in blood pressure regulation include the angiotensin converting enzyme (ACE) and the hormone aldosterone.

ACE converts angiotensin I into a small protein called angiotensin II, which causes vasoconstriction (narrowing of the blood vessels) and raises PAI-1 levels. Aldosterone, which regulates blood volume, also increases PAI-1 production.

Drugs that block the ACE enzyme, called ACE inhibitors, are widely used to lower blood pressure. By squelching excess production of PAI-1, they also can reduce the risk of a clot-induced heart attack. So can a class of diuretics that block the hormone aldosterone.

In 2002, Vaughan and his colleagues led by then post-doctoral fellow Mesut Eren (now a research assistant professor in Medicine) engineered a strain of mice that overexpresses a long-lasting form of human PAI-1.

As they age, about half the mice spontaneously form clots in their coronary arteries, without evidence of hypertension, atherosclerosis or high lipid levels. This is evidence, Vaughan says, that high PAI-1 levels, in themselves, can precipitate clotting and a resulting heart attack.



CANARY IN THE COAL MINE

Colorized image of a retinal scan reveals a tiny clot (white spot at the intersection of two blood vessels). This occasionally is the first sign of heart disease in patients being screened for something else – in this case, diabetic retinopathy. “The ‘canary in the coal mine’ analogy is particularly apt,” says Lawrence M. Merin, who directs the Vanderbilt Ophthalmic Imaging Center, “as the vast majority of these patients have no visual symptoms. The clinical significance of these lesions is most important; if left untreated, there is a 50 percent mortality rate within five years of identification of these lesions.”

Courtesy of Lawrence M. Merin



DOMINIC DOYLE

“Tug-of-war” between clotting and thinning the blood

Diabetes and obesity pull the dial to the left (toward clotting) by making platelets “stickier” and more sensitive to clot-forming thrombin, and by increasing production of PAI-1, which inhibits t-PA and thus clot-dissolving plasmin. Similarly, too much fat in the blood can increase fatty acid oxidation, which, in turn, accentuates the platelet-clumping actions of thromboxane over the blood-thinning actions of prostacyclin.

The Vanderbilt researchers are continuing their work to determine what factors increase PAI-1 levels both in animals and in patients.

In the meantime, drugs that specifically inhibit PAI-1 are being developed. Vaughan predicts that patients at risk of heart attack in the future may have their PAI-1 levels checked, just as they are currently screened for high levels of cholesterol.

The peroxide connection

The anti-coagulant system also is a delicate balance that can easily get out of whack.

Prostacyclin’s ability to prevent platelet clumping, for example, is matched by thromboxane, which does exactly the opposite – it stimulates platelet aggregation and constricts blood vessels, thereby limiting blood flow.

Prostacyclin and thromboxane are members of a family of lipid molecules that include the prostaglandins, and which are involved in everything from inflammation to smooth muscle constriction and blood pressure regulation. They are generated by the cyclooxygenase (COX) enzymes.

Thromboxane is produced in platelets by the COX-1 enzyme, while prostacyclin is a product of the COX-2 enzyme acting in the blood vessel lining. Both COX enzymes are inhibited by aspirin. During the past 30 years, John

Oates, M.D., founding director of Vanderbilt’s Division of Clinical Pharmacology, has helped define the role of these critical compounds in high blood pressure, cancer and other disorders.

In the mid-1980s, for example, Oates and Garret FitzGerald, M.D., currently chair of Pharmacology at the University of Pennsylvania, found that low doses of aspirin inhibited thromboxane production without unduly lowering levels of prostacyclin. Their work helped form the basis for the use of low-dose aspirin to reduce clotting risk in heart patients.

People with diabetes, however, seem to be “resistant” to aspirin’s protective effect. Oates, who is leading a fourth major project in the SCCOR, believes this may have something to do with peroxide.

The COX enzymes actually have two binding sites: one for arachidonic acid, the fatty acid precursor to prostacyclin, thromboxane and the like; and the other for peroxide.

Peroxide is a ubiquitous cellular messenger that in this case activates the COX enzymes like the starter of a car. It is produced when fats in the body are exposed to oxygen (lipid peroxidation) – the same thing that causes butter to go rancid.

Too much peroxide, however, will overcome aspirin’s ability to block COX activity. “We’ve found that when the enzyme is exposed to peroxide, aspirin binds less readily,” Oates says.

In 1990, Jason Morrow, M.D., Jackson Roberts, M.D., and their colleagues

at Vanderbilt discovered a series of bioactive prostaglandin-like compounds they called isoprostanes.

Produced by lipid peroxidation, isoprostanes are now recognized as the gold standard to measure oxidative stress. Smokers have high levels of isoprostanes. So do people who are obese or who have high levels of low-density lipoprotein, the “bad” form of cholesterol, in their bloodstream.

Another unhealthy consequence of too much fat thus may be aspirin resistance.

Genetics also may play a role. “It’s conceivable there may be a polymorphism (mutation) in the COX-1 gene related to aspirin resistance,” Oates says. “Once we identify groups of people who are susceptible to aspirin resistance we can devise all kinds of strategies” to reverse it.

Paradoxical effects

People with high levels of fats and glucose in their bloodstream are not the only ones at increased risk of dying from a clot – so are people with hypoglycemia – not enough glucose to satisfy the body’s energy needs.

Hypoglycemia is the complication most feared by patients with diabetes who must inject insulin periodically to lower their blood glucose levels, Davis says. Unless recognized and treated immediately, severe hypoglycemia can lead to convulsions, unconsciousness and, occasionally, death.

Several reports have linked severe hypoglycemia to serious cardiac and cerebral thrombotic events – heart attacks and strokes. Corticosteroids – hormones that regulate carbohydrate and fat metabolism – may be involved.

Davis and his colleagues helped pioneer methods for teasing out the complex interactions between insulin, corticosteroids and other factors that regulate the supply and delivery of glucose and other fuels required by body tissues.

Recently they found that experimentally-induced hypoglycemia resulted in significantly increased levels of PAI-1 in normal subjects. So did administration of drugs that mimic the actions of corticosteroids.

One of those hormones, cortisol, is secreted by the adrenal glands in response to psychological or physical stress, including hypoglycemia. Acting through corticosteroid receptors, it stimulates release of glucose by the liver. But it may also increase the risk of clotting.

Davis and his colleagues will try to find out whether activation of a specific corticosteroid receptor is responsible for hypoglycemia's pro-thrombotic effect.

"This information is urgently needed," he says, "bearing in mind ... that increasing numbers of (people with) type 2 diabetes are experiencing hypoglycemia due to the move toward intensive metabolic control."

While the Vanderbilt researchers say they are not out to discover new drugs,

HOW TO TELL IF YOU ARE AT RISK

The U.S. Centers for Disease Control and Prevention (CDC) defines obesity according to body mass index (BMI), which is calculated from a person's weight and height. If you're an adult and your BMI is between 25 and 29.9, you are considered to be overweight. You are considered to be obese if your BMI is 30 or higher. To calculate your BMI, go to www.cdc.gov and search for "body mass index."

Type 2 diabetes, formerly called adult-onset diabetes or noninsulin-dependent diabetes, is the most common form of the disease. Symptoms can include excessive thirst, frequent urination, hunger, fatigue, unexplained weight loss, sores that heal slowly, dry and itchy skin, tingling or loss of feeling in your feet and blurry eyesight.

For more information, visit the National Diabetes Education Program at www.ndep.nih.gov.

their work could lead to new avenues for drug discovery.

For example, Hamm's research could lead to a more effective way to block thrombin.

There is already a thrombin blocker on the market, bivalirudin, which binds directly to the circulating enzyme. The drug is given intravenously to patients undergoing coronary procedures such as angioplasty. The goal is to prevent clotting without thinning the blood too much.

Bivalirudin is superior to the classic blood thinner heparin in preventing bleeding complications during coronary procedures, but it is no better in preventing subsequent heart attacks or deaths. That may be because the drug also inhibits the paradoxical anti-coagulant properties that thrombin exhibits at low concentrations.

A drug that blocked the thrombin receptor on the platelet could avoid this

problem, says Hamm, president of the American Society for Biochemistry and Molecular Biology.

More drugs, however, are not enough. "There are big issues that haven't been answered," she says. Among them: why deaths from cardiovascular disease among women with diabetes remain stubbornly high compared to their male counterparts.

Is the disparity due to an increase in smoking among women? Are women less likely to receive appropriate treatment? Or do they have a different biology that isn't picked up in studies of new drugs conducted largely in men?

That's why basic research is so critical. "There are cures that are out there," Hamm says. "We just can't predict where (they) are going to occur." **LENS**

The importance of knowing your numbers

Despite recent medical advances, African-Americans remain disproportionately affected by cardiovascular disease. What's responsible?

Genetics, socioeconomic status and lifestyle all play a role, yet the problem remains "mind-bogglingly complex," says David Schlundt, Ph.D., associate professor of Psychology at Vanderbilt University.

Schlundt has been a member of the evaluation team for the Nashville REACH 2010 project (Racial and Ethnic Approaches to Community Health), part of a national initiative aimed at eliminating health disparities in more than 30 urban and rural communities.

During the past seven years, REACH volunteers have worked with hospitals and community groups to sponsor free medical screenings aimed at reducing the number of individuals with undiagnosed diabetes, hypertension and high cholesterol. When left untreated, these factors increase heart disease risk and mortality.

"Invariably, individuals are identified who have problems such as diabetes that they weren't aware of, and in particular, blood pressure and cholesterol are elevated," says James L. Potts, M.D., professor of Internal Medicine at Meharry Medical College who has participated in Project REACH.

Potts says that one of his favorite discussions with patients is to "know your numbers – blood pressure, cholesterol level, weight and blood glucose." These are what physicians call "modifiable cardiovascular risk factors" because they can be changed to reduce risk.

"We can't ignore genetics, patient attitudes and historical issues (of access)," Potts says, but significant decreases in risk, mortality and disparities would occur if everyone followed this simple advice: "Focus on changing the things that we can change."

Schlundt agrees. Due to cutbacks in federal funding, continuation of the Nashville

REACH project next year is not assured. However, it has begun to see positive results, including a decline in smoking rates among young African-American women and improved access to medical care through the establishment of night and weekend hours at free clinics.

Community programs, in partnership with physicians, can begin to narrow heart disease disparities, Potts says, if patients will do their part to educate themselves, live healthier lifestyles, and commit to change.

– ERIN TILLMAN

THE CHOLESTEROL CONUNDRUM

The tricky balance between “good”
and “bad” lipids

BY MELISSA MARINO

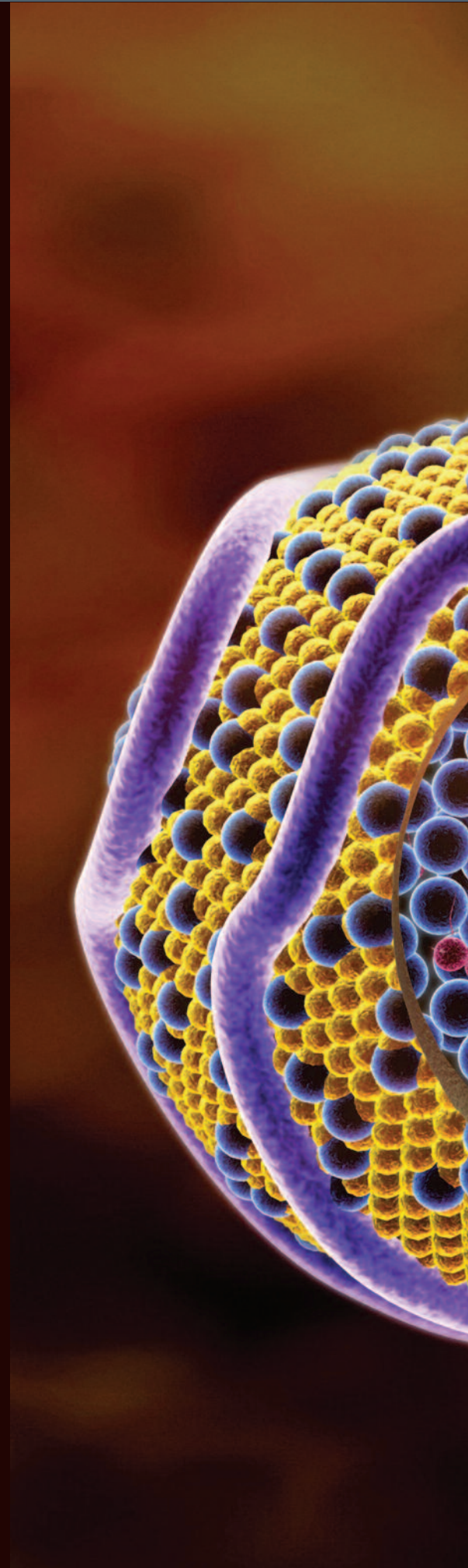


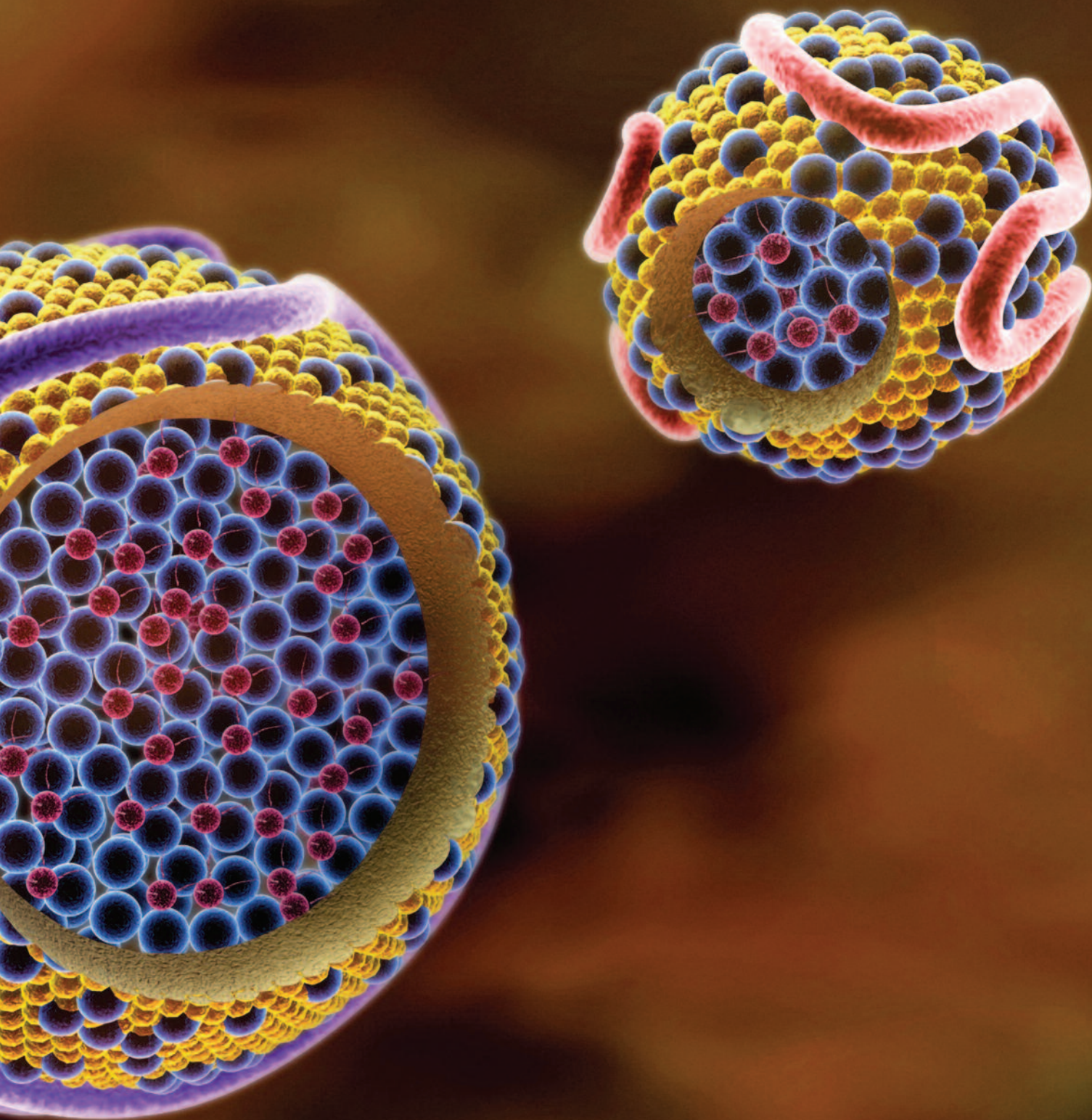
Cholesterol – that sticky, waxy, fat-like substance that clogs our arteries – has gotten a bad rap that is only partially deserved.

It’s a crucial component of our cell membranes. It helps prevent the diffusion of small water-soluble molecules into the cell, and keeps membranes fluid enough to maintain their firm, but pliable, consistency.

A sterol molecule, cholesterol also is the precursor for steroid hormones like estrogen, testosterone and cortisol, which are important for reproduction, metabolism, immune function and stress responses.

What gives cholesterol either a “bad” or “good” reputation is the company it keeps – the lipoproteins that transport it through the body.





Computer illustration of low-density (LDL, right) and high-density (HDL, left) lipoproteins

Hybrid medical animation /
Photo Researchers, Inc.

LIPOPROTEINS

are made by both the intestine and the liver and contain cholesterol, triglycerides and proteins. Triglycerides are the primary means by which the body transports and stores fatty acids, the basic unit of fat that our cells burn for energy.

High-density lipoprotein (HDL) is considered to be “good,” because it carts excess cholesterol off to the liver, where it is excreted in bile. Low-density lipoprotein (LDL), on the other hand, contributes to atherosclerosis.

LDL begins as a very low density lipoprotein (VLDL) produced in the liver. VLDL can be broken down in the bloodstream into fatty acids to provide an immediate source of fuel, and it also transports triglycerides to fat cells for later use.

In either case, after giving up its cargo of fat, VLDL becomes LDL, which then transports cholesterol to peripheral tissues. In some tissues like the skin, accumulation of cholesterol is inconsequential. The problem starts when cholesterol builds up along artery walls.

“For the same reason you don’t want too much calcium in your water, you don’t want too much LDL in your plasma – because your pipes will get encrusted,” says Sergio Fazio, M.D., Ph.D., who co-directs the Atherosclerosis Research Unit at Vanderbilt University Medical Center with MacRae F. Linton, M.D.

The artery wall doesn’t like the accumulation of cholesterol, and recruits cells from the blood, mainly macrophages, to try to clean it up. These macrophages become engorged with cholesterol,

and are known as “foam cells” due to their bubbly appearance.

“What starts with good intentions as a clean-up effort, ends up creating more of a mess,” Fazio explains. Atherosclerotic plaques are simply “big conglomerates of cells enriched with cholesterol.”

Diet and exercise can be very effective in lowering LDL levels, and can significantly reduce the risk of heart disease.

“We know what a healthy diet and lifestyle are,” says Linton, who has collaborated with Fazio since the early 1990s. “If you could wave a magic wand to get everyone in the country to live that way, you could eliminate – or at least dramatically reduce – the incidence of coronary disease and diabetes.

“The real problem,” he adds, “is it is hard to change people’s lifestyles.”

As a result, many patients and their doctors have turned to statins, a class of LDL-lowering drugs that have been shown to reduce the risk of heart attack and stroke by 30 percent to 40 percent.

Statins, however, are not without side effects, and many patients on the drugs still suffer adverse cardiovascular events – heart attack, stroke and sudden cardiac death.

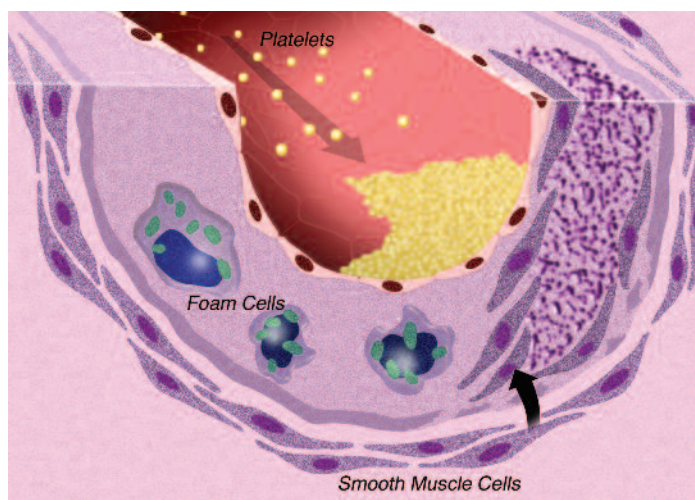
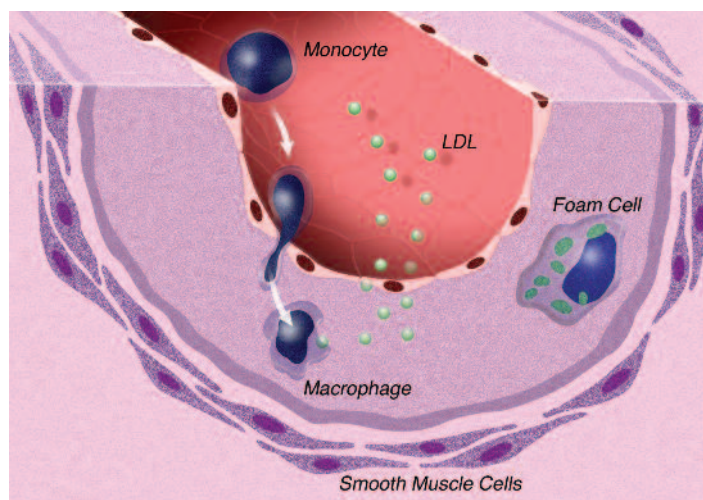
Another approach to reducing heart disease risk is eliminating excess cholesterol by raising HDL levels. Boosting this

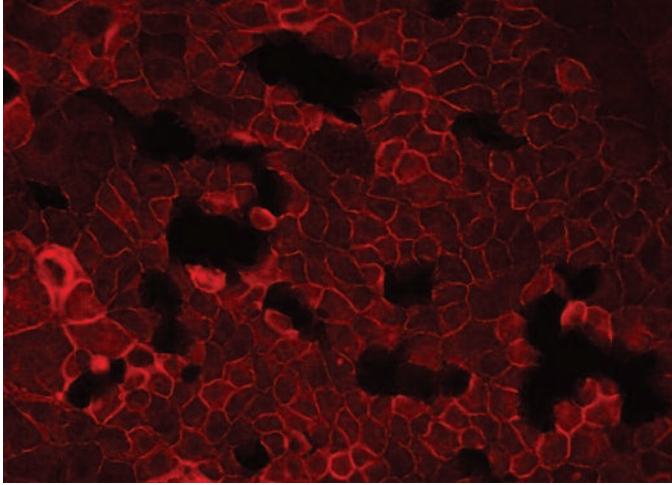
FROM INJURY TO CLOT

Endothelium that is injured, in this case by high levels of low-density lipoprotein (LDL) cholesterol, releases factors that attract blood cells called monocytes. Once inside the tissue, the monocytes differentiate into macrophages. Part of their job is to sweep up excess cholesterol. As they become engorged with cholesterol, the macrophages take on a foamy appearance, and now are called foam cells.

Interactions between foam cells and white blood cells trigger a chronic inflammatory process. Smooth muscle cells migrate to the arterial wall, proliferate and secrete proteins that form a fibrous plaque. As the foam cells die, the plaque weakens and can rupture. Platelets are attracted to the site of the rupture, and can quickly form a clot that blocks the vessel completely.

Illustrations by Dominic Doyle





Microscopic image of cultured mesothelial cells taken by graduate student Hillary Hager.

Courtesy of David Bader, Ph.D., Vanderbilt University Medical Center

Two sides of omentum ● ● ● ● ● ●

Tissue that surrounds the abdominal organs – the omentum and its overlying layer of mesothelium – could provide a promising source of stem or progenitor cells for heart repair therapies.

The omentum is fatty tissue that connects the stomach to the intestines. It is covered by mesothelium, which provides the tissue’s vasculature and which has remarkable regenerative potential.

Surgeons have used the omentum for many years as a sort of natural “bandage” to promote healing of surgical incisions and injuries, says David Bader, Ph.D., professor of Medicine and Cell & Developmental Biology at Vanderbilt, whose group first reported the angiogenic properties of mesothelium in the abdomen in 2005.

Bader is currently examining the mechanism behind the omentum’s healing properties and trying to determine if its mesothelial covering contains a source of stem or progenitor cells that could be used for regenerative therapies.

“It is very easy to turn these (mesothelial) cells into cells that make blood vessels,” Bader says. “They like to make stuff like blood vessels, smooth muscle, endothelium” – a capacity that would be very useful in heart repair.

During embryonic development, the mesothelium provides progenitor cells for the development of several organs.

“The adult structure has the capacity to produce these cells when stimulated,” says Bader. “I don’t know that the naturally-occurring process would be reparative, but we have found a way to ‘wake up’ that embryonic potential.”

Omentum is not without its dark side, however.

Central obesity, the accumulation of intra-abdominal fat, is a well known risk factor for cardiovascular disease. There is some evidence that removal of the omentum during gastric bypass surgery reduces that risk.

Omentum is not a neutral tissue. It is rich in macrophages, a type of white blood cell that produces inflammatory factors called “adipokines,” says Alfonso Torquati, M.D., assistant professor of Surgery in the Vanderbilt Center for Surgical Weight Loss.

Some adipokines are protective, while others can damage the endothelium, the inner lining of blood vessels.

This spring Torquati and his colleagues began a look at the effect in obese patients with diabetes of gastric bypass surgery on sub-clinical atherosclerosis (thickening of the wall of the carotid arteries as detected by ultrasound) and on levels of levels of inflammatory factors in the blood.

“Our theory is that with gastric bypass surgery, we induce a reduction of the ‘bad’ adipokines – TNF-alpha, IL-6 – and we increase the ‘good’ adipokines like adiponectin,” Torquati says.

– MELISSA MARINO AND BILL SNYDER

process, called “reverse cholesterol transport,” is considered desirable since high plasma HDL levels have been associated with a lower risk of heart disease.

An attempt to “ramp up” this process, however, was halted last year when it appeared that an HDL-raising drug, torcetrapib, increased rather than decreased the incidence of heart-related deaths in a clinical trial.

The drug significantly increased HDL levels by blocking an enzyme that normally transfers cholesterol from HDL to LDL, but it failed to slow the progression of atherosclerosis as expected.

Fortunately, there are other ways to raise HDL levels.

One possibility is niacin, a vitamin supplement available at most health food stores. But niacin supplementation can cause facial flushing. An extended release form of niacin has gained widespread clinical use. Clinical trials are now investigating a novel “flush-free” form of the vitamin.

Fibrates, another class of drug already on the market that potentially can raise HDL levels, are usually used in tandem with statins to treat high cholesterol. But they can cause potentially serious side effects, including kidney damage.

A few years ago, researchers showed that infusions of a synthetic form of HDL, called “ApoA1 Milano,” could significantly reduce atherosclerotic lesions as detected by intravascular ultrasound. But the need to inject it by vein every week makes this option impractical for widespread use.

For several years, Fazio and Linton have studied a protein that binds fatty acids in both macrophages and fat cells. As such, the adipocyte fatty acid binding protein (aP2) plays a crucial role in inflammation and insulin resistance, factors driving both diabetes and atherosclerosis.

“It turns out that in addition to cholesterol, fatty acids play critical roles in promoting both plaque build-up in the arteries and the development of adult onset diabetes,” Linton explains. “Coronary heart disease is the most common cause of death in diabetes,” he says, “and we believe that aP2 is a critical link between these disease processes.”

In a recent article published in the journal *Nature*, the Vanderbilt researchers and their colleagues at the Harvard School of Public Health and Bristol-Myers Squibb reported that an aP2 inhibitor prevented the development of atherosclerosis and diabetes in mice.

“These studies are tremendously exciting,” says Linton, “because they support the potential development of a single therapeutic approach for the treatment of diabetes and the prevention of coronary heart disease.” **LENS**

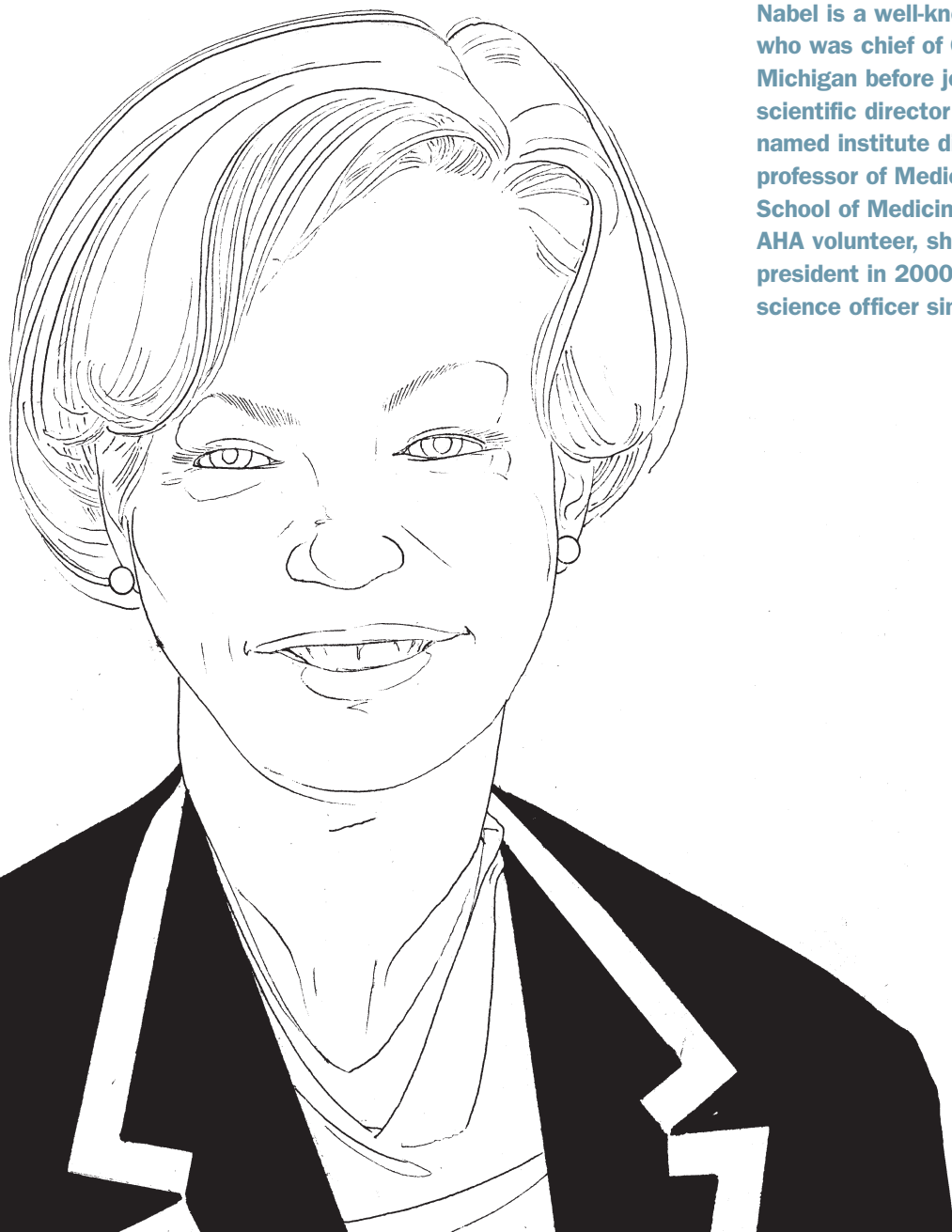


THE PEOPLE'S AGENDA

How public-private partnerships can advance cardiovascular research

In separate interviews with *Lens* editor Bill Snyder, Elizabeth G. Nabel, M.D., director of the National Heart, Lung, and Blood Institute (NHLBI), and Rose Marie Robertson, M.D., chief science officer of the American Heart Association (AHA), discussed the challenges in the fight against heart disease and stroke, and the value of collaboration.

Nabel is a well-known cardiovascular researcher who was chief of Cardiology at the University of Michigan before joining the NHLBI in 1999 as scientific director of clinical research. She was named institute director in 2005. Robertson is a professor of Medicine at Vanderbilt University School of Medicine. A longtime researcher and AHA volunteer, she served as the association's president in 2000-2001, and has been its chief science officer since 2003.



ILLUSTRATIONS BY DAVID JOHNSON

Death rates from heart disease and stroke have dropped by about two-thirds in the past 30 years. What can we expect in the next 30?

Nabel: The dramatic drop in coronary heart disease ... is largely due to identification of risk factors for heart disease and implementation of primary and secondary prevention programs. But ... we have not been fully successful in implementing (them) ... We need more research to understand the social and behavioral reasons why we haven't.

If everyone in the United States fully knew their risk factors for heart disease and fully implemented risk factor modification or reduction, could we eliminate heart disease in this country? I would predict that we probably could, except perhaps for those cases where there's a clear genetic cause of heart disease.

Robertson: Surely we will be able to better direct our interventions, of whatever sort they are – lifestyle improvements, drugs, devices, other new therapies – because we'll better understand the people to whom we're delivering them. We'll understand the genetic makeup of individuals and which interventions will most benefit them.

However, there are a number of aspects of heart disease that continue to be related to lifestyle, and so individuals can outdo our best efforts with drugs and devices if they don't eat well, exercise and avoid smoking.

And of course we have so many people who have no access to health insurance. If that isn't improved, there will be millions of people who may not benefit at all from whatever benefits we derive from biomedical research.

We need to fix that; people need to have access to the benefits that we can provide. I actually am encouraged that there seems to be more public will to address that issue than there has been before.

Which areas of research do you think will be most fruitful, and why?

Nabel: We've just initiated a clinical cardiovascular stem cell network to conduct in a collaborative way clinical trials in stem cell therapies for cardiovascular diseases ... Vanderbilt is one of those centers ...

Personalized medicine is another area that we're very keen on. We're very interested in understanding genetic

susceptibility to heart disease and we're doing this by sponsoring a number of genome-wide association studies, to understand the genotype of individuals who develop heart disease.

We're putting a lot of research dollars into molecular imaging to try to image vulnerable plaque or blockages within blood vessels.

And then the whole area of biomarkers: There are some people who do not have any of the established risk factors who still develop heart disease. (They) may have risk factors that we just haven't identified yet. So much of biomarker research will really be focused on trying to identify these new risk factors.

How has the flattening of the NIH budget affected your research agendas?

Nabel: It causes us to really think hard and focus on our priorities and on our core values.

About 70 percent of our budget goes toward investigator-initiated research ... grant applications that investigators submit based on their own ideas ... We will continue to support investigator-initiated research to the best level that we can.

Second, we want to support new investigators ... new faculty members who are applying for their first RO1 (research project grant) ... As a third priority, this year we are helping first-time RO1 investigators who are coming in for their first competitive renewal ...

NHLBI (also) has an important role to play in sponsoring randomized clinical trials, and addressing important questions that really impact public health and wouldn't be funded by the pharmaceutical industry ...



ROSE MARIE ROBERTSON, M.D.

We found that the use of a daily diuretic, which costs pennies, is just as effective as the more expensive, more sophisticated anti-hypertensives. That's not a study that a drug company is going to do. But it's a study that we did ... We felt that it was important to ask that question.

(We) are continuing to support our clinical trial networks, our large, population-based studies like the Framingham Heart Study, the Jackson Heart Study, our Hispanic Cohort Study, and ... our personalized medicine program. We have many more initiatives that we would like to fund, (but) ... when times get tough like this, progress in research is ... slowed.

Robertson: In our strategic planning there continues to be a strong feeling that the AHA needs to be the resource for early career development, and there needs to be a commitment to and focus on the young investigator ... We think that's critical for the future, and many research stars of today, including Nobel Prize winners in cardiovascular research, got their start with an AHA grant.

Of course, we also advocate strongly for the NIH budget ... The problem is that when you have these huge fluctuations, when you suddenly come to a point where the NIH budget actually decreases for the first time in 35 years, you sometimes lose the best people to other careers. They make a contribution, but they don't make the scientific contribution they could make in terms of the health of human beings ...

There is (also) concern ... that great research opportunities will be lost during these times. If you have to cut back or stop funding an important long-term study, there's no way to go back and reproduce that ...

The AHA can't compensate for flat congressional funding of the NIH ... On the other hand ... we can act as a catalyst for change. We can be a place where new models are tested. And we can partner with the NIH as we did recently in resuscitation studies.

Does our health care system make it difficult to apply the latest findings to the care of patients?

Robertson: I think there are several ways in which ... the system makes it difficult to translate results ... There's insufficient time in an office visit these days, for example, for physicians to do the really substantial work you need to do to learn about patients' lifestyles, to educate them and then to motivate them about ways to live healthier lives.

I think we would do better if we spent some dollars on the time to do prevention well, following evidence-based guidelines. Perhaps that would save us funds at the other end – certainly it would save lives.

Nabel: Absolutely, our health care system does not have good incentives for doing the right thing. Prevention is a good example. We desperately need health care reform in this country.

What can the institute do about this?

Nabel: We're not CMS (the Centers for Medicare and Medicaid Services). We don't set the policies and do the reimbursing. We're not the FDA (Food and Drug Administration), so we don't do the regulating.

We fund the research that generates the knowledge that goes into the evidence-based guidelines. If we do research that shows preventive measures are effective, then it's really up to the policy organizations to take those on and make sure that those activities are reimbursed.

How can people be better motivated to reduce their risk factors for heart disease?

Robertson: It's hard for the public to be responsible for things that it isn't educated about. I don't think we in this country educate our citizens very well about science and its importance in their lives ...

(In addition), people do need to have their basic needs cared for ... if you're worried about keeping your kids off drugs and having them not shot on the street, you may not focus on preventing long-term health risks ...

But we also need to build an environment in which the default is healthier. And some of that direct translation is actually done best by private organizations. So the American Heart Association with 20-plus million volunteers and supporters across the country, an extraordinary grassroots network and an ability to engage communities can do a lot to take research directly into action.

There's been a lot of research on nutrition and physical activity over the years, much of it funded by the NIH, which can be taken into a program like the Healthier Schools Program that the AHA is doing with the Clinton Foundation and the Robert Wood Johnson Foundation across the country. We've had some successes there, with a beverage agreement and snack

foods agreement that will make food and drink in schools healthier for kids.

And we can advocate for changes in regulation and legislation, something that the NIH isn't allowed to do.

Nabel: It's important for us to do research to understand what type of interventions make a difference. For example, what types of intervention will be effective in adolescents to help them make healthy lifestyle choices in terms of food selection and physical activity?

Remember that heart disease begins in your teens and your 20s, and that we have an obesity epidemic going on in this country, and obesity leads diabetes and cardiovascular disease. In fact, we're very concerned that the favorable trends that we've seen in heart disease in this country may be reversed by the next generation of young people who have obesity and diabetes.

(But) unless we can communicate our research advances to the public, we might as well pack up our bags and go home.

We are a research and education institution. We fund research, we support research findings, and then we have to be in the business of communicating those findings. We do have a very strong program that disseminates many of our research findings ... CARD – the Center for the Application of Research Discoveries.

From my perspective, that communication is best done in partnership with organizations and agencies that also are concerned about public health. And the American Heart Association is a great partner in that regard.

What are you doing to attract and prepare the next generation of scientists and physicians?

Nabel: At the high school and college level, we have a very vigorous summer internship program, where students can come to the NIH campus and intern in a laboratory over the summer and get exposed to scientific and medical research.

And we find that this is often an important imprinting period in which students develop a passion for scientific research and will come back to it at a later point in their career ... These are programs that have long existed in the institute, and we are making sure that during these difficult times we continue to support them.

Robertson: We think that training science teachers in the summer and giving them experiences in cutting-edge labs may make a real difference in how they educate and

motivate their students. We're planning to do more of that.

We've also recognized the need for young investigators to be trained in new ways ... Translation is not just from the bench to the bedside, but in its most effective mode, is from the bedside to the bench as well. You have to have people at the bedside who are scientists as well: patient-oriented investigators ...

If you have someone like this who is clinically expert, their colleagues send them their difficult patients, patients who don't fit the mold. When they see those patients, instead of saying, 'Well, you just don't fit, we'll work around that,' they say, 'Gee, isn't that interesting?' and then they may discover new diseases, or new manifestations of old ones.

Also, great advances do often happen at the edges between fields ... at the junctures between one field and another ... It's tricky to figure out how to facilitate that. Both we and the NIH talk about it a lot. It's the unusual place that does collaboration very well ... it's historically one of Vanderbilt's real strengths.

How can the public become more involved in cardiovascular research?

Nabel: I think that people in this country are very generous and really do want to help out and make a difference. Take a look at our Jackson Heart Study, where the response of the African-American community in Jackson, Miss., has just been overwhelming.

I think if these studies are done with transparency, full disclosure of risks and benefits and clear, informed consent, people in communities will participate.

Robertson: Having done clinical research for many years, I have always been remarkably impressed by the altruism of people. I think people are extraordinarily willing to participate in trials, even when the trial doesn't hold any specific benefit for them, but simply holds the potential for helping us learn about something that will help other people in the future. So why don't we support research better?

When you survey the public, they do feel that increased research funding for medical advances is a highly desirable goal, and they would like Congress to invest in that ... That's not always expressed vocally enough to make it happen.

So we do need to increase both the knowledge and the desire in the public, and some of that is just a matter of basic science education. **LENS**

Science of the soldier's heart

One of the more curious medical maladies is a condition known as "soldier's heart" or "head rush" disorder.

The formal medical description is "orthostatic intolerance," a disorder of the autonomic nervous system that causes a racing heart, nausea, headache, dizziness and fainting when a person stands up. It affects more than 500,000 people in the United States.

Researchers at Vanderbilt University Medical Center have made significant contributions – dating back 70 years – to understanding this disorder and how the nervous system regulates heart rate and blood pressure.

Their research, supported in a substantial way by the National Heart, Lung, and Blood Institute (NHLBI), illustrates how the study of a relatively rare disease can help advance an entire field. It also demonstrates the importance of public-private partnerships in research.

The autonomic nervous system is the crucial link between the brain and the cardiovascular system. It controls vital systems including blood pressure and heart rate for the most part without conscious control or sensation.

Part of the autonomic nervous system, the sympathetic nervous system, responds to stressors of various kinds by releasing the neurotransmitter norepinephrine. In turn, norepinephrine binds to adrenergic receptors to increase heart rate and blood pressure.

Advances in the treatment of orthostatic intolerance include the use of fludrocortisones, synthetic steroids that raise blood pressure. They were

introduced in 1956 by Grant Liddle, M.D., former chair of Medicine at Vanderbilt.

On the flip side, John Oates, M.D., founding director of the Vanderbilt Division of Clinical Pharmacology, discovered that methyldopa lowered blood pressure by impairing noradrenergic function.

In 1978, David Robertson, M.D., and his wife, Rose Marie Robertson, M.D., established at Vanderbilt the first center devoted exclusively to the study of autonomic disorders. With a current database of 2,900 patients, the Autonomic Dysfunction Center may be the world's largest registry of autonomic disorders.

In 1986, the Vanderbilt group reported that a rare, inherited deficiency in the enzyme that makes norepinephrine can cause orthostatic intolerance, and developed a successful drug therapy to treat the deficiency.

In 2000, David Robertson, Randy Blakely, Ph.D., Italo Biaggioni, M.D., and their colleagues described the first genetic defect in orthostatic intolerance – a mutation in the norepinephrine transporter, which regulates the supply of the neurotransmitter in the synapses, or spaces between nerve cells.

Jens Jordan, M.D., now at the Franz-Volhard Center for Clinical Investigation in Berlin, discovered while here in 2000 that drinking water profoundly increases blood pressure in patients with autonomic failure. Jordan and co-workers found that drinking water elicited a previously unrecognized physiological reflex and can be used to treat orthostatic intolerance and prevent fainting.

The researchers have since described the mechanisms of other autonomic disorders, including abnormalities in the choline transporter, which is essential to the production of the neurotransmitter acetylcholine.

In 1997, the Vanderbilt researchers received a major Program Project Grant (PPG) from the NHLBI to support their studies of autonomic cardiovascular regulation. That grant has been renewed twice, most recently this summer.

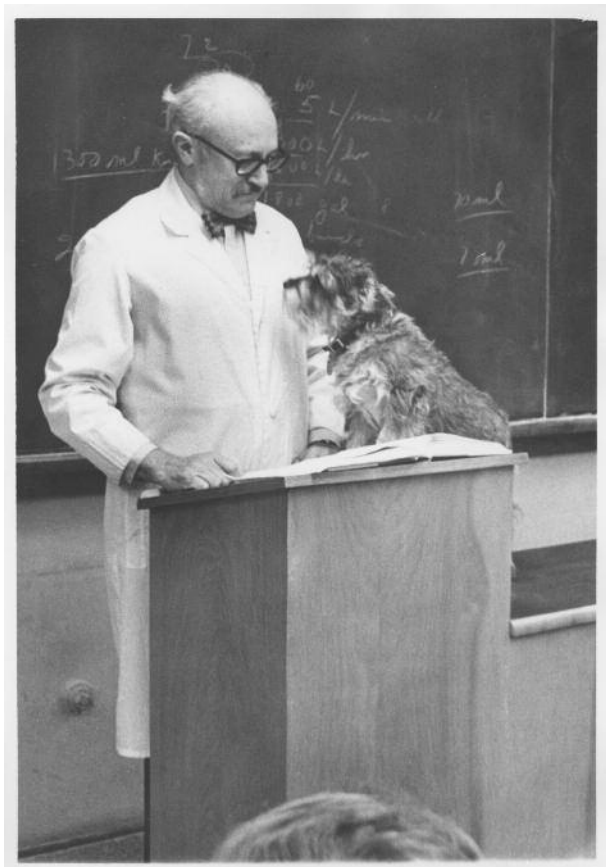
It is the only cardiovascular PPG based solely on clinical, patient-oriented research.

Researchers currently are exploring how variations in the choline transporter may contribute to heart rhythm disorders, the role of the autonomic nervous system in the cardiovascular and metabolic alterations associated with obesity, and how factors such as exercise can affect the autonomic response to hypoglycemia (low blood glucose) in people with diabetes.

David Robertson, who also directs Vanderbilt's Clinical Research Center, says patients are "absolutely critical" members of the research team. Their experiences have helped advance understanding about how bright light, hyperventilation and drinking water can affect blood pressure.

"I wish we could better harness that knowledge," he says. "I wish we could learn the things that people have discovered in themselves. If we could harness that, it could really be great for medical science."

– BILL SNYDER



From auto parts to cell parts

By Leigh MacMillan

Jack Roberts wasn't supposed to become a scientist.

When he started his undergraduate studies at Cornell College in Mount Vernon, Iowa, he planned to learn some things about business and return home to run his family's three auto parts companies. A chance elective – a physiology course taught by Edwin Rogers, Ph.D., a biology professor everyone called “Doc” – changed the course of his life.

“I had no aspirations to go into science in any way, shape or form,” Roberts says. “It had never even crossed my mind.”

But something about the way “Doc” taught; the way he made students think and ask questions – along with the material itself – captivated him.

“I thought, this is really, really interesting stuff,” Roberts recalls. So he followed his first science course with another, and then another. He went on to medical school at the University of Iowa, residency training, a fellowship in clinical pharmacology, and an illustrious scientific career.

In January, Roberts elected to recognize the man who sparked his interest in science by naming a newly endowed chair at Vanderbilt University Medical Center in his honor. Roberts is the first holder of the T. Edwin Rogers Chair in Pharmacology.

Rogers, now 90 and living in Iowa City, says he was “astonished” when Roberts called “out of the blue” to talk to him about the honor. Though Roberts was a student of his more than 40 years ago (he earned his bachelor's degree in 1965), Rogers remembers him well.

“His mind was so active,” Rogers recalls. “He was constantly asking questions and making contributions. His participation kept the class at a much higher level than I'd ever seen it, including for the professor.”

Rogers was not aware of the impact he'd made on his student.

“I guess there are lots of people we touch ... that we never know about,” he says.

Pictured here: Edwin Rogers, Ph.D., accompanied by his dog, Sasha, gives a biology lesson at Cornell College in Mount Vernon, Iowa, in 1973.

Courtesy of Cornell College

“I am very highly flattered and pleased about the named chair. I can't begin to explain how much this honor means to me.”

Roberts is internationally renowned for his research related to free radicals – highly reactive molecules derived from oxygen. Damage to the body's cells and cellular components by free radicals is called “oxidative stress.” Anti-oxidants including vitamins E and C combat the damage of free radicals.

With Jason Morrow, M.D., director of the Vanderbilt Division of Clinical Pharmacology, Roberts discovered a series of compounds called isoprostanes that are produced when free radicals attack the lipid building blocks in cell membranes. This discovery has made it possible for researchers to reliably detect and monitor oxidative stress – something that hadn't been possible before.

“Measuring isoprostanes has been shown to be far and away the most accurate way to assess oxidative stress status *in vivo*,” Roberts says. “This has allowed us to define a fundamental role for free radicals in the pathogenesis of a remarkably diverse, large number of diseases.”

Isoprostanes have been used to implicate free radicals in atherosclerosis, neurodegenerative diseases, the normal aging process, and other diseases, suggesting value for antioxidant therapeutics, a subject of research in many laboratories.

Last year, Roberts received top honors for his research: the Earl Sutherland Prize for Achievement in Research from Vanderbilt University and the Discovery Award from the Society for Free Radical Biology and Medicine.

In June, he received the Distinguished Alumnus Award for Achievement from the University of Iowa Carver College of Medicine. Joining Roberts at the banquet table in Iowa City was “Doc.” It was the first time the two had seen each other in more than 40 years.

“If he hadn't sparked my interest in science, I would be running our family's auto parts companies,” Roberts says, adding with a sly smile, “how boring.” **LENS**

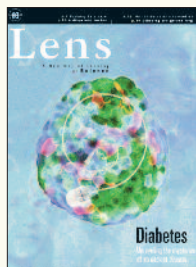
Share your *Lens* with a friend

With this, the 10th issue of *Lens* magazine, we're celebrating five years of sharing the excitement of biomedical research with our readers.

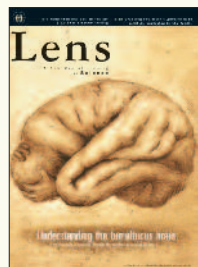
Back issues are available at no charge. If you're missing one or would like to share with a friend, contact: *Lens* editor Bill Snyder at william.snyder@vanderbilt.edu or (615) 322-4747.

Available issues include:

Spring 2003 –
Diabetes



Fall 2003 –
Brain disorders



Spring 2004 –
Viral "invaders"



Fall 2004 –
Inflammation



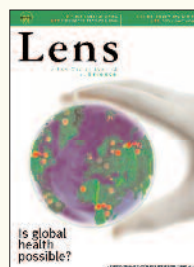
Summer 2005 –
Drug discovery



Winter 2006 –
Imaging science



Summer 2006 –
Global health



Winter 2007 –
Cancer



A sharper *Lens*

Please let us know what you think of this issue by filling out a short questionnaire. Just click on www.surveymonkey.com/lens.

Lens Editorial Board

Jeffrey R. Balsler, M.D., Ph.D.
Anesthesiology, Medicine, Pharmacology
Associate Vice Chancellor for Research

Andrea Baruchin, Ph.D.
Medical Education & Administration
Chief of Staff, Office of Research

Gordon R. Bernard, M.D.
Medicine
Assistant Vice Chancellor for Research

Randy D. Blakely, Ph.D.
Pharmacology
Director, Center for Molecular Neuroscience

Peter I. Buerhaus, Ph.D., RN
Nursing
Director, Center for Interdisciplinary Health Workforce Studies

Richard Caprioli, Ph.D.
Biochemistry, Chemistry, Pharmacology
Director, Mass Spectrometry Research Center

Ellen Wright Clayton, M.D., J.D.
Pediatrics, Law
*Co-Director
Center for Biomedical Ethics and Society*

John H. Exton, M.D., Ph.D.
Molecular Physiology and Biophysics,
Pharmacology

Steven G. Gabbe, M.D.
Obstetrics and Gynecology
Dean, School of Medicine

William N. Hance, B.A., J.D.
Director, Office of News and Public Affairs

George C. Hill, Ph.D.
Microbiology & Immunology
*Associate Dean for Diversity
in Medical Education*

Michael C. Kessen, B.A.
*Director, Corporate & Foundation Relations
Medical Center Development*

Joel G. Lee, B.A.
*Associate Vice Chancellor
Medical Center Communications*

Lee E. Limbird, Ph.D.
Pharmacology
*Vice President for Research
Mebarry Medical College*

Mark A. Magnuson, M.D.
Molecular Physiology & Biophysics,
Medicine
Director, Center for Stem Cell Biology

Lawrence J. Marnett, Ph.D.
Biochemistry, Cancer Research
*Director
Vanderbilt Institute of Chemical Biology*

John A. Oates, M.D.
Medicine, Pharmacology

Light microscopic image of a mouse embryo.

Courtesy of Richard Behringer, Ph.D., University of Texas M. D. Anderson Cancer Center and Cold Spring Harbor Laboratory Press

IN THE NEXT ISSUE:

Secrets of the embryo

Developmental biology is providing insights to the replacement of diseased and defective tissues.

The stem cell “cure”

The ultimate solution to type 1 diabetes may lie in the reprogramming of cells.

Neuronal engineers

Experts in neurodevelopment are working at the frontiers of brain repair and preservation.



Lens

Vanderbilt University
VUMC News and Public Affairs
D-3237A Medical Center North
Nashville, TN 37232-2390

PRSR STD
U.S. POSTAGE
PAID
NASHVILLE TN
PERMIT NO.
777