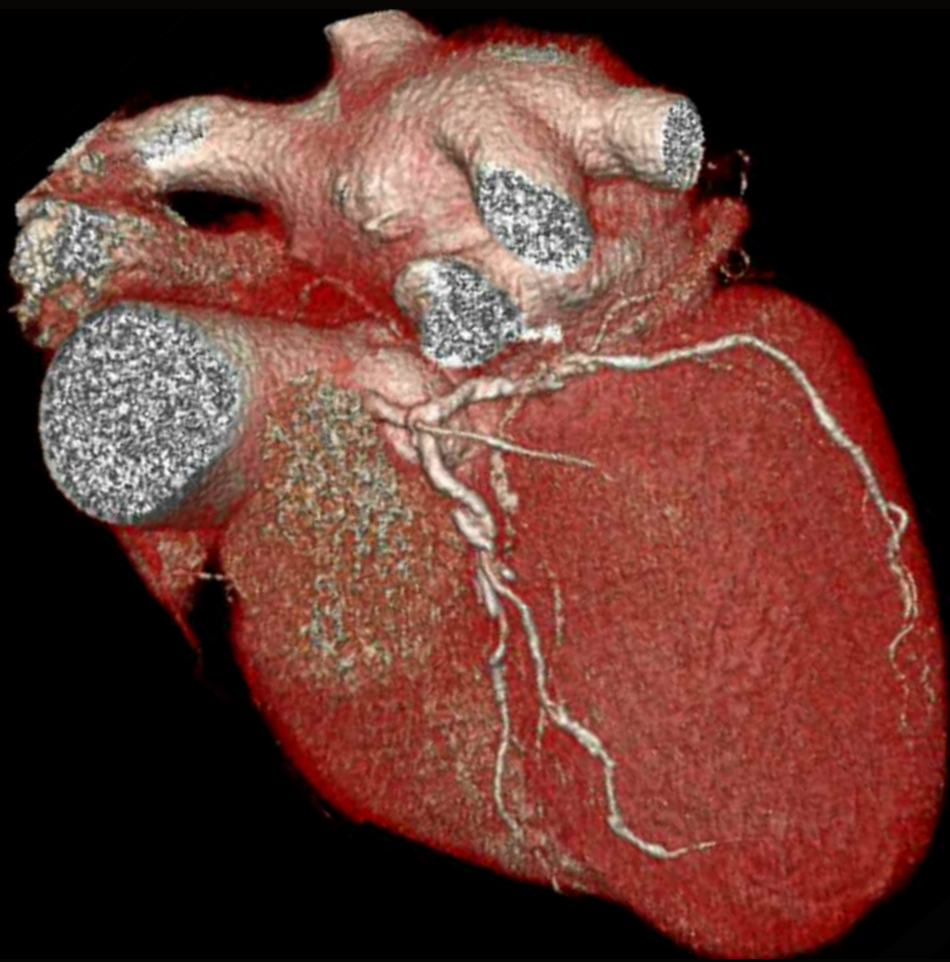


INNOVATIONS | 2008 EDITION



Heart and Vascular Institute



Mission

The mission of Johns Hopkins Medicine is to improve the health of the community and the world by setting the standard of excellence in medical education, research and clinical care. Diverse and inclusive, Johns Hopkins Medicine educates medical students, scientists, health care professionals and the public; conducts biomedical research; and provides patient-centered medicine to prevent, diagnose and treat human illness.

Vision

Johns Hopkins Medicine provides a diverse and inclusive environment that fosters intellectual discovery, creates and transmits innovative knowledge, improves human health, and provides medical leadership to the world.

Core Values

Excellence & Discovery
Leadership & Integrity
Diversity & Inclusion
Respect & Collegiality

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Heart and Vascular Institute

Dear Colleague:

Every aspect of our professional life at the Johns Hopkins Heart and Vascular Institute is devoted to patient care. Both our clinical work and our research are designed to develop enhanced treatments for our patients.

We are pleased to share with you a glimpse into our ongoing efforts, innovations and discoveries on the journey to superior patient care. Inside, you'll find our latest research that is helping to translate into better patient outcomes, innovations that bring treatments to a new level, and steps we're taking every day to improve quality, outcomes and patient safety.

Each patient we care for remains our first priority. When you refer to us, you've placed tremendous confidence and trust in us, and we'll work with you to ensure the best possible results.

This book is part of an ongoing initiative to relay information about activities in the Heart and Vascular Institute, report on our innovations and discoveries, and enhance patients' access and experience. We look forward to sharing our commitment to excellence.

Warm regards,

Gordon Tomaselli, M.D.
Chief of Cardiology

William Baumgartner, M.D.
Chief of Cardiac Surgery

Bruce Perler, M.D.
Chief of Vascular Surgery

Joel Brenner, M.D.
Director of Pediatric Cardiology

Jonathan Lewin, M.D.
Chief of Radiology

If you have any questions or would like to speak to any of the Johns Hopkins Heart and Vascular Institute physicians, please see page 68 for contact information.

For more information on the Johns Hopkins Heart and Vascular Institute, visit hopkinsmedicine.org/heart.



GORDON
TOMASELLI, M.D.



WILLIAM
BAUMGARTNER, M.D.



BRUCE PERLER, M.D.



JOEL BRENNER, M.D.



JONATHAN
LEWIN, M.D.

Overview of Cardiovascular Medicine and Surgery at Johns Hopkins

Recognized for advancing the understanding and treatment of cardiovascular disease, the Johns Hopkins Heart and Vascular Institute has been consistently ranked among the top four cardiovascular programs in the United States in the *U.S. News & World Report's* “Best Hospitals” ranking.

Our mission at Johns Hopkins, first articulated more than 125 years ago, has been to seek new understanding of human diseases through clinical and basic research and to translate that knowledge to patient care. When surgery chief Alfred Blalock and pediatric cardiologist Helen Taussig showed in 1944 that it was possible to correct the constellation of congenital defects known as tetralogy of Fallot, their achievement exemplified the power of that mission. So, too, did the vision of a young cardiologist named Victor McKusick, who—inspired by the Marfan syndrome patients he was treating in the 1950s—ended up launching the field of medical genetics.

Today, this tradition of pioneering work continues at the Johns Hopkins Heart and Vascular Institute, where our physicians and surgeons are leaders in improving outcomes and quality of life for heart patients all over the world.

Working on every aspect of cardiovascular disorders, from prevention to medical management, from minimally invasive procedures to organ transplant surgery, our physician-scientists are able to harness a wealth of resources for the benefit of each individual patient. We believe that no case is routine, that every patient deserves the full benefit of the collective expertise and compassionate touch so widely available here.

We also develop the next generation of leaders in cardiovascular medicine and surgery by melding our deep research environment with a strong clinical training program for residents and fellows.

2008 Highlights of Clinical Innovations and New Discoveries

In this booklet, we describe clinical innovations, discoveries, patient experiences, and quality and safety initiatives spanning five cardiovascular themes:

AORTIC AND VASCULAR DISEASE

- Near-zero mortality during 30 years of aortic root replacement (*page 12*)
- Treating adults who grew up with heart disease (*page 14*)
- New insight into the biology of thrombosis (*page 16*)
- Safer carotid endarterectomy (*page 17*)
- Minimally invasive heart surgery—without the robot (*page 18*)

INHERITED HEART DISEASE

- Surgery for the aggressive aneurysms of Loeys-Dietz syndrome (*page 22*)
- A Marfan syndrome breakthrough (*page 24*)
- Clinical genetic testing for ARVD (*page 26*)

SUDDEN CARDIAC DEATH

- New uses for MRI (*page 30*)
- Genetic underpinnings (*page 32*)
- Primary prevention and the role of ICDs (*page 34*)
- MRI for patients with heart devices (*page 38*)

ATRIAL FIBRILLATION

- Image integration for ablation procedures (*page 40*)
- 320-slice CT detects early signs of heart disease (*page 42*)
- The advantages of biventricular pacing (*page 44*)
- New ablation guidelines (*page 46*)

HEART FAILURE AND CARDIOMYOPATHY

- Insights into the mechanisms of heart failure and cardiomyopathy (*page 48*)
- The proteomics of heart disease (*page 50*)
- Heart and mind connections (*page 52*)
- Work with mesenchymal stem cells (*page 54*)
- Tracking delivery of cell transplants (*page 56*)
- Better ways to identify risk in women (*page 58*)

Safety and Quality Measures

Our approach to quality has always been shaped by our mission of discovering and translating new information into improved care and outcomes. Some recent examples include:

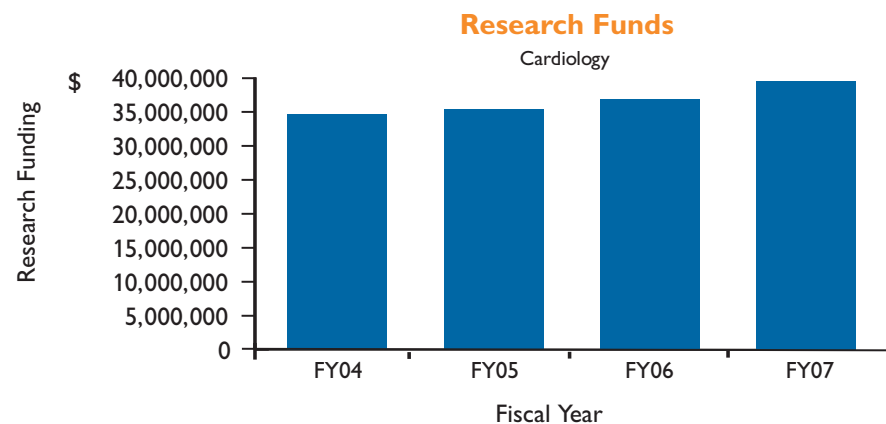
- **Culture of Safety.** We are committed to improving patient safety through research and continuous assessment of current practices. Data generated here has given hospitals around the country a framework to measure and monitor patient safety progress. Named as one of *Time* magazine's 100 most influential people in the world, Johns Hopkins critical care specialist **Peter Pronovost** has shown that following a simple checklist can slash the number of hospital-acquired infections in intensive care units to near zero.
- **Telewatch Home Monitoring of Heart Failure Patients.** Our researchers developed a telemedicine system to monitor congestive heart failure patients from anywhere in the world. The system enables appropriate health care interventions as early as necessary and decreases outpatient visits. Studies show that the system improves patient outcomes as well as quality of life.
- **Surgical Site Infection Collaborative.** We are part of a group of academic medical centers that is formulating ways to monitor hospitals' surgical-site infection rates.

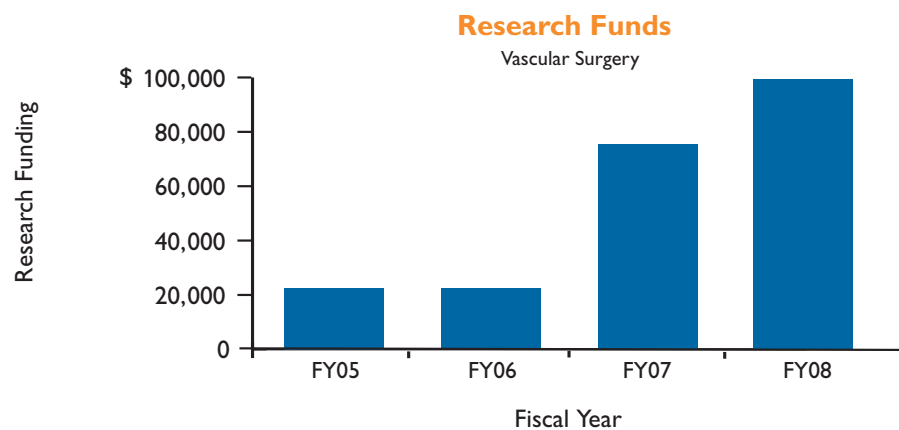
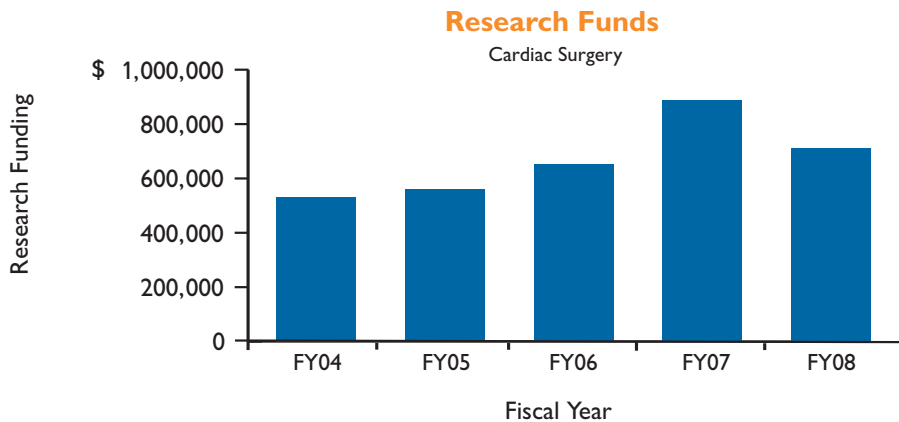
Research

The Heart and Vascular Institute receives millions of dollars each year in federal funding for pursuing research into the causes, treatment and prevention of cardiovascular disease. Almost one quarter of the research within the Department of Radiology and Radiological Sciences is related to the heart or vascular system, with around \$28 million per year in external research funding. Finding better treatments, new methods of earlier detection and effective prevention therapies remain our top priorities.

Among our recent studies is work focused on:

- **Genetics.** We are seeking the causes of and targeting treatment for inherited heart diseases (*see page 26*). We've also discovered genes that have been linked to common forms of sudden cardiac death (*see page 32*).
- **Neuroprotective Strategies.** For more than 15 years, cardiovascular surgeons and neuroscientists here have been collaborating on ways to protect the brain from injury during cardiac surgery. Soon, they'll start a phase 1 clinical trial to evaluate the safety and efficacy of a commonly used anticonvulsant as a neuro-protective agent during heart operations. This is a direct translational result of understanding the mechanisms of injury.

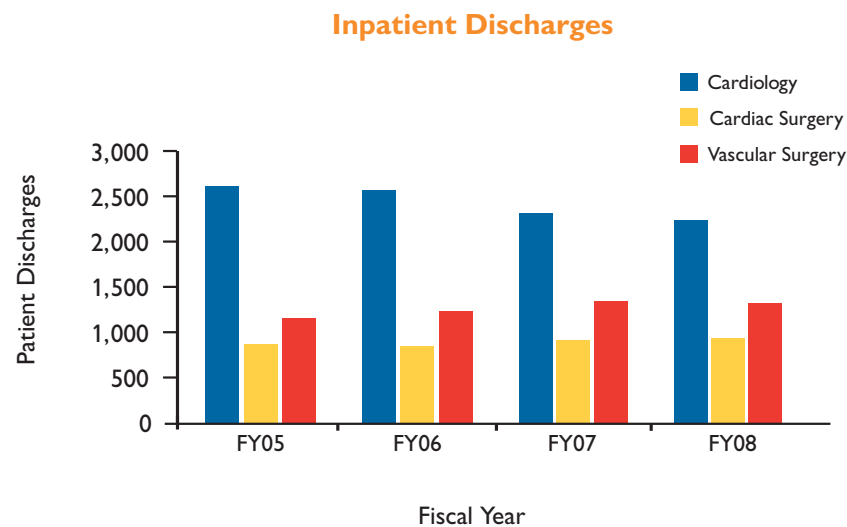




Experience and Outcomes

Johns Hopkins Heart and Vascular Institute physicians collaborate to diagnose and treat the full range of cardiovascular diseases. For example, our cardiomyopathy service performed 916 invasive procedures, including 575 endomyocardial biopsies. In addition, we had over 2,500 catheterization/interventional cases, and over 1,000 invasive electrophysiology cases. There were 1,248 cardiac surgical operations, of which 263 were pediatric cases. Pediatric cardiovascular services had 192 interventional catheterization procedures.

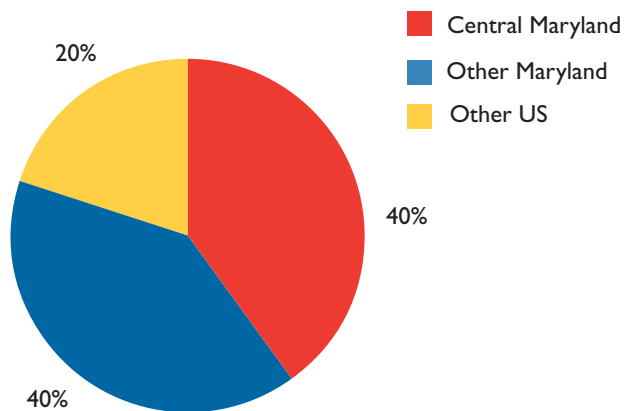
Our surgeons performed 24 heart transplants and 21 lung transplants. In addition, they implanted 50 ventricular assist devices. We performed more than 300 aortic reconstructive procedures within Johns Hopkins' Broccoli Center for Aortic Diseases, including stent-graft procedures and traditional open surgical repair. Our surgeons have also applied stent-graft technology to address the more complex thoracoabdominal aneurysms in a "hybrid" fusion of endovascular and open surgical techniques, which drastically reduces the risk posed to the patient.



Patient Origin

Patients from all over the United States come here for treatment. Last year, 20 percent of our patients were from out of state.

Cardiovascular Services Patient Origin
FY2008



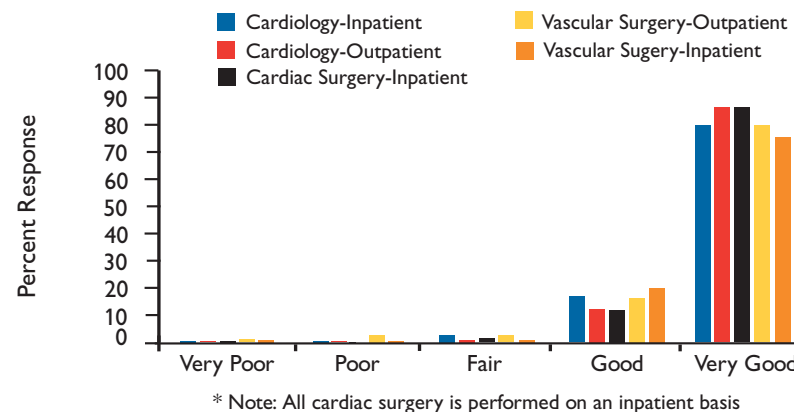
Patient Satisfaction

In our efforts to provide our patients with the best treatment and care, we continually solicit patient feedback and use this information to help improve the patient experience. Results

from our most recent patient satisfaction surveys, July 2007 to May 2008, indicate that the majority of patients would recommend the practice and feel the quality of care is good or very good.

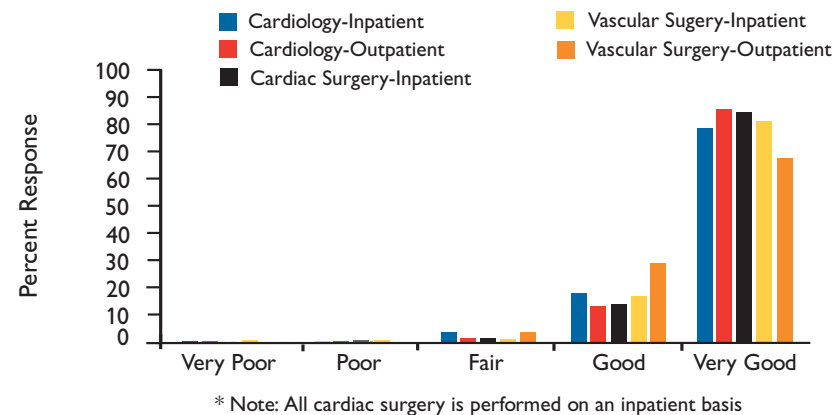
Likelihood to Recommend Practice

July 2007 – May 2008



Overall Quality of Care

July 2007 – May 2008



AORTIC AND VASCULAR DISEASE

Demonstrating Clinical Innovation

Save the Root, Spare the Valve

The growing importance of cardiac surgery outcomes research was nowhere more evident than at the 2008 annual meeting of the Society of Thoracic Surgeons, where all three of the prestigious J. Maxwell Chamberlain Memorial Papers shared this overarching theme.

Presenting the Chamberlain Paper for Adult Cardiac Surgery, aortic diseases expert **Duke Cameron** reported on three decades of Johns Hopkins experience with aortic root

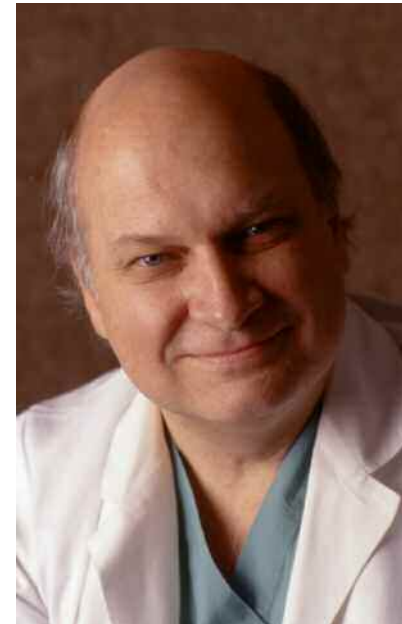
replacement in 372 patients with Marfan syndrome.

The team's most notable result was zero operative and 30-day hospital mortality in 327 patients who underwent elective prophylactic operations. Among the 45 patients who presented for an emergent operation, the only deaths occurred in two patients who arrived moribund to the operating room from aortic rupture.

Operative Results in 372 Marfan Patients with Aortic Root Replacement

Surgery	No. of Patients	30-day Mortality (n)	30-day Mortality (%)
Elective	327	0	0
Urgent/Emergent*	45	2	4.4%
Total	372	2	0.5%

*Within 7 days after surgical consultation



Duke Cameron, M.D.

Immediate improvement is, of course, the short-term goal. But Cameron and colleagues also documented actuarial survival of 85 percent at 10 years, 75 percent at 20 years and 45 percent at 30 years. Furthermore, 10 years after surgery, more than 90 percent of their patients were free of throm-

boembolism and endocarditis, and 88 percent required no surgery on the distal aorta.

Over the years, the Hopkins team, Duke Cameron and **Luca Vricella**, have significantly refined the technique of valve sparing aortic root replacement. Although they initially used the remodeling technique, in 2002 they switched to the reimplantation technique, which combines sinus reconstruction with annular stabilization.

Today, the team with the world's longest experience treating Marfan patients is translating that acumen to the care of patients with the even more aggressive aortic root dilatation seen in Loeys-Dietz syndrome (*see page 22*).

Growing Up With Heart Disease

It has been more than 60 years since cardiac surgeon Alfred Blalock and his assistant Vivien Thomas, working with pediatric cardiologist Helen Taussig, pioneered the “blue baby” operation at Johns Hopkins. Now patients with congenital heart disease at the hospital span the ages from the fetus to the octogenarian.

“That operation demonstrated that this whole field was possible,” says **Joel Brenner**, pediatric cardiology director. “As a result of innovative approaches developed at Johns Hopkins and advances in medicine and surgery worldwide, there are now more adults than children living with congenital heart disease.”

Now that patients with complex heart defects are living longer, Brenner says, physicians have been challenged to find new methods of managing ongoing, complex medical issues.

For example, some patients with valve atresia or ventricular hypoplasia may develop life-threatening arrhythmias in adolescence or adulthood. Because their anatomy is different from the usual four-chambered heart, it is often difficult to

position catheters in the right place for ablation procedures.

Pediatric electrophysiologist **Jane Crosson**, working as part of a multidisciplinary team with pediatric cardiologists and adult electrophysiologists, uses a new software program that creates real-time, three-dimensional electrical maps of the heart and blood vessels. Physicians place a locator, like a GPS device, behind the patient’s back, and as the catheter moves around, the program creates a 3-D map. This map may be merged with 3-D MRI or CT images, providing an extremely detailed model of each patient’s anatomy, thereby enabling physicians to successfully ablate the arrhythmia focus.

Another issue is coarctation of the aorta, an abnormal shelf-like narrowing within the main artery of the body that strains the heart and increases blood pressure in the arms and head. Although this is a congenital heart defect originating before birth, many patients with this disorder are not diagnosed until late childhood or

adulthood. Also, in some patients who undergo corrective surgery as babies or young children, the aorta loses its ability to grow, says **Richard Ringel**, director of pediatric and congenital heart disease catheterization, so the obstruction returns as they become teens or young adults.

Ringel is directing a 16-center research trial aimed at getting the first stent approved by the Food and Drug Administration for use in

treating coarctation of the aorta. The Coarctation of the Aorta Stent Trial (COAST), conducted in collaboration with researchers at Children’s Hospital Boston, is investigating the safety and efficacy of platinum-iridium metallic stents for this indication. This device, the Cheatham-Platinum Stent, is already widely used around the world, and cardiologists like Ringel would like to see the device available for use in the United States.



Pediatric Cardiology Director Joel Brenner, M.D.

Moving Discovery Forward

When Platelets Clump

The discovery of a pathway that regulates thrombosis could herald new treatments.

Long known as the most abundant neurotransmitter in the brain, glutamate is also present in blood. But until recently, its role there was unknown. Now, however, cardiologist **Charles Lowenstein**, working with **Craig Morrell** in the Department of Molecular and Comparative Pathobiology, has found that glutamate activates platelets and amplifies thrombosis.

“This has important clinical implications,” Lowenstein says. “We can use new drugs to target the glutamate receptor on platelets to

treat patients with thrombosis.”

Drugs that block glutamate receptors were originally developed to treat diseases of the brain. Lowenstein and Morrell have found that a glutamate receptor blocker could also treat blood-clotting disorders in mouse models.

“Glutamate receptor antagonists greatly prolong bleeding in mice,” he says. These new discoveries suggest that the antagonists might be useful in the treatment of heart attacks, strokes and other thrombotic disorders in humans.

Lowenstein and his team are collaborating with a drug company to show efficacy in mouse models of myocardial infarction and hope to extend testing to larger animals soon and eventually begin clinical trials.

RESEARCH PUBLISHED:

Morrell CN, Sun H, Ikeda M, Beique JC, Swaim AM, Mason E, Martin TV, Thompson LE, Gozen O, Ampagoomian D, Sprengel R, Rothstein J, Faraday N, Haganir R, Lowenstein CJ. Glutamate mediates platelet activation through the AMPA receptor. *Journal of Experimental Medicine* 2008;205:575–584.



Charles Lowenstein, M.D.

Quality and Safety

Beyond Lipid Lowering

Work performed at Johns Hopkins indicates that statins can make a very safe and highly effective stroke-preventing operation—carotid endarterectomy (CEA)—even safer.

Hopkins vascular surgeon **Bruce Perler** and colleagues were the first in the nation to look at the possible benefit of statins in improving the outcome of CEA, the common plaque-removing procedure used to prevent stroke, a leading cause of death, dementia and disability in the United States.

The problem, says Perler, is that even in the best of hands, stroke itself is a potential complication of CEA.

Perler noted that patients with cardiovascular disease are often medically managed to lower their cholesterol with statins, which have been shown to be highly effective in preventing stroke in those patients. Besides lowering cholesterol, statins improve endothelial function, have anti-inflammatory, anticlotting and antioxidant activity, and stabilize atherosclerotic plaques.

In the Hopkins study, investigators looked at the outcome of nearly 1,600 patients undergoing CEA and found that among those who were taking statins at the time, there was a highly statistically significant, threefold reduction in the incidence of perioperative stroke and a fivefold reduction in the incidence of perioperative death, and a 50 percent reduction in the incidence of perioperative myocardial infarction.

Further work is needed to better define these mechanisms and to determine the optimal agents, dosing and timing of drug administration among patients undergoing carotid interventions.

RESEARCH PUBLISHED:

Perler BA. The effect of statin medications on perioperative and long-term outcomes following carotid endarterectomy or stenting. *Seminars in Vascular Surgery* 2007;20:252–528.

Perler BA. Should statins be given routinely before carotid endarterectomy? *Perspectives in Vascular Surgery and Endovascular Therapy* 2007;19:240–245.



Cardiac surgeon David Yuh, M.D.

To Robot or Not To Robot

For minimally invasive heart surgery, it's hands on.

Ask cardiac surgeon **David Yuh** what he believes is one of the most important aspects of cardiac surgery, and he'll tell you it's in part the pursuit of perfection.

It was that quest that first attracted Yuh to surgical robotics for minimally invasive heart surgery. "At first, I saw the robot as a device that could help achieve that kind of precision," he says.

But, Yuh—who is building one of the region's highest volume programs for minimally invasive cardiac surgery—has stepped back from the very technology he once championed.

"As an investigative center, we've realized the shortcomings of a general-purpose robot," he says. "It's cumbersome, and the procedures take longer." Up to two to three hours longer than minimally invasive procedures using conventional instrumentation, and that was too long for Yuh to expect of his patients.

Yuh works exclusively with a team of cardiac anesthesiologists, perfusionists, physician assistants and specially trained nurses to perform aortic, tricuspid and mitral valve replacement and repairs; atrial septal defect closures and radiofrequency ablation for atrial fibrillation; and to remove cardiac tumors. Though the robot is out of the picture—for now—other enabling technologies such as retracting instruments designed to work through small incisions are helping to grow the list of minimally invasive cardiac procedures offered.

That's good for patients, more of whom are seeking less invasive approaches to cardiac surgery on their own, says Yuh.

"Not only are we seeing lower complication rates with minimally invasive procedures versus open-heart sternotomies," he says, "but recovery times are reduced from the typical six to eight weeks down to about two weeks."

There's zero margin for error with an incision one-third the size of traditional sternal-splitting procedures, but Yuh's outcomes are successful. His trickier challenge may be in communicating to physicians and patients the limitations of minimally invasive cardiac surgery.

"Off-pump surgery is often confused with minimally invasive procedures," he says. "Also, with or without the heart-lung machine, I believe that most CABGs are still best performed through a sternotomy."

And, though robotic devices play a role in other surgical subspecialties, in minimally invasive cardiac surgery, the technology isn't up to speed.

"It will catch up," says Yuh. "But, right now it's not where I want it to be."

The Patient Experience

Right Place, Right Time, Right Team

How a car wreck saved a life.

When William Roberts was tail-ended last March, he was transported to a shock trauma center where emergency personnel performed a full-body scan to assess the extent of his injuries. The imaging revealed a problem having nothing to do with the accident: an abdominal aortic aneurysm more than 2 inches in diameter.

Roberts' car was totaled, but the accident meant that the weakening in the wall of the abdominal portion of his aorta could be fixed just in time. Once they rupture, abdominal aortic aneurysms, or AAAs, are fatal in more than 50 percent of cases. Asymptomatic until they burst, about 90 percent are discovered by accident. "I knew it was a ticking time bomb," says the 74-year-old Hanover, Maryland, resident.

This wasn't Roberts' first bout with heart trouble: Diagnosed with coronary artery disease after a heart attack at age 50, he was first referred to Johns Hopkins in 1986 for a quadruple bypass. He later received an implanted cardioverter

defibrillator (ICD) to treat arrhythmia, and in 2006, he underwent an ablation and revision to his ICD.

"I've been through quite a few different procedures," he admits. "None of them fun, but they keep me going."

Now he found himself again at Hopkins, where a team gathered to perform a minimally invasive endovascular stent graft repair of his aneurysm. Physicians insert a catheter into the aorta by way of a smaller artery in the groin and advance a collapsed stent graft through the catheter to the aneurysm, then deploy the stent to reinforce the aorta.

All went well, says vascular surgeon **James Black**, until a complication—a dilated blood vessel—during stent deployment put Roberts into full shock in a span of six heartbeats. Using additional stents, the entire team worked together quickly to control the bleeding.

Over the next few hours and weeks, Roberts was monitored closely in the ICU. "Every member of our team understood the complexities and medical nuances of our patient," Black says, "which led to Bill's full recovery."



Patricia and William Roberts, out and about again

Roberts also knew that he was in good hands at Hopkins. "It doesn't matter what's wrong with you or whatever comes up," he says. "They can take care of it."

Today Roberts is back to bike riding and along with Patricia, his wife

of 53 years, welcomes frequent visits from his children, grandchildren and a great-grandchild.

"We're grateful," he says, "for the opportunity to continue enjoying life together for a while longer."

INHERITED HEART DISEASE

Demonstrating Clinical Innovation

Getting to Loeys-Dietz in Time

Surgical intervention thwarts aggressive aneurysms.

Five years ago, one of the scores of children whose flimsy aortas cardiac surgeon **Duke Cameron** has reinforced became the first person in the world known to be undergoing valve-sparing aortic root replacement for the newly recognized Loeys-Dietz syndrome. To the gratification of Cameron, who along with **Luca Vricella**, today leads the team with the world's longest experience repairing aortic aneurysms in patients with Marfan syndrome, the operation proved equally successful for Loeys-Dietz.

Well before pediatric cardiologist **Hal Dietz** and his Johns Hopkins colleagues published in 2005 their groundbreaking description of Loeys-Dietz—an autosomal dominant genetic condition similar to but clinically and genetically distinct from Marfan—they saw that it's far more aggressive. Not only is dissection

and rupture of the ascending aorta more likely at a younger age and at a significantly smaller root diameter than in Marfan patients, but aneurysms may occur throughout the arterial tree.

The good news, says Cameron—whose growing number of operations on patients with Loeys-Dietz includes children as young as 9 months—is that despite becoming surgical candidates when their aortic root diameter measures as little as 3 to 4 centimeters, these patients can be operated on with minimal morbidity.

Loeys-Dietz aneurysms appear most often in the ascending aorta, but they also can threaten the transverse, descending thoracic and abdominal aorta, and the thoracic arterial, head or neck, and abdominal arterial branches.



Hal Dietz, M.D., realized early on that Loeys-Dietz syndrome is more aggressive than Marfan.

As a result, patients require regular monitoring via head-to-pelvis computed tomography angiography so that these distal aneurysms also can be repaired as soon as they're diagnosed.

“There's a misconception that the tissues are excessively fragile,” says vascular surgeon **Jim Black**. “In fact, they hold sutures very well.”

Given the unpredictable and aggressive nature of Loeys-Dietz aneurysms, Johns Hopkins' current approach is to perform surgery very early in the course of the disease.

“We also hope,” says Cameron, “that newly developed mouse models of the syndrome will point the way to effective medical therapies.”

Moving Discovery Forward

Genes Behaving Badly

Getting to “rational therapy” for Marfan syndrome.

When cardiologist **Hal Dietz** identified the genetic mutations that cause Marfan syndrome in 1991, it became the stuff of scientific history. Still, the discovery opened no practical avenue for treatment of the distinctive aortic ballooning and thickening mitral valves that could be fatal for Marfan patients—particularly the youngest.

Fifteen years later, Dietz made another discovery that turned the world of Marfan syndrome upside down, revealing not only where the breakdown of cellular communication occurred but also a clue to successful therapy.

While Dietz’s initial revelation identified mutations in the gene for fibrillin-1, a connective tissue protein, it didn’t explain all Marfan symptoms, such as bone overgrowth or thickened mitral valves. For that, Dietz looked toward a second pathway. What he found was that fibrillin-1 also regulates a key developmental signaling molecule called transforming growth factor-beta. And, it is

an excess of TGF-beta activity that triggers the cascade of inappropriate cell behavior that becomes Marfan.

In the aorta, for example, TGF-beta might tell cells to make enzymes to break down tissues. Block the TGF-beta pathway, Dietz hypothesized, and cell behavior might return to normal. Lab studies proved that hypothesis when antibodies injected into Marfan mice normalized heart valves and blocked aortic aneurysms.

“What this showed was that TGF-beta is not just a player, but the major player,” says Dietz. “And it gave us insight into possible treatment.”

Frequent injections of TGF-beta antibodies weren’t practical, but with a therapeutic target in view, Dietz enlisted the help of cardiologist **Dan Judge** to begin scouting for a drug that would block the culprit molecule. That search turned up the hypertension medication losartan, and their subsequent research showed that Marfan mice treated with the drug are indistinguishable from normal mice.



Hal Dietz, M.D., with a young Marfan syndrome patient.

Today, a clinical trial funded through the National Institutes of Health is under way to determine whether losartan has the same robust effect in people as in mice.

“We always thought that the Human Genome Project would revolutionize medicine,” says Dietz. “Now we have an excellent example of how finding the genes responsible for a disease can lead to rational therapy.”

For more information about the losartan clinical trial, visit www.marfan.org.

RESEARCH PUBLISHED:

Habashi JP, Judge DP, Holm TM, Cohn RD, Loeys BL, Cooper TK, Myers L, Klein EC, Liu G, Calvi C, Podowski M, Neptune ER, Halushka MK, Bedja D, Gabrielson K, Rifkin DB, Carta L, Ramirez F, Huso DL, Dietz HC. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science* 2006;312:117–121.

Quality and Safety

Mining the Genetics of ARVD

A new window opens in the quest for early and accurate diagnosis.

One of every 5,000 people has arrhythmogenic right ventricular dysplasia, or ARVD. It's one of the most mysterious causes of sudden cardiac death, and its presence too often becomes clear only after an autopsy reveals such telltale signs as a severely dilated right ventricle whose walls are thinned and replaced with fibro-fatty tissue.

But, in their quarter-century campaign to accurately diagnose ARVD, scientists are closing in on their quarry with the aid of clinical genetic testing.

While getting an accurate early diagnosis can avert deaths in affected people, the condition's genetic links also give it a ripple effect: Parents, siblings, and children of someone with this condition are also at risk and should be tested for it.

That link further magnifies the value of accurate early diagnosis. Confirmed cases can trigger prudent family-wide screening, but cases that are merely suspected can bring unnecessary worry and, worse, unnecessary treatment that often includes an implanted device.

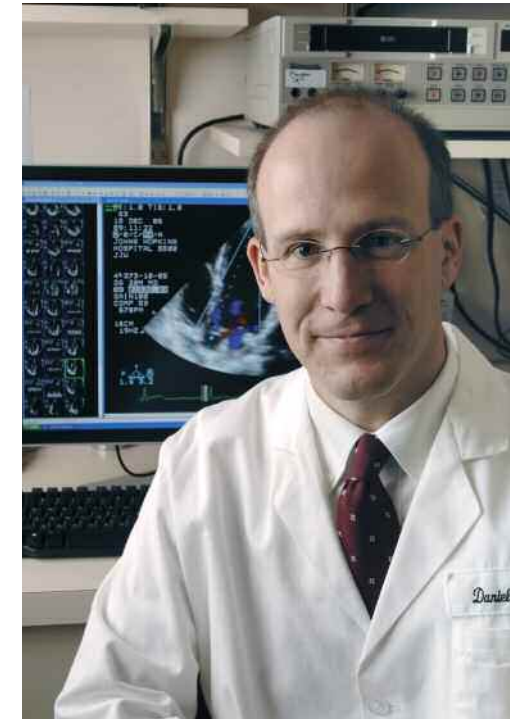
That concern is no minor detail, says cardiologist **Hugh Calkins**. A recent study scrutinized cases of reported ARVD in which patients were treated. Calkins describes how, following an elaborate battery of tests using the full gamut of established criteria, most of the suspected diagnoses proved incorrect.

The process of diagnosing ARVD has always been taxing, says Calkins, who heads up a team of 10 specialists at Johns Hopkins and serves on a task force charged with revising the condition's diagnostic criteria.

While a family history of ARVD is obviously a strong indicator, research conducted at Johns Hopkins has recently brought mutations in one gene—plakophilin-2—to the fore. PKP2 errors are associated with up to 45 percent of ARVD patients, says cardiologist and senior study author **Dan Judge**. Patients with a PKP2 mutation also are more likely to develop ARVD at an early age, which hints at the condition's especially tragic distinction—its disproportionate toll on young athletes.

Today, Johns Hopkins is the only U.S. medical center offering clinical genetic PKP2 testing for ARVD. Caught in advance, the condition can be temporarily relieved with ablation therapy. The more optimal long-term solution is defibrillator implantation, says Calkins.

“But,” he adds, “we want to be certain we’re identifying the right patients first, as early as possible.”



Cardiologist Dan Judge, M.D.

The Patient Experience

Beyond Blue Baby

Life-saving surgery prompts pursuit of a genetic factor.

In 1975, Bryan Knepper was born with the four-part congenital heart condition tetralogy of Fallot (TOF). He underwent corrective surgery at age 3, and his cardiac health was mostly uneventful throughout his childhood and early adult years. Then, he joined the roughly 15 percent of TOF patients who develop an aortic aneurysm.

Conventional wisdom in such cases holds that regular monitoring of the weakened blood vessel is the most prudent course of action. But when Knepper's father died suddenly in 2004 of a ruptured thoracic aortic aneurysm, the young man's view of his own clinical outlook changed dramatically. How long did he have until his fate became that of his father? Were there any options to avoid it?

Knepper's search for answers led him to Johns Hopkins cardiologist **Hal Dietz** and cardiac surgeon **Duke Cameron**. Even though Knepper's aneurysm had been stable for about five years when he came to Hopkins, the possibility of a genetic factor complicated his diagnosis.

"Some had believed my anatomy was normal and the end result of being born with a congenital heart defect," says Knepper. "Drs. Cameron and Dietz understood the gravity of my situation—they understand aortic connective diseases."

Cameron—renowned for valve-sparing aortic aneurysm surgery in children and adults—performed corrective surgery that removed the dangerous aneurysm, while replacing the aortic and pulmonary valves. For Knepper, weighing the statistical realities made surgery the easy answer.



Jennifer and Bryan Knepper

"I had a 20 percent chance of dying in five years if I did nothing versus a 1 percent mortality risk from surgery," he says. "I felt like I had a ticking time bomb."

But, where surgery gave Knepper peace of mind, his case also brought to the fore other questions about the genetics of TOF.

For Dietz, whose accomplishments include identifying the genetic mutations underlying Marfan syndrome and the discovery of Loeys-Dietz syndrome—conditions that also carry high risk of death from ruptured aortic aneurysms—it presented the chance to look closer at a condition where research had yet to go.

"We want to understand the genetic factors that predispose people to aortic aneurysms," he says, "and studying familial tetralogy of Fallot can help us in those efforts. We now have the first opportunity to observe people with TOF in young and mid-adult life. By taking the steps to find a gene and create an animal-based model, we can study this illness further."

Knepper's goal is closer to home: "I can be here to raise my child."

SUDDEN CARDIAC DEATH

Demonstrating Clinical Innovation

A New View on the Risk for Sudden Cardiac Death

Cardiac magnetic resonance (CMR) imaging has long been recognized for its role in accurately and reliably assessing the anatomy and vessels of the heart. Now Johns Hopkins cardiovascular physicians and scientists are optimizing the ever-evolving technology to go where no test has been able to hit its mark: determining the risk and guiding treatment for sudden cardiac death.

One CMR study of the heart wall showed that people whose muscle wall thickness contained more than 25 percent scar tissue were about nine times more likely to test positive for ventricular arrhythmia—a leading cause of sudden cardiac death. It's the kind of revelation that may more accurately identify those patients who would benefit most from an implanted defibrillator, or ICD.

“There are tests widely available to screen patients with coronary artery disease at risk for sudden cardiac death,” says cardiologist **Henry Halperin**. “But those tests are not so effective for identifying the many people

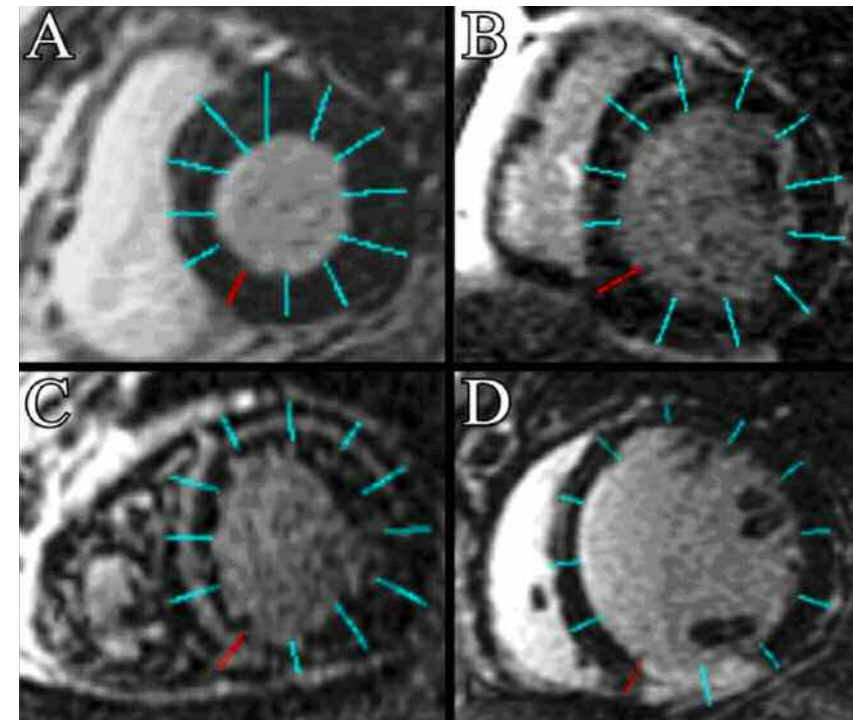
who will die suddenly from arrhythmias.”

Another study looked at left ventricular systolic dysfunction after heart attack, a scenario that increases the risk for arrhythmia-related sudden cardiac death. Patchy fibrosis creates regions of electrical conduction block at the borders of the healing infarct, the stuff of cardiac disaster.

Conduction through the myocardium becomes sluggish, and if an appropriate trigger is present, reentry-type tachyarrhythmias may be the fatal result. The essential question is how the size, geometry and transmuralty of the infarct and its borders influence sudden cardiac death risk.

Using CMR, cardiologist **Katherine Wu** and colleagues are phenotypically characterizing patients with prior myocardial infarction and left ventricular dysfunction who've been referred for prophylactic insertion of an ICD.

“CMR can accurately measure ejection fraction, left ventricular volumes and infarct size,” says Wu. And, because it's noninvasive,



Midventricular short-axis images from patients with reduced ventricular function but without coronary artery disease

A. No scar B. 1% to 25% C. 26% to 75% D. 76% to 100%

CMR also can safely generate serial images for following the course of left ventricular remodeling.

By looking at left ventricular ejection fraction, left ventricular volumes and mass, total infarct size, and a novel measure of tissue heterogeneity in the infarct periphery, Wu's team is prospectively relating these variables to appropriate ICD firings and clinical outcomes.

Both of those studies also offer

promise that CMR may be useful in screening people at moderate risk of sudden cardiac death from arrhythmias—those without significant coronary artery disease and ejection fractions between 30 percent and 50 percent. Another therapeutic implication is that identifying telltale heart scar patterns may improve existing procedures to ablate regions of the heart muscle that are substrates for arrhythmias.

Moving Discovery Forward

Rhythm in the Genes

Getting to the biology of sudden cardiac death.

At the Johns Hopkins Donald W. Reynolds Cardiovascular Research Center, dozens of investigators whose expertise spans cardiology, genetics, radiology, epidemiology, biomedical engineering, electrophysiology and biological chemistry are collaborating with each other and with investigators at other institutions to discover novel genetic and biological risk factors for sudden cardiac death.

Among their most important endeavors is the identification of inherited factors in sudden cardiac death, still a poorly understood component that existing evidence shows is a significant factor.

In published studies, having one parent who died of cardiac arrest increased the child's risk for sudden cardiac death by 70 percent to 80 percent. The risk was increased 900 percent if both parents died of sudden cardiac death.

In the search for sudden cardiac death's genetic underpinnings, rare mutations in ion channel genes have surfaced that are associated with long- and short-QT syndromes. Given the rarity of these syndromes, most people at risk for sudden cardiac death don't have these mutations. So, where else in the human genome's 3 billion nucleotides could trouble be lurking?

Working alongside investigators in Hopkins' McKusick-Nathans Institute of Genetic Medicine, Reynolds Center researchers are looking at hundreds of thousands of genetic markers in the population to find those associated with sudden cardiac death. But, they're not focusing their scrutiny on genes already known or suspected to influence cardiac rhythm. Instead, the Hopkins-led team has been using the whole-genome association method, which taps chip-based technology to rapidly detect subtle genetic deviations—those that may contribute to lethal arrhythmia.

“This approach,” says investigator **Aravinda Chakravarti**, “allows us to find targets that we never would have imagined.”

They've already found one candidate gene—*NOS1AP*—whose common variant explains normal variations in the QT interval and shows that there are heritable differences in cardiac electrical activity, and increases the risk of sudden cardiac death. The product of *NOS1AP* called CAPON regulates nitric oxide signaling but had never been suspected of having a role in cardiac repolarization.

“This finding,” says Chakravarti, “opens a completely new area of cardiac biology.”

Thinning the Haystack

Preventing sudden cardiac death in the general population, especially among patients whose first sign of heart disease is a fatal arrhythmia, amounts to looking for a needle in a haystack.

The goal of the Johns Hopkins Donald W. Reynolds Cardiovascular Research Center, says Director **Robert Weiss**, is to make that haystack smaller. Researchers here expect that potent new biological tools, phenotyping methods and population science resources will make it possible to devise new, effective ways to identify and treat sudden cardiac death patients—including those not suspected of having heart disease.

Quality and Safety

The Future of ICD

Toward primary prevention of sudden cardiac death.

In the early 1970s, Johns Hopkins created its Arrhythmia Service—the first such service in Maryland and one of the first in the United States. The goal was threefold: provide leading-edge clinical care for patients with arrhythmias, conduct research to determine the causes and develop therapies for patients who have arrhythmia-related problems, and train the next generation of clinical and research electrophysiologists.

“Quality, safety and providing the best clinical care possible for all of our patients—everything we do starts from this simple fact,” says cardiologist **Hugh Calkins**, director of the Johns Hopkins Arrhythmia Service.

One of its most notable early successes was the development and use of the first implantable cardioverter-defibrillator, or ICD, in a patient who had experienced numerous episodes of life-threatening arrhythmias. Developed by cardiologists **Michel Mirowski** and **Morton Mower**, the device was implanted by cardiac surgeon **Levi Watkins** in 1980 at The Johns Hopkins Hospital. Today, ICDs have saved hundreds of thousands of lives and are recognized as the most effective treatment in the secondary prevention of sudden cardiac death.

But for Arrhythmia Service cardiologists, that’s hardly good enough.

For patients who survive near-fatal arrhythmias, ICD implantation is essential to their continued survival. The more complicated question centers on the role of ICDs in

the primary prevention of arrhythmia-related sudden cardiac death. What about the large population of patients who’ve not experienced fatal arrhythmias before ICD implantation? Which of those patients should have prophylactic ICDs to prevent sudden cardiac death?

Such enduring questions of quality and safety are the bedrock of discovery and innovation and, in one study called the Prospective Observational Study of the ICD in SCD (PROSE-ICD), cardiologists like **Gordon Tomaselli** are seeking the answers.

“Among our goals is the development of a sudden cardiac death risk score,” he says. “But we’re also trying to better understand the mechanisms of sudden cardiac death and to discover novel biomarkers of risk.”

To that end, the PROSE-ICD study has the most extensively phenotyped and genotyped primary prevention ICD cohort to date, including DNA and serum protein samples, cardiac magnetic resonance imaging and digital ECGs.

“We want to be very thorough when it comes to primary prevention of sudden cardiac death with ICD implantation,” says Tomaselli, the PROSE-ICD principal investigator. “We want to understand which patients are most likely to benefit from this therapy.”

The Patient Experience

Surviving Sudden Cardiac Death

An arrhythmia nearly killed Kim Bauhs. Genetic testing gave her a second chance.

In November 2006, Kim Bauhs stepped up to a podium to address a group of colleagues in Philadelphia. Seconds later, she was splayed on the floor in cardiac arrest. Without warning, Bauhs' 46-year-old heart crashed.

Her diagnosis was sudden cardiac death. She survived the near-fatal arrhythmia, but even after ablation, beta-blockers and an ICD, Bauhs was battered months later by cardiac events that left her literally breathless.

Ironically, she was already familiar with sudden cardiac death. Though Bauhs' own family history was clear of heart issues, her husband's mother had died in her 40s, his brother had died at 19, his sister had been saved at age 39 by a portable defibrillator, his nephew had been diagnosed with an inherited arrhythmia, and her husband had long been under the care of Johns Hopkins arrhythmia expert **Gordon Tomaselli**.

Now, Bauhs herself needed every bit of Tomaselli's accumulated wisdom.

For Tomaselli, who's devoted his

life to unearthing the underlying biology of arrhythmias, not urging Bauhs to come in for a genetic diagnosis was out of the question. Suspecting a flaw in her DNA, he prescribed in-depth screening at the Johns Hopkins Center for Inherited Heart Disease, one of a handful of such centers nationwide for cardiac genetic testing.

Although Tomaselli suspected that an inherited arrhythmia might be at the root of Bauhs' ordeal, she had none of the classic signs that usually show up on a stress test or ECG. Even her first round of genetic testing came up empty. But Tomaselli persisted, and another genetic test finally revealed the type 2 variant of long QT syndrome (LQTS), or LQT2. It's the second most common gene location affected in LQTS, making up about one-third of cases.

"Getting to that diagnosis was enormously comforting," says Bauhs. "It means there are things you can do to manage it."

Emotional stress is a big trigger for people with long QT, says Tomaselli. Coffee and other stimulants, getting over-tired, not drinking enough water



Arrhythmia patient Kim Bauhs

or getting enough sleep, even loud noises can bring on an episode. "Anything that causes a burst of adrenaline," Tomaselli says, "can be a problem."

Bauhs admits that coming to terms with her new reality hasn't been easy. "I know my life depends on doing the right thing, though," she says. "So, I leave work on time, telecommute one day a week, stay hydrated, take naps, watch everything that goes into my body and take care of my health.

"Yes, it's been a challenge," she adds. "But, for me, it's life or not."

Preemptive Strikes

Finding new and better treatments is one weapon in Johns Hopkins' arsenal against heart disease. Warding off myocardial infarctions, strokes and other cardiac events in the first place is the aim of the Johns Hopkins Ciccarone Center for the Prevention of Heart Disease.

Co-directors **Roger Blumenthal** and **Charles Lowenstein** focus on preventive care and education to minimize patients' future cardiovascular risk. Using data from their own state-of-the-art research, they help even high-risk patients avert first or subsequent cardiac events and work to halt or reverse existing heart disease and reduce future complications.

At the core of Ciccarone Center clinical research are results showing that traditionally used risk factors inadequately predict coronary heart disease in many asymptomatic women and men with metabolic syndrome or a family history of heart disease.

In addition, basic science research has led to the development of peptides that decrease the size of heart attacks in mice and to the discovery of new drugs that block thrombosis. Data emerging from projects like these may lead to a new generation of drugs to treat heart attacks and strokes.

Making MRI and Heart Devices Play Nice

Until a few years ago, patients with implanted heart devices were out of luck when it came to powerful magnetic resonance imaging tests. It was feared that the machine's electromagnetic fields could heat the devices' metal components or dislodge them, causing tissue damage, device malfunction or even death.

But Johns Hopkins electrophysiologists **Henry Halperin**, **Saman Nazarian** and colleagues have painstakingly determined how to safely perform MRI scans on patients with modern pacemakers and defibrillators, which are made of titanium and better protected from radiofrequency energy.

To prevent misfires, they repro-

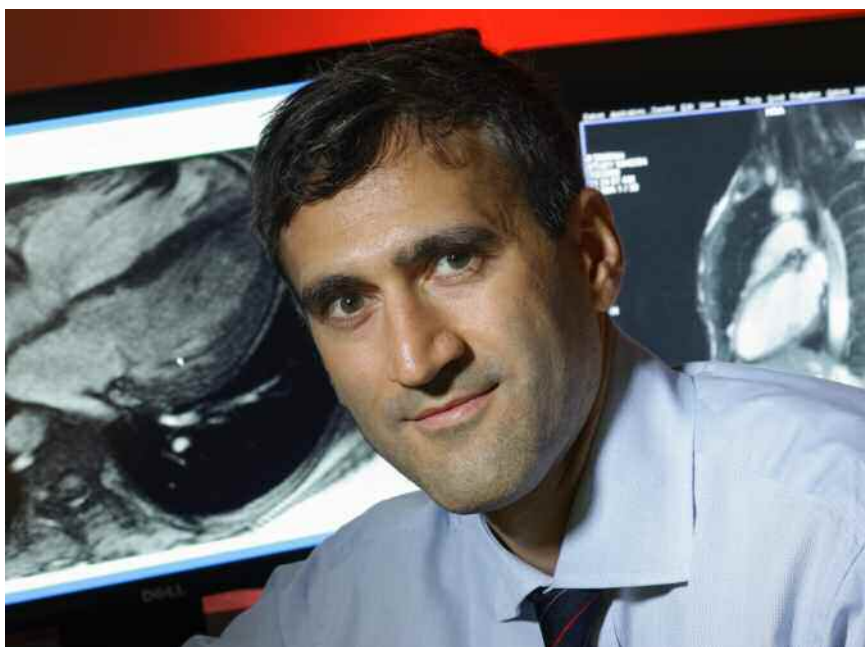
gram each device so its electronics won't mistake the MR radiofrequency for an arrhythmia. They also turn off a defibrillator's shocking function for the 30 to 60 minutes needed to perform the imaging test. In addition, they halve the amount of energy used at peak scanning, reducing the strength of the electromagnetic field from as much as 4 watts per kilogram to 2 watts per kilogram per patient. And during the scan, they closely monitor every patient using electrocardiography and pulse oximetry.

The Hopkins team has been able to make definitive diagnoses in some 180 patients who have been scanned so far, helping plan artery-opening procedures, measuring tumor growth, detecting strokes and a brain mass, and diagnosing a blood clot in the spine that had been missed by CT scanning. They also pinpointed the cause of one woman's seizures.

Diana Falls of Pinellas Park, Fla., considers herself lucky to have found the Hopkins program.

Falls, 53, received a pacemaker in 2001. Awhile later, she started experiencing double vision. Doctors in Tampa ran some tests, including a CAT scan, and found she had a chordoma, a rare, slow-growing malignant brain tumor. Following an MRI of the tumor at Hopkins, Falls' surgeons received more detailed images of the mass, which helped them plan an April 2007 operation to remove part of it. Six months later, as they planned a second surgery, they performed their first MRI on Falls while Hopkins experts guided them via telephone.

Falls is now in Boston undergoing proton therapy, a precise form of radiation treatment that minimizes damage to healthy tissue. She's due for a repeat MRI this fall but says, "I'm going back to Hopkins. I feel safer there."



Electrophysiologist Saman Nazarian, M.D.

ATRIAL FIBRILLATION

Demonstrating Clinical Innovation

Image Is Everything

Guiding ablation procedures for atrial fibrillation.

In the last decade, catheter ablation of atrial fibrillation has continued to evolve and show great success. Despite that, the procedure has been limited by a navigation system that doesn't account for true cardiac anatomy, an essential tool for guiding ablation procedures.

Today, says cardiologist **Hugh Calkins**, that's history.

"In the past, you had to move the catheter from place to place and try to recreate the anatomy of the heart," Calkins explains. "It was a

tedious, time-consuming process that resulted in a cartoon-like depiction of cardiac anatomy."

And, where precision is the goal, image is everything.

Leading the way toward that goal, John Hopkins was the first hospital in the world to introduce image integration, a novel technology that enables the assimilation of electroanatomic maps with preprocedural CT or MR images. That's been a significant benefit to patients with atrial fibrillation, the most common type of arrhythmia.

Traditionally, catheter ablation has been guided by fluoroscopy and mathematically reconstructed 3-D maps that offer limited information and replication of cardiac anatomy. CT and MR imaging could reproduce true cardiac anatomy, but no electroanatomic mapping system could blend those images for accurate catheter navigation.

Image integration not only is able to align preprocedural CT/MR images with real-time 3-D maps, it also can track and display the real-time

catheter tip location and orientation at a given point in the cardiac cycle.

"It's a superior technique," says Calkins. "Now you can take true anatomy based on the CT or MR and use that to guide manipulation of the catheter during the procedure." The system also reduces procedure time and radiation exposure, and lowers complication rates.

Calkins now expects that the technology will evolve even beyond accurate reconstructions of cardiac anatomy.

"We want to be able to look at characteristics of tissues in real time during the ablation procedure," he says. "Detecting gaps in our ablation lesions, detecting scars that cause arrhythmias, identifying specifically where to ablate—this is where the research is taking us."

The real future may be in using real-time MR imaging to guide catheter ablation procedures. **Henry Halperin**, professor of medicine and biomedical engineering at Johns Hopkins, has recently demonstrated that electrophysiology studies and catheter ablation procedures can be guided by MR imaging. He is making rapid strides in perfecting this promising new approach.

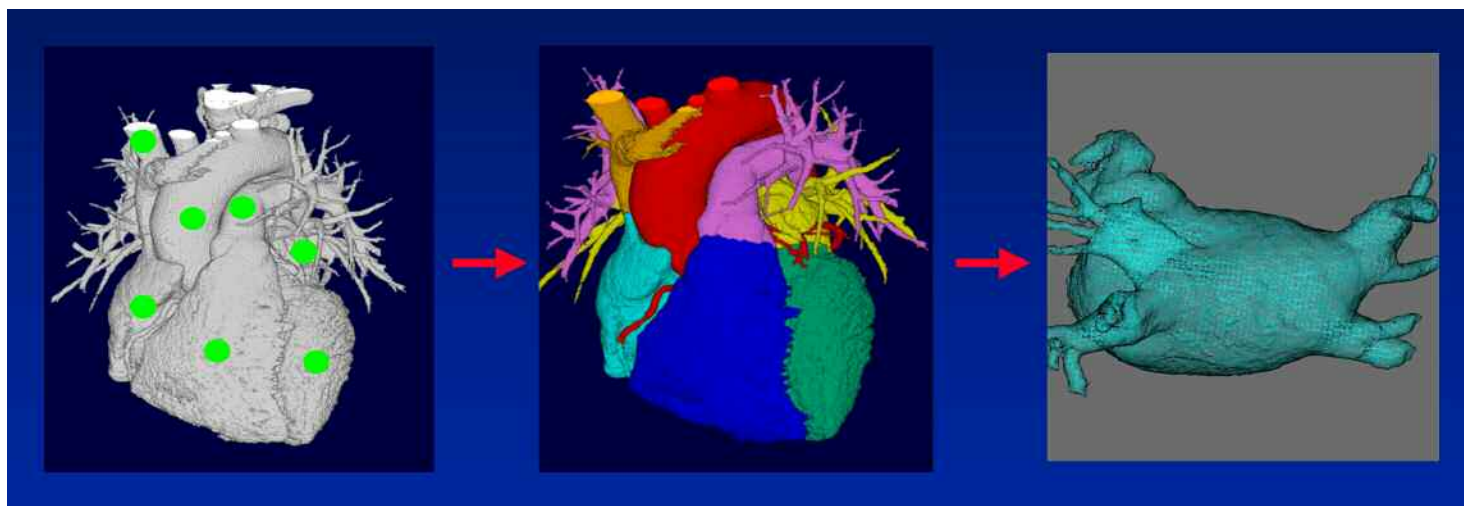


Image segmentation and extraction: Carto XP with CartoMerge Image Integration Module

Getting the Picture: Cardiovascular Imaging Center of Excellence

Johns Hopkins physicians are international leaders in cardiovascular imaging, including ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET).

Joao Lima, cardiovascular imaging director, says innovative imaging can show disease earlier than ever, many times before symptoms even appear. The role of imaging in clinical use continues to grow.

For example, Hopkins was the first hospital in the world to introduce image integration, a novel technology that enables the assimilation of electroanatomic maps with preprocedural CT or MR images. That's been a significant benefit to patients with atrial fibrillation, the most common type of arrhythmia (*see story, page 40*). Continuing research on speckle-tracking ultrasound enables echocardiologists better visuals that were inscrutable before by regular echocardiography methods.

Hopkins researchers spearheaded Core 64, a study on CT vs. invasive angiography, in which out-

comes showed that sophisticated CT scans of the heart and its surrounding arteries are almost as reliable and accurate as more invasive procedures to check for blockages and help cardiologists more quickly rule out those who can skip the more invasive procedures. The study also showed that early detection with 64-slice CT is a good predictor of who will need angioplasty or coronary bypass surgery to open up new blood supply routes to the heart.

Today, Johns Hopkins is one of only two hospitals in the nation offering studies on the 320-slice CT scanner, the most powerful imaging machine in its class, able to detect the signs of heart disease long before symptoms appear—even in the setting of arrhythmias and irregular heartbeats—in an almost literal blink of an eye.

Research using imaging technology leads to ever-increasing benefits to patients. For instance, Hopkins physicians are using cardiac MRI to create methods to detect myocardial damage that predisposes patients to sudden



Cardiovascular imaging director Joao Lima, M.D.

death, as well as to help stratify patients who need defibrillators vs. those who don't.

Hopkins is one of six centers participating in an NIH-funded study that uses MRI tagging to determine who develops heart failure in the community through MESA (Multi-Ethnic Study on Atherosclerosis). Results show that

diabetes and high blood pressure, two conditions rooted in genetics and environmental surroundings, play a much greater role than race alone in determining who is most likely to develop heart failure.

Hopkins imaging specialists, Lima says, will continue applying imaging advances to further research and advance patient care.

Moving Discovery Forward

Back in Sync

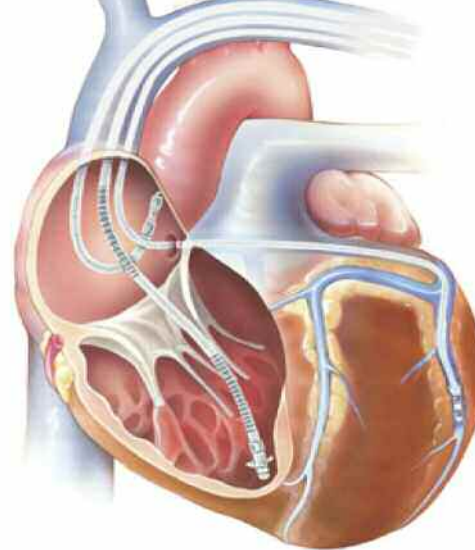
Biventricular pacing helps heart failure patients keep the beat.

Electrophysiologist **Ron Berger** half-jokingly calls himself a mechanic, but there's little doubt he gives one mean tune-up. He's one of the pioneers behind the study of biventricular pacing. The implanted device has changed the life of thousands of patients suffering from the type of congestive heart failure in which the left ventricular wall contracts out of sync—hence the term 'dyssynchrony'—greatly reducing the amount of blood the organ can pump.

With biventricular pacing, a three-lead pacemaker in the chest allows cardiac resynchronization therapy to take place. Berger was part of a team led by **David Kass** that showed “with biventricular pacing, you actually use less oxygen yet improve the performance of the heart. That's unlike other medical heart failure therapies,” says Berger. “You can whip the heart harder—that's what the drugs will do, make the heart squeeze more forcefully—but at the cost of burning more fuel, more oxygen. Those therapies have

been shown to be beneficial in the short term but end up actually hastening one's demise. Biventricular pacing prolongs life, makes patients feel better and makes their hemodynamics better.”

Since that study, the mechanic has set about to fine-tune the tool. In numerous papers with Hopkins colleagues such as **Melissa Byrne**, **Robert Helm**, **Gregory Nelson** and **Albert Lardo**, Berger has studied the electrical micro-nooks and crannies of the heart. He's hoping to both increase the ejection fraction of biventricular pacing devices—they currently improve the blood flow out of a diseased heart by 20 percent to 30 percent—and better understand the organ changes (called remodeling) that occur in heart failure before and after device implementation. Of his work, Berger says, “What we're good at here at Hopkins is taking a rather small number of patients, studying a problem in excruciating detail, and reporting on our discoveries of mechanisms. How something works. Why something works.”



Cardiac resynchronization therapy (CRT)

Most fascinating is that, unlike most clinical applications, which start at the bench and move to the bedside, biventricular pacing is taking the opposite track. Because single-lead pacemakers had a long, safe history going back to the 1960s, technologically, biventricular pacing came about and was approved before all of its mechanistic underpinnings were established. Now, with MRI improvements, says Berger, “we can use the imaging to see the dyssynchrony and how it reverses after device implantation. An awful lot of the work with biventricular pacing has moved out of the clinical setting. We started to study it in the cath lab, found tantalizing pieces of evi-

dence explaining why it made patients better, then moved from patients to the animal lab to the biochemical lab.” (For more about the important basic science discoveries involving dyssynchrony and biventricular pacing, see David Kass' work on page 48).

“It's a wonderful example of academic collaboration,” says Berger, sounding like a man grateful for colleagues willing to join him for a peek under the hood.

RESEARCH PUBLISHED:

Byrne MJ, Helm RH, Daya S, Osman NF, Halperin HR, Berger RD, Kass DA, Lardo AC. Diminished left ventricular dyssynchrony and impact of resynchronization in failing hearts with right versus left bundle branch block. *Journal of the American College of Cardiology* 2007;50:1484–1490. Epub Sept 24, 2007.

Helm RH, Byrne M, Helm PA, Daya SK, Osman NF, Tunin R, Halperin HR, Berger RD, Kass DA, Lardo AC. Three-dimensional mapping of optimal left ventricular pacing site for cardiac resynchronization. *Circulation* 2007;115:953–961. Epub Feb 12, 2007.

Quality and Safety

The Ablation How-To

Some of the world's most prominent heart organizations last year released the first international clinical consensus statement on the use of catheter and surgical ablation techniques to treat atrial fibrillation.

Johns Hopkins electrophysiologist and catheter ablation pioneer **Hugh Calkins** was tapped to lead the consortium, whose statement provides physicians with a state-of-the-art review of procedures to treat the disorder.

“These guidelines are a major step toward helping physicians provide better, safer and more consistent care for heart patients worldwide,” says Calkins, director of the arrhythmia service and electrophysiology laboratory at The Johns Hopkins Hospital. “Our statement provides recommendations regarding ablation techniques, procedural end-points, anticoagulation strategies, physician training and patient follow-up.”

The statement notes that ablation should be considered for patients whose AF symptoms are se-

vere enough to interfere with their quality of life and who have failed or can't tolerate treatment with at least one antiarrhythmic medication.

Because ablation of AF is more difficult, associated with greater risks and requires more careful follow-up than other ablation procedures, the statement stresses that training for ablation of AF should encompass six fundamental principles:

- appropriate selection of patients
- knowledge of the anatomy of the atria and adjacent structures
- conceptual knowledge of strategies to ablate AF
- technical competence
- recognition, prevention and management of complications
- appropriate follow-up and long-term management

Convened by the Heart Rhythm Society, the task force of international specialists represented the



Arrhythmia Service Director Hugh Calkins, M.D., performing an ablation

American College of Cardiology, the American Heart Association, the European Heart Rhythm Association, the European Cardiac Arrhythmia Society and the Society of Thoracic Surgeons. The guidelines were presented in 2007 at the HRS' 28th Annual Scientific Sessions in Denver.

RESEARCH PUBLISHED:

Calkins H, Brugada J, Packer DL, et al. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: Recommendations for personnel, policy, procedures and follow-up. *Heart Rhythm* [online] 2007;doi:10.1016/j.hrthm.2007.04.005.

HEART FAILURE AND CARDIOMYOPATHY

Demonstrating Clinical Innovation

A Healing Repertoire

If **David Kass** hadn't been a cardiologist, he would've been a wonderful composer. For where others hear the song that is the human heartbeat, Kass inhales the chords, the notes, the very vibrations that stir the air and bounce beautiful crescendos off the inner ear.

Or, as the case may be, the dissident tones that indicate a damaged heart.

Kass made his name and fame in a landmark paper that showed how biventricular pacemakers could resynchronize the entire heart (the paper has been cited in more than 600 subsequent publications). The next step was to figure out exactly what this pacing was doing to the heart, and how, in some cases, it was undoing some of the

cellular damage (remodeling) that had already occurred. Kass' cellular and molecular studies have focused on the heart's biomechanical and electrical activity, especially as it regards both heart failure and heart attacks. The Kass lab has turned out numerous papers, showing among other things:

- How Viagra blunts the development of heart growth and failure when hearts are exposed to high blood pressure for a sustained period of time. This work has led to an upcoming NIH multicenter clinical trial looking at older patients with high blood pressure and heart failure symptoms including hypertrophy. "It's a very common syndrome, but we have no evidenced-based medical therapies," says Kass.

- How a vitamin-like co-factor called BH4 gets depleted during heart failure, leading to runaway production of an oxidant that causes tissue damage, fibrosis and dilation of the heart. "You can take this BH4 as a pill and profoundly suppress the evolution of cardiac failure," says Kass, who notes that BH4 is already FDA-approved for people suffering from the genetic disease phenylketonuria (PKU).
- That high doses of folic acid apparently give the heart's energy supply a boost during heart attacks, as tissue exposed to folic acid doesn't die as quickly when an artery is blocked and blood flow and oxygen are cut. There also appears to be less damage to the heart muscle when the blockages are cleared.

- Kass says both the BH4 and folic acid papers could well lead to large, multicenter clinical trials. Those would be on top of three such trials he's already involved with, one of which is looking at patients who present with heart failure symptoms—shortness of breath, leg swelling and the like—but whose hearts are actually ejecting the proper amount of blood. The problem? An earlier Kass study suggests that in this group, "their heart rate stays slow, even during exercise." A solution could be a different kind of cardiac pacing, a speeding up of the heart.

For the maestro, it'll be just another sweet-sounding rhythm in his ever-expanding healing repertoire.

Moving Discovery Forward

The Protein Prober

When it comes to challenges, **Jenny Van Eyk** has tasked herself with a doozy. Van Eyk's milieu is proteomics, which, if you compare it with its older-sister discipline, genomics, is a bit like trying to parse out each individual grain of sand from the entire beach. For while the latter is the study of genes, of which there is a finite, fairly fixed amount in the body,

Van Eyk delves into their prolific progeny, proteins (each gene can produce hundreds), which are forever in flux throughout the course of a human lifetime.

Specifically, Van Eyk is focusing on how proteins affect the heart in different disease states. "It's the proteins that actually make the cells work," says Van Eyk, whose lab has developed many technologies to se-



Jennifer Van Eyk, Ph.D., making proteins reveal their secrets

quence different proteins to accommodate their molecular weights, pI and solubility. Though proteomics is a rapidly evolving field, Van Eyk's findings have already been eye-opening, yielding dozens of papers offering the promise of both drug development and better clinical biomarkers for the onset of cardiovascular disease.

Working with colleagues including **David Kass**, **Brian O'Rourke** and **Gordon Tomaselli**, her lab is isolating biomarkers for ischemia, which could help physicians better triage people who present with acute coronary syndrome. In essence, such a biomarker could tell who is suffering from benign chest pain versus someone at imminent risk for a heart attack.

They've also been studying a protein, Connexin-43, which may play a key role in how the heart contracts. In normal hearts, Cx-43 lines up at the head of each cell (think of the coupler at the front of each car of a long train), sending electrical signals from cell to cell. But in heart failure, these proteins slide to the

side of the cell, either sending out stray electrical signals or shutting down altogether, impairing electrical conduction and thus contraction of the heart. These slackers "would be a drug target if we can figure out how to manipulate the protein that's causing the Cx-43 to move incorrectly," says Van Eyk.

In addition, she and colleagues are identifying which proteins cause plaques to thin and break free from arterial walls, where they can become deadly clots that cause ischemia.

For Van Eyk, studying proteomics is like being a kid in a candy store. Each day brings a new treat: finding proteins no one knew existed, parsing out their work detail, seeing how they change, and teasing out what those changes augur for an individual's cardiovascular health. From understanding stem cells to mitochondrial function, she and her nearly two dozen lab partners stand on the forefront of a field that could well have all the revolutionary impact of genetics. "It truly is discovery," she says. "That's what we do."

Don't Go Breaking My Heart

Cardiac researchers at Johns Hopkins have been making headlines over the past several years for a range of studies examining connections between depression and heart disease.

Ilan Wittstein received international attention for his work describing “broken heart syndrome,” a condition in which people who undergo sudden, severe emotional stress—triggered by the death of a loved one or other catastrophic event—suffer episodes that mimic heart attacks but without lasting damage. He and **Hunter Champion** have since found that such cases of stress cardiomyopathy are more prevalent than previously thought and also can result from stroke, severe migraines, asthma attacks or other physical ailments. A registry has been established at Johns Hopkins to track these patients and learn more about the condition.

In another example of how sadness takes its toll on the heart, work directed by **Roy Ziegelstein** and **David Bush** at Johns Hopkins' Center for Mind-Body Research

suggests that people who are depressed or sad often exhibit heart-unhealthy behaviors such as smoking and not exercising. In turn, some depressed heart attack survivors are so convinced they'll never be healthy again that their belief becomes a self-fulfilling prophecy; their unwillingness to alter lifestyle habits then puts them at risk for early death.

The power of positive thinking also is apparent in research by **Diane Becker** at Johns Hopkins' Center for Health Promotion, which indicates that people with a positive attitude are only half as likely to experience heart problems as their less optimistic peers, regardless of age, race or sex—possibly because they produce lower levels of stress hormones. Her work also has found that greater spiritual well-being is strongly associated with less depression among outpatients with heart failure.

Ziegelstein's research also sheds light on the importance of assessing depression both at the time of acute coronary syndrome and on an ongoing basis. One study found that



Cardiologist Hunter Champion, M.D.

depression at the time of heart attack was prospectively related to increased mortality and reduced mental and overall health as much as four months later, though the effects on mortality appeared to wane over time. He and colleagues also are investigating the merits and effectiveness of nonpharmacological approaches to manage emotional stress, including social support, relaxation therapy, yoga, meditation, controlled slow breathing and biofeedback.

RESEARCH PUBLISHED:

Bekelman DB, Dy SM, Becker DM, Wittstein IS, Hendricks DE, Yamashita TE, Gottlieb SH. Spiritual well-being and depression in patients with heart failure. *Journal of General Internal Medicine* 2007;22:470–477.

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Stem Cell Revelations

Millions of patients in the United States have congestive heart failure due to coronary artery disease; despite the use of aggressive prevention strategies, hundreds of thousands of new patients still develop cardiac dysfunction each year. Many therapies focus on decreasing cardiac workload and improving remodeling, but there are no currently approved treatments aimed at actually regenerating new heart muscle. Until recently, in fact, it was believed that the heart was not capable of growing new muscle cells.

Research at Johns Hopkins and elsewhere, however, indicates that stem cell therapy is capable of enhancing the growth of new heart tissue in the post-infarction setting. One cell type, mesenchymal stem cells, which are derived from bone marrow, is the focus of studies at Johns Hopkins. Previous animal experiments conducted here demonstrated that administration of mesenchymal stem cells following infarction resulted in the growth of new heart muscle cells

and improved heart function. A recent phase I clinical study conducted by Johns Hopkins in collaboration with Osiris Therapeutics in Columbia, Maryland, and other medical centers studied the effects of intravenous administration of mesenchymal bone marrow cells to patients following a heart attack. Interim results presented in abstract form indicate that the strategy is safe and improved some important clinical outcomes. The full results are expected to be reported shortly.

Cardiologists at Johns Hopkins will study different types of stem cells in patient populations in collaboration with cardiologists at the Cedars Sinai Medical Center in Los Angeles and the University of Miami Miller School of Medicine. The study currently enrolling patients is examining the effects of administering mesenchymal stem cells directly into the border regions of cardiac scar tissue during coronary bypass surgery in patients with impaired heart function due to a prior heart attack. Cells are obtained from the patient's own bone mar-

row, so there is a “perfect match” in terms of eliminating any rejection problems. After the mesenchymal stem cells are isolated, they are “expanded” in the Johns Hopkins Cell Therapy Laboratory. Patients are randomized to two different doses of cells (20 million or 200 million) or to placebo and followed for 18 months.

In addition to studying the safety of this approach, the researchers aim to determine whether this strategy forms new heart muscle, decreases the size of the scar, improves exercise ability and decreases symptoms due to heart dysfunction. The study is supported by the National Heart, Lung and Blood Institute and approved by the FDA. **John Conte**, **Steven Schulman** and **Gary Gerstenblith** are the investigators at Johns Hopkins.



RESEARCH PUBLISHED:

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Interim results of phase I clinical trial by Osiris Therapeutics: <http://investor.osiris.com/releasedetail.cfm?ReleaseID=296078>

Moving Discovery Forward

MR-Guided Therapy

Scientists around the world have been investigating gene, protein and cell-based therapies as a means to create new blood vessels, though until recently it was impossible to track how the body absorbed the treatments.

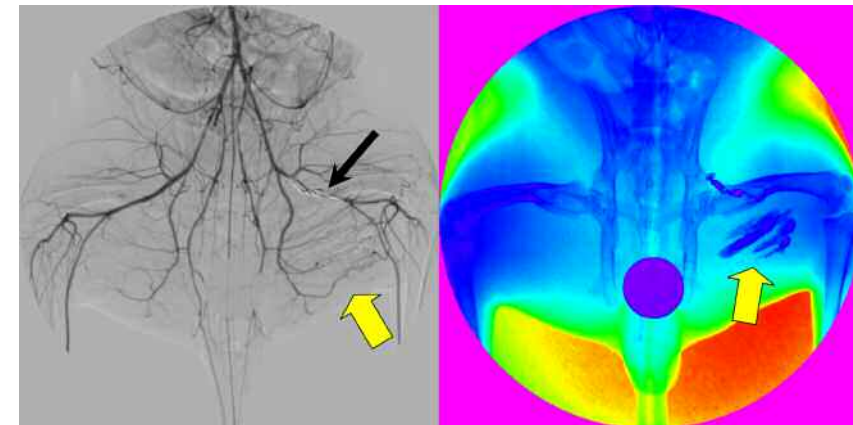
Over the past few years, Johns Hopkins radiology researchers **Dara Kraitchman**, **Aravind Arepally**, **Jeff Bulte** and **Brad Barnett** have developed a novel method to track delivery and enhance engraftment of cell transplants. The investigators created tiny porous capsules using a compound based around alginate, a gooey material produced by seaweed, then used a machine that creates small microdroplets of the mixture to surround and encapsulate clusters of stem cells or islet cells. The microcapsules, which can be filled with contrast media to be seen with magnetic resonance imaging, computed tomography or X-ray machines, permit the diffusion of nutrients and waste products while blocking antibodies that normally would attack the transplanted cells.

“We’re really excited because we can track where we put the cells and make sure their protective housing stays intact and that the cells don’t move,” explains Arepally,

an associate professor of radiology and surgery. “This could solve the mystery of why current transplantation techniques work only for so long.” Up to 95 percent of transplanted stem cells, for example, fail to survive more than 24 hours.

In a recent animal study, the team successfully used a related technique to deliver unprotected mesenchymal stem cells to dogs with heart muscle damage similar to that of a human heart attack. Over a two-month follow-up period, the group observed through cardiac MRI that the damaged area decreased by 20 percent without the loss of normal tissue that often leads to heart failure in patients. The team anticipates that protected stem cells will demonstrate improved benefits. Other experiments with protected stem cells found that the method could be used to place stents and to spur new blood vessel growth in the hind limbs of rabbits with peripheral arterial disease.

The work has broader applications and benefits for patient care because MRI technology is widely available and avoids the risk of X-ray radiation, Kraitchman says. For example, she and her colleagues also have used the technique in the livers of swine, delivering



Left: In a rabbit model of arterial disease, an angiogram shows vessel regeneration after stem cell microcapsule injection. *Right:* The location of the microcapsules.

islet cells that continued to secrete insulin three weeks after transplantation.

RESEARCH PUBLISHED:

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Quality and Safety

Heart Disease in Women: Tools for CVD Risk, Early Diagnosis

Over her three decades of practice, cardiologist **Pamela Ouyang** has seen “the look” time and again. Shock, surprise, confusion—perhaps a mixture of all three—when she’s told a woman that her backache, her reflux, aren’t what they appear to be, but far worse: indicators of advanced cardiovascular disease. The number one killer of women, CVD—which includes heart attacks and strokes—claims 500,000 lives annually. Yet, as Ouyang notes, “there are many, many women who don’t realize the importance of CVD risk factors or who have atypical symptoms that are not being recognized as CVD.”

Ouyang’s mission is to give physicians the tools to recognize CVD risk factors and to uncover the role sex hormones play in CVD as women enter menopause. Traditionally, many physicians have evaluated and treated women based on recommendations from the 50-year Framingham Heart Study. The problem, says Ouyang, is that the study had far more male participants. “Women are underserved by relying on Framingham,” she says. “Those risk scores are largely built

for men,” she adds, noting that women generally develop cardiovascular issues about 10 years later than men.

Ouyang was tapped as an expert for a recent groundbreaking American Heart Association panel that created better guidelines for measuring and standardizing female CVD risk. This included a scoring sheet to determine risk levels—low, intermediate and high—and clinical recommendations for lowering risk through lifestyle changes, nutritional supplements and drug therapies.

“Physicians are a little hesitant to treat men and women equally aggressively,” says Ouyang, who specifically looked at guideline data regarding hormones, antioxidants and cardiovascular risk. The guidelines, she adds, now allow doctors to place women into appropriate risk categories and to treat them accordingly. “It’s even more helpful to an internist than a cardiologist,” says Ouyang. “People who first see the patient. Or the internist or gynecologist who sees women throughout their lifespan.”

Ouyang sees the new guidelines as a constantly evolving resource for the larger medical community, reflecting



Pamela Ouyang, M.B.B.S.

the latest findings about how cardiovascular disease presents in women. She often speaks to physician groups about diseases now linked to greatly increasing risk for stroke and heart attack in women, such as end-stage renal disease and leg claudication (clots). She also discusses how women present with CVD and heart attack differently than men. Women tend more toward microvascular blockage, says Ouyang, and the pain that indicates the onset of heart damage may come while at rest and in areas of the body other than the chest.

Though her studies focus on hormonal changes in middle age, she’s the first to admit that the guidelines can’t wait until menopause to be implemented. “What we really want to do is identify at-risk women early and not wait until they’re presenting with their cardiovascular events,”

says Ouyang. “The guidelines will show the areas where our data is strong. Physicians know how to manage cardiovascular disease in men and identify it, but they still want to learn more about the risk for women.”

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The Patient Experience

Back in the Game

As a coach and umpire for a competitive men's softball team, Steve Simone thrives on calling fouls and balls at up to 14 games a week. But until a visit with a cardiologist, he had no idea how close his heart was to striking out.

"I knew I was slowing down," says Simone, 55, of Wilmington, Delaware. "I couldn't move from home to first base as quick."

Then one day while coaching, Simone, a diabetic who has some neuropathy, had a small spell

where his equilibrium was off and he was short of breath.

Simione's internist ordered an ECG, which looked abnormal, and sent him to a cardiologist. The verdict? His heart was enlarged and damaged and had coronary artery blockages, resulting in silent heart attacks. A cardiac catheterization showed that his heart function was 10 percent of what it should have been. The cardiologist told Simione he would trust only one doctor to fix the problem: Johns Hopkins

heart surgeon **John Conte**.

Conte reviewed Simione's medical records, looked at him and said, "Steve, we can fix this."

In an uncommon procedure called surgical ventricular restoration (SVR), Conte repaired Simione's heart by returning it to a more normal shape. First, he removed the nonfunctioning, scarred tissue. Then he inserted a plastic mold into the ventricle, filled it with saline until it was the right size, then deflated and withdrew the mold before closing the ventricle. Along the way, he also fixed Simione's leaking mitral valve and bypassed a few arteries that were blocked.

SVR enables hearts to pump more efficiently, says Conte, director of Johns Hopkins' heart and lung transplant programs and a teacher of national training courses for the operation: "The procedure can take patients off the heart transplant waitlist or prevent them from going on the waitlist to begin with."

Without SVR, Conte says Simione likely would have been implanted with a biventricular pacemaker or put on different heart medications, neither of which would have addressed his treatable problem.

Cases like his "are exactly why we do this procedure," Conte says. "Once patients develop ventricular dilation, they slowly progress until they wind up in severe heart failure or die."

Simione says he noticed an improved exercise capacity and energy level almost immediately, and heart studies have shown that his heart function has improved dramatically. He started walking three miles a day within a week and planned to be back at work as equipment superintendent for the state of Delaware within a month, until a broken ankle set him back a few weeks. He also made a triumphant return to the ball field.

"The quality of my life is better than what it was before," says Simione. "I owe my life to Dr. Conte."



Steve Simone underwent surgical ventricular remodeling and avoided the need for a heart transplant.

And the Beat Goes On

Carolyn Kramer's transplanted heart took many lickings but kept on ticking. And ticking and ticking. Nearly 23 years later, Kramer is one of Johns Hopkins' longest-surviving heart transplant patients.

Her prognosis wasn't always so good. In December 1984, Kramer, then 33, gave birth to her third child. Weeks later, she began retaining fluids, coughing and feeling short of breath. As symptoms worsened, she couldn't hold her infant daughter. She was diagnosed with peripartum cardiomyopathy, a rare disorder in which pregnancy causes heart failure.

In May 1985, Kramer became the 27th person to undergo heart transplantation at Johns Hopkins. Though the operation went smoothly, her body repeatedly tried to reject the new heart.

"Every side effect they thought they might see, I had, and I also developed new ones," she says. "So we all learned together."

At the time, antirejection treatments were still in their infancy. One medication had to be injected in Kramer's thighs through huge needles; it was so unpleasant that

her nurses used to draw lots to see who would do it.

Six months after her transplant, Kramer was still hospitalized. The transplant team had given her every combination of steroids and immunosuppressant drugs they could. Most set off violent allergic reactions; none halted her immune system from producing cells that attacked the new organ.

Finally, a few days before Christmas, **William Baumgartner**, then chief of cardiac transplantation, told her they were out of options—all they could do was hope. She went home to Bel Air, Maryland, to celebrate the holiday with her family. Amazingly, when Kramer returned to Hopkins two weeks later for a heart biopsy, the test revealed that her body had finally accepted the new organ.

"It truly was a miracle," Kramer says. "I have a very strong faith, and I had a lot of people praying for me."

She started planning the rest of her life in short increments, like hoping she could live long enough to see her son go to kindergarten. As her time grew, so did her plans.

Kramer is now a dedicated volunteer, serving on the board of the

nonprofit Heart Transplant Foundation and helping Johns Hopkins' transplant center plan annual educational conferences, picnics and holiday parties for other patients and their families. She also staffs an information booth at the hospital each year during National Organ and Tissue Donor Awareness Week, and organized

making a quilt to commemorate organ donors.

She's also planning to throw a black-tie party in honor of her 25th transplant anniversary and says that Baumgartner, now chief of cardiac surgery, owes her a dance.

"I don't know if I'll be able to pull it off," she says, "but it's within reach."



From left, heart transplant coordinator Debra Carter, heart surgeon Bill Baumgartner, M.D., transplant recipient Carolyn Kramer and social worker Helen Michalisko. "I turned my life over to the hands of this transplant team," Kramer says, "and here I am 23 years later."

Until There's a Heart

As an Army paratrooper, Jose Vargas showed no fear. Besides jumping out of airplanes, Vargas performed guerilla warfare exercises to train soldiers in basic combat skills. Little did he know that his biggest foe resided in his chest.

At 23, Vargas couldn't understand why he was exhausted after running, had lost his appetite and was increasingly lethargic. Several medical tests by military doctors

revealed the surprising cause of his condition: congestive heart failure.

Vargas, who was put on medical retirement from the military and moved to Fort Meade, Maryland, started with heart medications, though doctors told him there was so much damage he wouldn't last five years without a new heart. As his health deteriorated, he was hospitalized in 2006, first at Walter Reed Army Medical Center, then at Johns Hopkins.



Jodie and Jose Vargas

“He was about as sick as you can get without being dead,” his cardiologist, **Ilan Wittstein**, told a military newspaper. In fact, Vargas' condition was so poor that cardiac surgeon **John Conte** wasn't sure he could operate. Three days after hospital admission, Vargas suffered four cardiac arrests. Then his doctors discussed the possibility of using a left ventricular assist device (LVAD) to help his failing heart.

In a series of operations, Conte first implanted a short-term pump for Vargas' left ventricle and, because his right ventricle was too weak to pump blood to the left side, a right ventricular assist device as well. Later Conte was able to replace the short-term LVAD with a long-term LVAD and eventually could remove the right-side device.

Through it all, Vargas was unconscious for three weeks—long enough that once he woke up he had to relearn to walk and chew food. Once stabilized, he became an active volunteer with Johns

Hopkins' LVAD program, coming to the hospital to speak with surgeons from around the country attending training courses on campus. Johns Hopkins runs one of the largest, most innovative LVAD programs in the country. Led by John Conte and **Ashish Shah**, it participates in all major clinical trials. Depending on patients' conditions, the devices can be used as a bridge to transplant or for long-term management of heart ailments. Johns Hopkins also manages the largest base of outpatients—some 32 patients are living with the pumps at home.

Nineteen months after receiving his LVAD, Vargas received a heart transplant on May 29.

“I feel like a brand new man,” says the 29-year-old. “I'm extremely thankful for someone to be that generous to give me a second chance at life, and one day I hope to meet my donor's family.”

Johns Hopkins Heart and Vascular Institute Faculty

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 Armin Arbab-Zadeh, M.D.
 Ernest Arnett, M.D.
 Thomas Aversano, M.D.
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 Gary Gerstenblith, M.D.
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How to Refer a Patient

The Johns Hopkins Heart and Vascular Institute welcomes referrals of new patients. We look forward to working with you to determine the most appropriate care for your patients.

There are several ways to refer a patient. For urgent physician-to-physician referrals or consultation, please call the Hopkins Access Line (HAL) at **1-800-765-5447**.

You may also refer patients to the **Cardiovascular Access Line (CAL)** by calling **1-888-502-0550**.

To reach the following departments directly, please refer to the numbers listed below:

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410-955-6666

Cardiac Surgery
410-955-2800

Vascular Surgery and
Endovascular Therapy
410-955-5165

Interventional Radiology
410-502-2835

For more information about the Johns Hopkins Heart and Vascular Institute, visit our Web site at www.hopkinsmedicine.org/heart.

Locations

The Johns Hopkins Heart and Vascular Institute offers inpatient services at:

- The Johns Hopkins Hospital
- Johns Hopkins Bayview Medical Center

We also offer patient consultations at comprehensive outpatient centers throughout the Baltimore metropolitan area, including:

- The Johns Hopkins Hospital Outpatient Center
- Johns Hopkins Bayview Medical Center
- Columbia
- Greater Baltimore Medical Center
- Green Spring Station in Lutherville
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For directions and maps, please visit our Web site at www.hopkinsmedicine.org/directions.

Referral Assistance

Johns Hopkins USA

Johns Hopkins USA provides one point of contact for our out-of-town patients. Our staff can help patients identify appropriate physicians or specialists, coordinate multiple medical appointments, arrange second opinions, and obtain general information on Johns Hopkins' numerous services. In addition, Johns Hopkins USA staff can provide information regarding transportation, lodging and other travel needs. Call **410-735-HUSA (4872)** to talk with Hopkins USA. For family accommodations on the patient floor, see information regarding the Marburg Pavilion on page 70.

Johns Hopkins Medicine International

The professional staff of Johns Hopkins Medicine International coordinates all aspects of international patients' medical care, paying special attention to personal, cultural and travel-related needs. The staff will arrange consultations, second opinions or treatments, and will

coordinate appointments in a time-efficient manner. The staff also provides medical records reviews before the patient travels to the United States, language interpreters, cost estimates and assistance with travel arrangements.

For more information, call **+1-410-955-8032** or visit the Web site at www.jhintl.net.

Accommodations Assistance

Accommodations Office

The Johns Hopkins Hospital has arranged special rates (and shuttle service in some instances) at local hotels for patients and their families. A full-service travel agency is available to help patients and their families with air, hotel or ground accommodations. It is open Monday through Friday, 8:30 a.m. to 5 p.m. Please call **1-800-225-2201** or **410-614-1911** for assistance.

Marburg Pavilion

Located in the historic Marburg Building, the Marburg Pavilion offers deluxe accommodations for adult patients. A limited number of private rooms and two-room suites are available for an additional charge and feature fine wood furniture, private baths, entertainment centers and an array of services, such as expanded dining menus and overnight sleeping accommodations for family members. For more information call **410-614-4777**.

Patient Relations

Patient representatives are available to help resolve any concerns about patient care, interpret the policies and procedures of the hospital, and arrange for services patients may need. At The Johns Hopkins Hospital, call **410-955-CARE (2273)** to speak with a patient representative. Hours are 8:30 a.m. to 5 p.m. The office is located in the hospital at Carnegie 100.

At Johns Hopkins Bayview Medical Center, call **410-550-0626** to speak with a patient representative about any patient care concerns. Hours are 8:30 a.m. to 5 p.m. The office is located in the Bayview Medical Office on the main level.

Sign Language

Deaf and hearing-impaired patients can arrange for interpreters or use the TTY in the patient relations offices at both The Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center.

For more information, please visit The Johns Hopkins Hospital Web site at www.hopkinsmedicine.org or the Johns Hopkins Bayview Medical Center Web site at www.hopkinsbayview.org

For patient information and a visitor's guide to The Johns Hopkins Hospital, visit www.hopkinshospital.org/patients

Johns Hopkins Medicine Overview

Johns Hopkins Medicine—established in 1995 to unite Hopkins biomedical research, clinical teaching and business enterprises—brings together the Johns Hopkins University School of Medicine and its faculty with the facilities and programs of the Johns Hopkins Health System. The Health System, which has its origins in the founding of the world-famous Johns Hopkins Hospital, now comprises three hospitals as well

as other elements of an integrated system, from a community physicians group to home care. The components of Johns Hopkins Medicine are consistently named at the top of national rankings for best hospital and best school of medicine, and its faculty consistently is awarded the largest share of NIH research funds. Results of this research continue to advance efforts to diagnose, treat and prevent many diseases.

For more information about our published research, visit PubMed at www.pubmed.gov. Articles and abstracts are indexed by author, topic or journal.

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