

GETTING TO THE

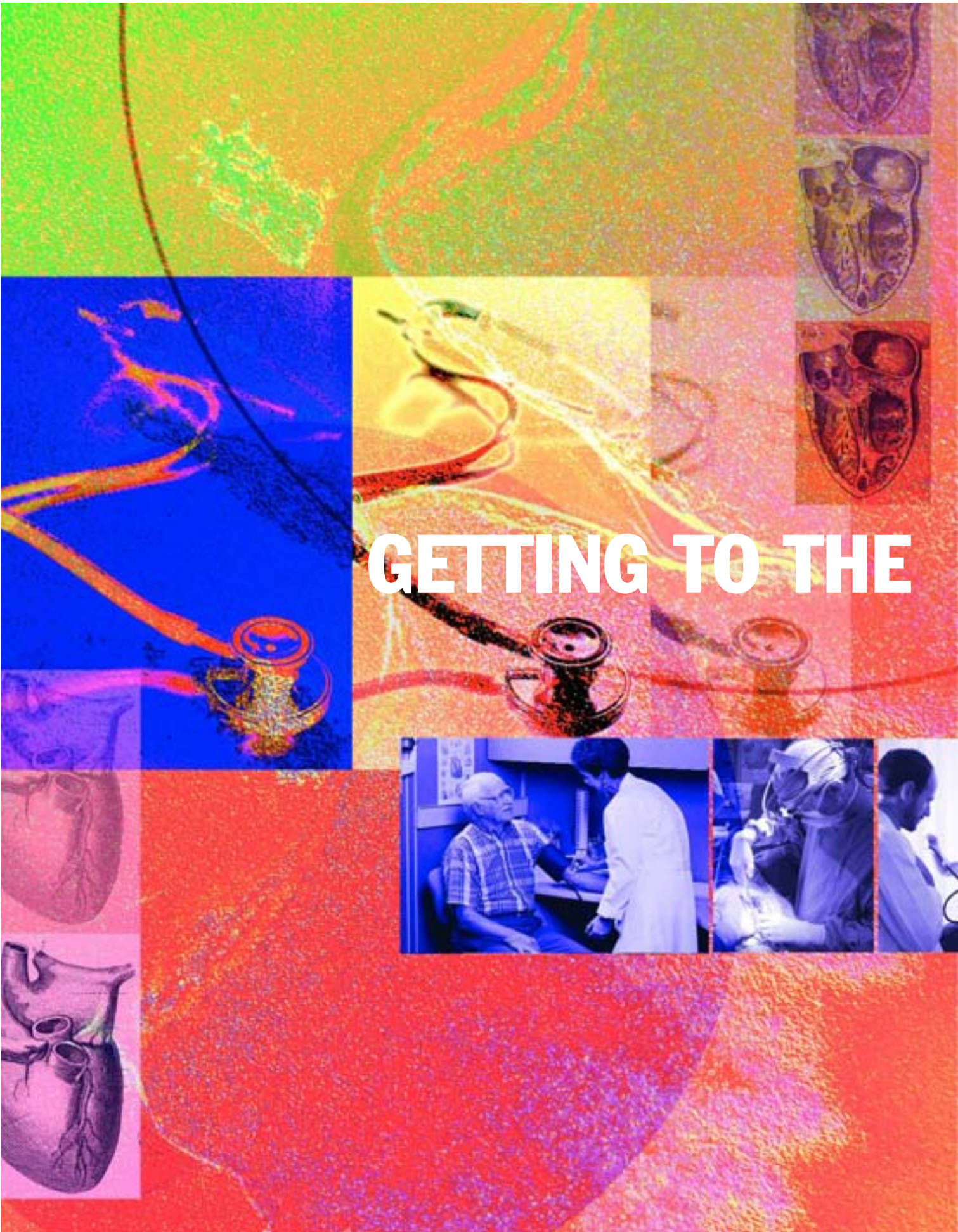


Illustration: Shayne Davidson

**U-M's first-of-its-kind, integrated
Cardiovascular Center amasses
its considerable resources and
aims them squarely at diseases of
the blood vessels and heart**

by Sally Pobjewski
photos by Martin Vloet

HEART OF THE MATTER

Just today alone, nearly 3,000 Americans will die from our nation's deadliest epidemic. This year, it will kill 8 million people worldwide — almost 1 million in the United States and 35,000 in Michigan. Since one in five Americans already has some form of the disease, its next victim could be you or someone you love.

If you think it's cancer, think again. America's No. 1 killer is cardiovascular disease.

Heart attacks, stroke, high blood pressure, heart failure and other diseases of the heart and blood vessels claim more lives in the U.S. each year than cancer and the next four most-common causes of death combined.

The real tragedy, says Kim Eagle, M.D., the Albion Walter Hewlett Professor of Internal Medicine in the U-M Medical School, is that at least half of these deaths could be prevented.

"It's a nationwide problem, but especially serious in Michigan, where we are facing a growing epidemic of cardiovascular disease," Eagle says. "Death rates from coronary heart disease in Michigan are the 7th-highest in the country, and death rates from all forms of cardiovascular disease are the 13th-highest in the country." ➤



“As the state’s major public health care institution, the U-M Health System and physicians from the Medical School have an obligation to work with the public, our patients, their families and other institutions to try to solve Michigan’s and the nation’s No. 1 health problem,” Eagle adds.

Kim Eagle is one of four Medical School physicians who have made a personal commitment of time, talent and energy to fight cardiovascular disease by accepting leadership responsibility for the University of Michigan’s new Cardiovascular Center.

Being built on the site of the former Old Main Hospital, where U-M patients were treated from 1925 until 1986, the \$199-million first phase of new construction for the Cardiovascular Center should be completed early in 2007. But even though a new building won’t be ready for several years, the center’s work has already begun.

As clinical director, Eagle is one of four co-leaders of the Cardiovascular Center. Its scientific director is David J. Pinsky, M.D., the J. Griswold Ruth, M.D., & Margery Hopkins Ruth Professor of Internal Medicine and chief of cardiovascular medicine in the U-M Health System. Richard L. Prager, M.D. (Residencies 1976, 1978), clinical professor of surgery, is director of cardiac surgery. And James C. Stanley (M.D. 1964, Residency 1970), professor of surgery and director of the Conrad Jobst Vascular Research Laboratory, is responsible for vascular surgery.

Working together upon the foundation of years of work by many in the U-M Health System, the four co-leaders are building a network of scientists, physicians and clinical specialists from many disciplines to conduct research, develop new treatments, train the next generation of physicians, and provide integrated clinical care for the entire spectrum of cardiovascular disease.

Departments and divisions participating in the center include Internal Medicine (Cardiovascular Medicine), Surgery (Adult and Pediatric Cardiac Surgery, Vascular Surgery), Radiology (Interventional), Anesthesiology (Adult and Pediatric Cardiac), Neurology (Stroke) and Nursing.

“We are all working together to achieve one common vision,” Pinsky says. “We want to take disciplines that have been spread across the Medical School and the university and bring them together under one roof in an integrated effort to understand cardiovascular disease, discover new cures and apply that knowledge to the treatment of human disease.”

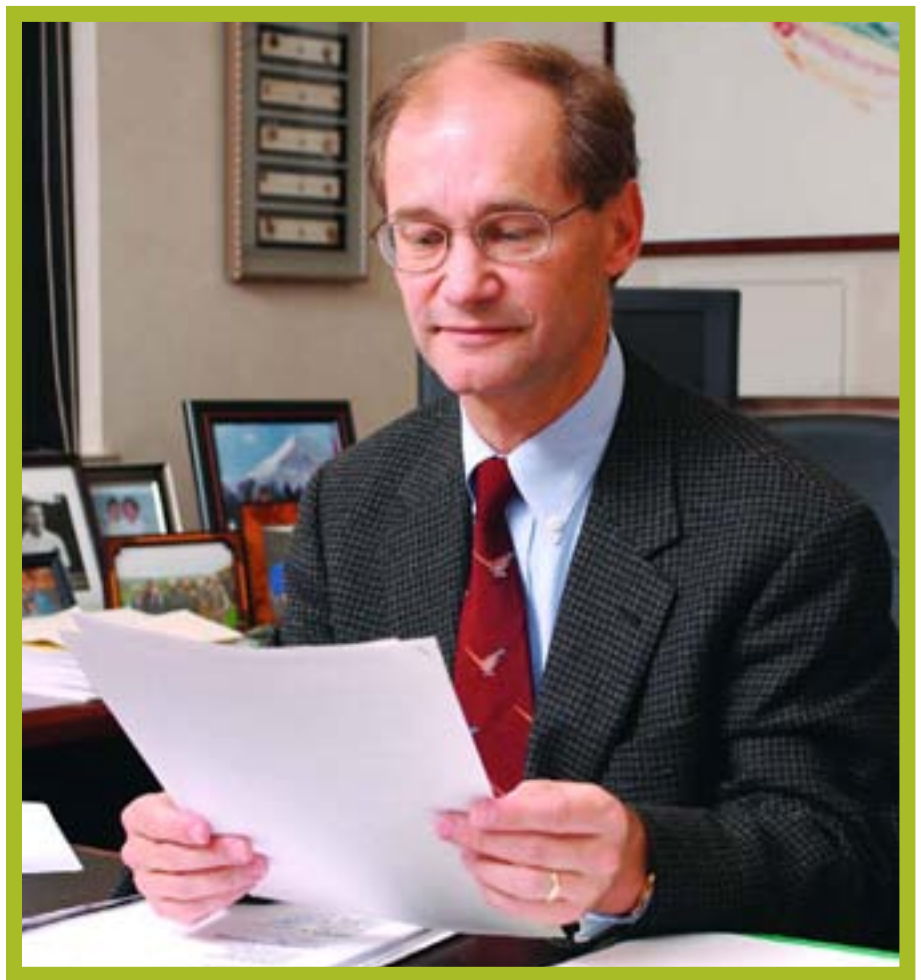
OUR OWN WORST ENEMY

One reason for today’s epidemic of cardiovascular disease is that we tend to take a healthy heart for granted. We assume that little 10-ounce ball of muscle in our chest will just keep beating 100,000 times each day — pumping the equivalent of 4,300 gallons of blood

through our veins and arteries — no matter how we treat it.

We know a healthy heart needs exercise, but most Americans aren’t even close to getting the recommended 30 minutes per day. We know junk food is bad for us, but the number of overweight and obese American adults and children continues to climb.

“In Michigan, we have a major problem with obesity,” Eagle says. “Michigan residents are less likely than people living in other states to exercise regularly. The trend in consumerism toward biggie-sizes of everything from french fries to soda pop is not subtle. It’s killing us and it’s killing our children.” ➤



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Rajendra Mehta, Cecelia Montoye and Kim Eagle

Care that Benefits the Patient Most

“Guidelines Applied in Practice” bring consistency to cardiovascular care based on best outcomes

Kim Eagle is an evangelist for the use of clinical care guidelines in the treatment of cardiovascular disease. Developed by the American College of Cardiology and the American Heart Association, guidelines are based on the latest scientific research linking specific treatments with patient outcomes. The goal is to help physicians select the safest and most effective treatment for their patients with heart disease.

“The evidence shows there are about a dozen things, some as simple as prescribing aspirin, that can have a substantial impact on the quality and outcome of cardiovascular care,” Eagle says. “But in the helter-skelter pace of modern medicine, it’s easy for health care providers to forget or overlook them. If these key priorities are embedded in the clinical care process and if simple reminder systems are provided for the doctor, nurse and patient, it helps everyone do a better job.”

In 1994, Eagle began analyzing the impact of guideline-based care on U-M Health System patients who were recovering from a heart attack. His initial study led to a pilot grant from the American College of Cardiology to expand the project to 10 other hospitals in southeast Michigan. Since then, Eagle and others on his research team have introduced the American College of Cardiology’s “Guidelines Applied in Practice” to hospitals and cardiac care centers throughout Michigan and in Ohio, Montana, West Virginia, Italy and Spain. Eagle works closely with program co-director Cecelia Montoye and Rajendra Mehta, M.D., a clinical assistant professor of internal medicine in cardiology.

A major obstacle to widespread adoption of clinical care guidelines, according to Eagle, is getting physicians to agree on a common set of priorities. “Medicine continues to be a cottage industry,” he says. “State to state, town to town, we see micro-climates of health care influenced by various care providers, institutions, insurers or employers. Getting all that variability to fall into line requires strong physician leadership.”

Eagle is proud of the means his team has developed to make it easier for doctors to use guidelines in treating cardiovascular patients. In the U-M Health System, for example, every medical student and resident receives a summary of the most important guidelines printed on a laminated card that fits inside the pocket of their lab coat. More detailed information is posted on the health system’s Web site where it is available to every physician in all U-M hospitals and health centers. Nurses even review patient charts after discharge and report back to the cardiovascular care team if guidelines aren’t followed.

“The program has improved the quality of care and affected the lives of thousands of patients worldwide,” Eagle says. As the Cardiovascular Center continues to grow, Eagle is looking forward to spreading the word on the importance of guidelines to more physicians.

After all, he says, treating a heart attack patient without clinical care guidelines is like piloting a 747 without using the pre-flight checklist. Maybe you will remember all the different steps involved, but with people’s lives on the line, do you really want to take that chance?

Poison for Patients?

Lethal gas might save lives



*Front: David J. Pinsky, Yasushi Yoshikawa (at microscope), Sunitha Yanamadala
Back: Maksim Fedarau, Koichiro Iwanaga, Hiroaki Hirada, and Elena Filippova*

Carbon monoxide is a gas with a split personality. Every winter, people die in their sleep after breathing carbon monoxide from faulty space heaters or furnaces. It kills by binding to hemoglobin in red blood cells — preventing them from carrying oxygen to cells and tissues in the body.

But scientists have discovered that carbon monoxide also has a life-giving side, according to David Pinsky. In recent research, Pinsky found that inhaling carbon monoxide protected laboratory mice from lethal lung injuries produced when blood flow to one lung was temporarily shut off.

Pinsky doesn't know exactly how breathing carbon monoxide saved his mice from certain death, but he intends to continue his research until he finds out. He believes carbon monoxide inhibits a genetic "master switch," which is activated by lack of oxygen. When this switch is turned on, it triggers a series of pathological changes in blood vessels in the oxygen-deprived organ. The result is inflammation, swelling, excess fluid and the formation of blood clots.

"When blood flow is interrupted, the blood vessels first try to dilate and do other things to promote the flow of blood," Pinsky explains. "But if there's a major obstruction, such as during a heart attack or stroke, and blood doesn't resume flowing quickly, then this master switch is activated. Now the blood vessels change their approach. Instead of trying to get more blood into the affected organ, blood vessels try to isolate it by forming blood clots and calling in immune system scavenger cells. Normally this helps heal injuries, but in this case, it just makes things worse. So you get this spiral — this out-of-control spiral of inflammation and blood coagulation that can kill you."

The body makes proteins and enzymes to dissolve blood clots, but once the cellular death spiral begins, it suppresses production of these healing proteins. When Pinsky's mice inhaled carbon monoxide, it somehow prevented the suppression of clot-dissolving enzymes. With less lung damage, the mice were able to recover, once blood started flowing through both lungs again.

If Cardiovascular Center scientists can discover exactly how carbon monoxide protects against organ damage caused by lack of oxygen, it could lead to new treatments for patients with heart attacks or stroke. Pinsky warns, however, that any clinical use of carbon monoxide would require clinical testing, close medical supervision and careful monitoring, since the difference between a therapeutic dose and a lethal dose could be very small.

Pinsky points out that carbon monoxide would not be the first poisonous gas with life-saving therapeutic benefits. Consider the case of nitric oxide — a corrosive gas and industrial pollutant, which is not the same as nitrous oxide or "laughing gas" used as an anesthetic.

"Just a few years ago, no one would have dreamed of giving nitric oxide to patients," Pinsky says. "But in 1998, three scientists received a Nobel Prize for their discovery that this so-called poison is produced by cells in the body and has important biological functions, including the dilation of blood vessels. Now there are tanks of nitric oxide in virtually every intensive care unit in the country."



This is why preventive cardiology with its emphasis on patient education and motivating people to make heart-healthy choices in diet and lifestyle will be an integral part of the new Cardiovascular Center's program. "If we combine lifestyle changes with cholesterol-lowering drugs called statins, we can quickly lower high cholesterol levels and reduce the patient's immediate risk of a heart attack or stroke," says Eagle.

"The eventual goal is prevention, not therapy," agrees Stanley. "But that's not going to happen, unless we pay attention to the very early stages of the disease, which probably begin in childhood and adolescence."

WHAT CAUSES CARDIOVASCULAR DISEASE?

For a disease that kills nearly one million Americans every year, researchers know surprisingly little about how cardiovascular disease begins. Most of what we know was discovered within the last decade. For example, physicians used to think of atherosclerosis, or blocked arteries, as a simple plumbing problem caused by a build-up of fatty cholesterol called plaque. Now they know that the process is far more complicated.

"Over the last decade, we have learned that the factors contributing to this rapid accumulation of plaque in blood vessel walls are largely inflammatory," Pinsky explains. "Cholesterol is involved, too, but the cells responsible for the growth of plaque in arteries are largely inflammatory cells. It's the same process the body uses to heal an injury, but something goes wrong. As long as the plaque remains stable within the blood vessel wall, it's fine. But if something causes the plaque to rupture, it creates a surface on which blood tends to clot. You can go from a partial blockage to complete closure within a matter of minutes. The result is a heart attack or stroke."

"The blood vessel is an active participant in the process, not just a passive conduit for blood to flow through," Pinsky adds. "Endothelial cells lining the inside of blood vessels orchestrate the immune response and the formation of blood clots. We need more research to understand what changes the endothelial

cells' response from a normal healing, protective mechanism to one that promotes inflammation and clotting."

According to Stanley, inflammation also is responsible for the development of aortic aneurysms — a ballooning or pouched-out area, similar to a hernia, which forms in the walls of major arteries carrying blood from the heart to the kidneys and lower body.

"These inflammatory changes appear to degrade the 'glue' that holds the artery wall together," Stanley says. If the aneurysm becomes large enough and weak enough, it will rupture, causing

massive internal bleeding and often death.

"We are just beginning to understand the process, and much more research will be needed before the bits and pieces come together," Stanley adds. "But it's a very exciting time, because it appears that what we learn about degenerative changes in coronary arteries will be applicable to renal arteries or leg arteries, also. Very few institutions consider the entire vascular tree as one related system. But the bottom line is that cardiovascular disease begins in the blood vessel. If there's trouble in the blood vessel, then the heart will be in trouble, too." ►



"Our success as a cardiovascular center will depend on our ability to bring scientific discoveries into the clinical arena and clinical results back to the laboratory. But no matter how good we are, research pays in ideas rather than dollars. We have a major philanthropic hurdle to overcome, if we are to continue making these advances. Philanthropy will drive the major research breakthroughs in cardiovascular disease in the next decade."

—David Pinsky



Pinsky believes that greater understanding of the genes and molecular processes responsible for inflammatory changes in blood vessels could lead to major advances in clinical care for coronary heart disease and vascular disorders like aortic aneurysms. He is already recruiting new scientists to expand Medical School research into the basic mechanisms behind blood vessel inflammation — one of the Cardiovascular Center's major research priorities.

The genetics of cardiovascular disease is another research priority, according to Pinsky. With the completion of the Human Genome Project, scientists now have coded instructions for all the genes in the human body, but they still know very little about what each gene does and how they interact.

Interactions between multiple mutated genes are responsible for a group of cardiac disorders called cardiomyopathies. People with this condition have an enlarged heart that cannot pump blood efficiently. As the heart continues to enlarge, it gets progressively weaker, until the patient dies from heart failure. Cardiac arrhythmias, or irregular heart beats, also caused by mutated genes, can lead to sudden heart failure and death — often in young people who appear to be in excellent health.

In addition to creating new knowledge about the workings of the heart and vascular system, genetics research has tremendous potential to improve the treatment of cardiovascular disease, especially in the field of pharmacogenetics. Scientists have discovered that people often have slightly different versions of the same genes called polymorphisms. Even variations as small as one unit of DNA can mean big differences in a person's risk of developing cardiovascular disease or their response to medication.

"My job is to bring together a critical mass of people to bridge the gap between basic and clinical science," Pinsky says. "To do that, we need to recruit people on both ends of the research spectrum — from geneticists and cell biologists studying fundamental mechanisms in the laboratory to physician-scientists trained to conduct clinical trials and take discoveries into the clinic.



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"Our success as a cardiovascular center will depend on our ability to bring scientific discoveries into the clinical arena and clinical results back to the laboratory," Pinsky adds. "But no matter how good we are, research pays in ideas rather than dollars. We have a major philanthropic hurdle to overcome, if we are to continue making these advances. Philanthropy will drive the major research breakthroughs in cardiovascular disease in the next decade."

HOW DO YOU HEAL A BROKEN HEART?

For decades, patients have been drawn to the U-M Health System by the reputation and skill of its physicians who pioneered innovative procedures to treat renal vascular hypertension, repair defective heart valves and aneurysms, perform coronary bypass surgery, and treat end-stage heart disease.

When the new Cardiovascular Center building opens in 2007, patients will receive the same superior clinical care they expect from U-M, but in a facility designed to make it more accessible and pleasant for patients and their families. The 350,000-square-foot facility will include operating rooms, patient rooms, clinics, classrooms and clinical laboratories. Specialized services and diagnostic facilities will be together in one place, enabling more patients to receive coordinated care from multidisciplinary teams.

"The new building will be more welcoming, more comfortable, easier to access and much more efficient than our current facilities," says Richard Prager, director of cardiac surgery for the Cardiovascular Center. "We have great people here, caring people, but our clinics and specialists are scattered throughout the health system. It makes it more difficult to provide the level of integrated care our patients need and deserve. ➤

Silent Time Bombs

The ‘public health threat no one knows about’

Sixteen thousand times each year, someone in the U.S. dies suddenly and violently when a bulge in the wall of their aorta — the major artery carrying blood from the heart to the lower half of the body — rips open. Doctors call it a ruptured “triple-A,” for abdominal aortic aneurysm. Eighty percent of these aneurysms occur in men, and the risk increases with age. While only 20 percent of AAAs occur in women, they are more likely to die from a ruptured aneurysm or from complications after surgery.

The good news about aortic aneurysms is that they take years to develop and, if detected before they become too large, can be repaired. The bad news is that there are usually no symptoms or warning signs, and they aren’t easy to detect during a routine physical exam. Aneurysms are most often discovered when they show up on a CAT scan or during an ultrasound exam for an unrelated medical condition.

Gilbert Upchurch, M.D., an assistant professor of surgery in the U-M Medical School, calls ruptured aortic aneurysms the “public health threat no one knows about.” “Only one in five patients with a ruptured AAA will live,” Upchurch says. “Fifty percent of them die before they even make it to a hospital. There is no medical therapy. The only way to treat an aneurysm is to catch it early and perform an elective repair.”

The U-M Cardiovascular Center is a major referral center for repair of aortic aneurysms. Depending on the size and location, the damaged area of the aorta can be repaired with a conventional open abdominal operation or a less invasive endovascular procedure where the physician threads a polyester tube, called a stent-graft, through blood vessels to reinforce the damaged area of the aorta from the inside.

When he’s not in the operating room repairing aneurysms, Upchurch is in the laboratory directing research aimed at finding answers to the many questions about this dangerous condition. One of the biggest mysteries is what causes aortic aneurysms in the first place.

“An aneurysm is an inadequate response to injury,” Upchurch explains. “Something happens to damage elastin fibers in the blood vessel wall and, for some reason, the immune system’s normal healing response doesn’t work. Instead, the immune system increases production of destructive enzymes called metalloproteinases or MMPs. They eat away at smooth muscle cells in the wall of the aorta until it starts to fall apart.”

The constant stress of blood pounding against the bulging arterial wall is a contributing factor, and people with high blood

pressure are at increased risk. Genetics plays a role, too. Aneurysms tend to run in families and, for reasons scientists don’t understand, women are more likely than men to pass on the genetic mutations involved to their children.

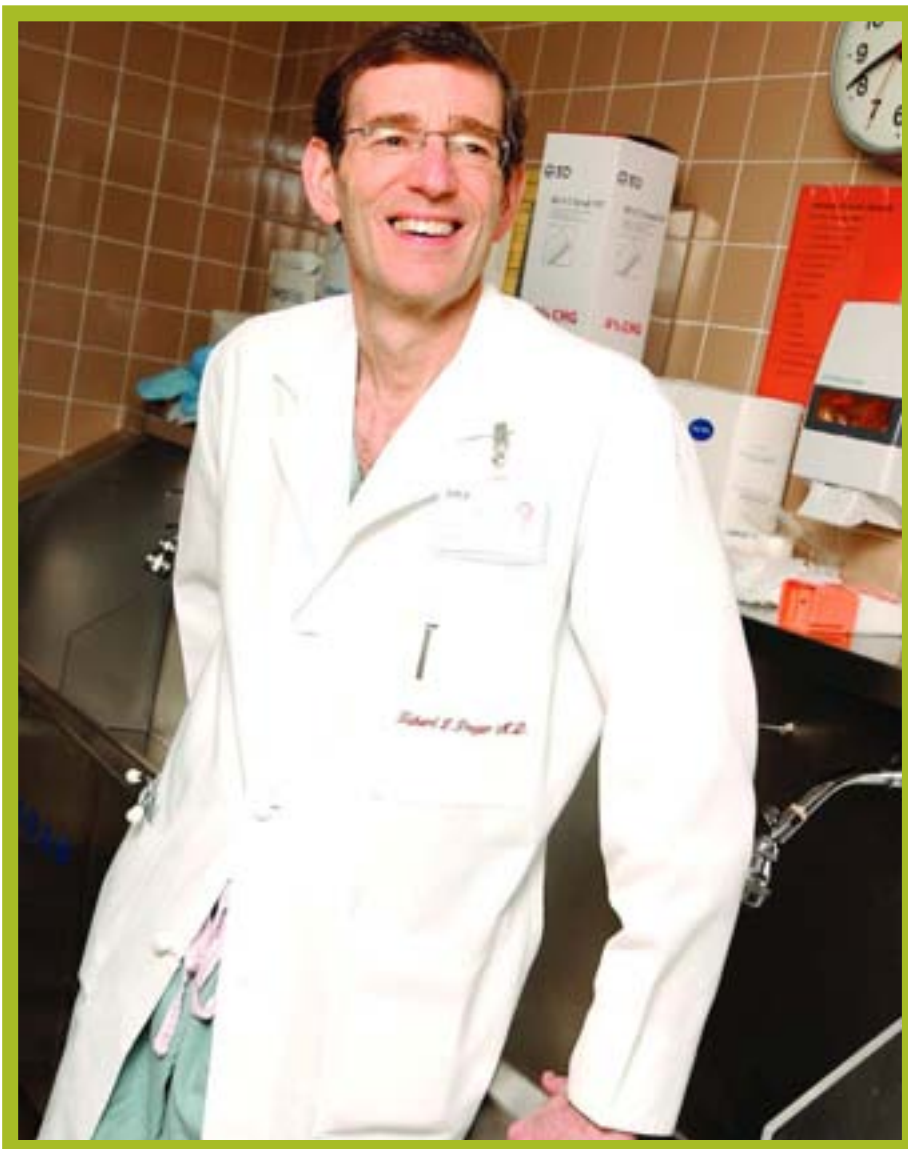
Scientists working in Upchurch’s lab have found an intriguing relationship between a particularly nasty cell-digesting enzyme called MMP-9 and nitric oxide — a molecule produced by cells lining the inside of blood vessels that makes them relax to increase blood flow. In studies with laboratory animals, U-M scientists found that reducing the amount of nitric oxide in the animal’s aorta caused levels of MMP-9 to increase. Giving extra nitric oxide made MMP-9 levels go down and prevented the formation of aneurysms.



Vladimir Grigoryants, Derek Woodrum, Gilbert Upchurch and Kevin Hannawa

“There’s clearly a relationship here, even if we don’t yet completely understand it or know how to translate it to the human condition,” Upchurch says. He is currently testing an antibiotic called doxycycline, which also inhibits MMP-9s, as a potential medical therapy to reduce the growth of aortic aneurysms in humans. In future research, Upchurch also hopes to evaluate use of nitric oxide as a possible treatment.

“If we can find a way to slow the growth of the aneurysm by 50 percent, that could increase the length of time before the aneurysm must be repaired by three to seven years,” Upchurch says.



“What our students and house officers will see is an optimal communications system for diagnosis, decision-making and treatment, facilitated by a structure that makes it easier, and an intellectual commitment to designing and implementing the system that should be second to none.”

—Richard Prager

“Whether you come to the Cardiovascular Center for complex surgery or a simple diagnostic procedure, our goal is to have you feel that we have created this entire culture around you to meet your needs and expectations,” Prager says.

Since educating tomorrow’s doctors is the primary mission of the Medical School, physicians affiliated with the

Cardiovascular Center already are developing programs to teach integrated patient care by exposing medical students and residents specializing in cardiology or cardiac surgery to many different disciplines. Cardiology fellows work as members of the cardiac surgery team caring for patients in the Cardiothoracic ICU. Cardiac surgery residents


learn the latest imaging techniques by working with the cardiac echocardiography team. Specialists in vascular surgery and vascular medicine see patients together in the same clinic.

“Residents and students get excellent training here now, but the Center’s new building will be a model for tomorrow’s medicine,” says Prager. “What our students and house officers will see is an optimal communications system for diagnosis, decision-making and treatment, facilitated by a structure that makes it easier, and an intellectual commitment to designing and implementing the system that should be second-to-none.”

“The traditional silos of surgery, internal medicine, radiology and vascular surgery are artificial,” Eagle says. “It’s all the same disease. The future of medical education will be more of a disease-based approach. The new building and our closer proximity to one another will make it possible to provide more opportunities for interdisciplinary education.”

Today, the site of the new building for the Cardiovascular Center belongs to architects, construction workers, bulldozers and dump trucks. But the center’s leaders are planning for the day in 2007 when the arrival of patients and physicians, staff and students will bring the building to life.

And, today, many of the people whose lives will be saved in the Cardiovascular Center may not even know that they have cardiovascular disease. Some of the scientists, who will spend hours in the center’s laboratories searching for genes that control the ability of blood vessels to expand or contract, are still in college. And the physician who will discover tomorrow’s treatment breakthrough is just beginning her first year of medical school.

All because of the Michigan effort and shared vision a broad team of physicians, researchers, nurses, technicians and administrators, working over a number of years and led now by four dedicated individuals, is taking into reality today. 

Visit the Cardiovascular Center’s Web site at www.med.umich.edu/cvc.

How Does It Pump, and Why Does It Fail?

Scientist and surgeon collaborate to understand the heart's complex biochemistry

Babies fall asleep lulled by its steady rhythm. Doctors monitor it for signs of disease. If you listen carefully in a quiet room, you can hear its reassuring sound, even without a stethoscope. What you can't hear is the complex biochemistry behind the beating of a human heart.

Margaret Westfall, Ph.D., an assistant professor of cardiac surgery in the U-M Cardiovascular Center, is trying to decipher these biochemical signals by studying proteins that modulate the contractions of individual cardiac muscle cells called myocytes. It is the coordinated action of millions of individual myocytes that make it possible for the entire heart muscle to contract and relax in rhythm — allowing it to pump blood through the body.

Basically, myocytes contract when calcium ions are released in the cell and relax when calcium is removed. But there's a lot of complicated biochemistry required to keep all that calcium moving to the right place at the right time. This biochemistry is the focus of intense investigation by scientists.

Westfall focuses on several proteins involved in this process. One of them is called protein kinase C, or PKC for short. "We know there are about 12 variations called PKC isoforms, and that each isoform acts on a different group of proteins within the cell to modulate the heart's pumping action," Westfall says. "Myocytes from healthy hearts contain different isoforms than myocytes from diseased hearts. One of the questions we hope to answer in our research is what is the relationship between specific PKC isoforms and contractile function during the development of cardiac hypertrophy or heart failure?"

Unlike most muscle cells, myocytes can't divide to make new copies. So when the heart has to work harder for long periods of time — as happens with high blood pressure or to compensate for heart attack damage — it can't just make more cells. Instead, existing heart muscle cells grow larger, a condition doctors call hypertrophy. This causes the heart's muscular wall to thicken and the heart to enlarge, which eventually makes the heart less effective at pumping blood. Over time, heart muscle dies, scar tissue forms, and the heart gets weaker. The result is progressive heart failure, a condition that affects almost 5 million Americans."

"One problem for many people in heart failure is that it takes too long for myocytes to relax," Westfall explains. "Stiffness increases as the heart progresses into failure, and results in an impaired ability of the heart to relax completely with each beat. We don't understand all the components of the diastolic or relaxation phase yet, but we believe it is modulated by PKC."

To obtain the human myocytes she needs for her research, Westfall works closely with Sharlene Day, M.D. (Residency



Frank Pagani, Margaret Westfall and Sharlene Day

1998), a lecturer in cardiology, and Francis Pagani, M.D. (Residency 1996), Ph.D., an associate professor of surgery who leads the U-M's Heart Transplant Program. Pagani treats some advanced stage heart failure patients by surgically implanting a heart-assist pump, which takes pressure off the deteriorating heart muscle and partially restores heart function. To implant the pump, Pagani must remove a nickel-sized plug of heart tissue. Westfall and Day study myocytes from this tissue, or from the patient's own diseased heart after the patient receives a heart transplant.

"As a scientist, the advantage of collaborating with surgeons is that it lets us compare PKC isoforms in myocytes from the same patient before and after the heart-assist pump is implanted," Westfall says. The long-term goal of Westfall's research is to develop gene transfer technology capable of delivering genes and proteins to restore normal function in failing myocytes.

"A unique feature of the new Cardiovascular Center is that it will bring scientists and surgeons together in one facility making it easier for them to develop more collaborative research studies between researcher and clinician," says Richard Prager, who directs adult cardiac surgery at the U-M Cardiovascular Center. "Collaborations like this are especially important, because they help translate scientific discoveries in the laboratory into new treatments and therapies for people with cardiovascular disease."