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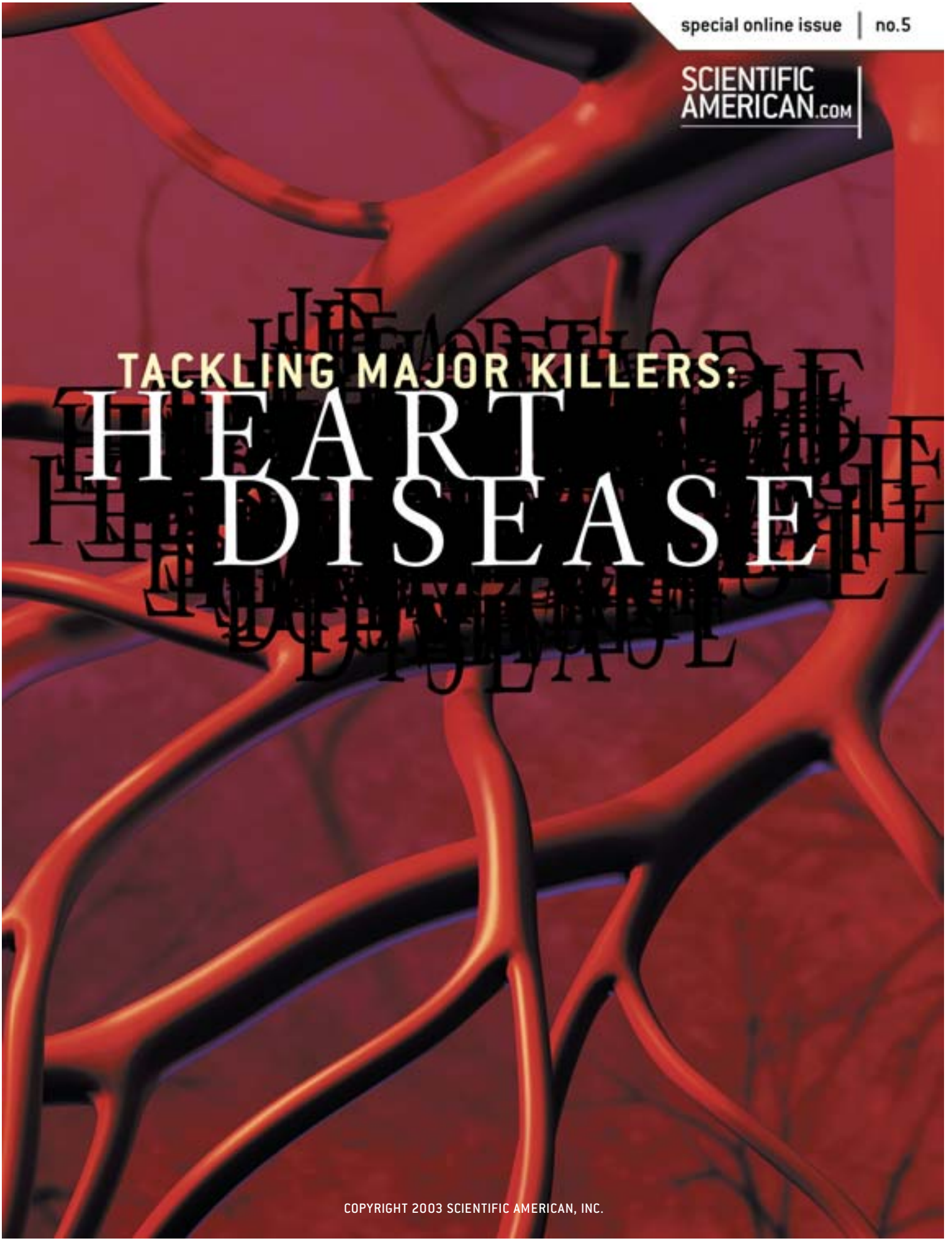

TACKLING MAJOR KILLERS:

HEART DISEASE

How are your New Year's resolutions holding up? Make sure that cutting back on your drinking, quitting smoking and getting more exercise top the list. Such lifestyle changes go a long way towards warding off heart disease, one of the leading causes of death among adults around the world. In the meantime, medical researchers continue to gain more insight into what directly causes heart disease—discoveries that are helping them develop more effective treatments.

In this special online issue, Peter Libby explains the latest ideas about how blood vessels deteriorate in the case of atherosclerosis, and Rakesh K. Jain and Peter F. Carmeliet describe how, by manipulating angiogenesis, or the formation of new blood vessels, researchers may find drugs to treat the condition. Alternatively, other authors explore the history of defibrillation; operations to treat cardiac arrhythmias; new procedures for coronary bypass surgery; and, when all other interventions have failed, the use of artificial hearts.—*the Editors*

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A YEAR AFTER DOCTORS BEGAN IMPLANTING THE ABIOCOR IN DYING PATIENTS, THE PROSPECTS OF THE DEVICE ARE UNCERTAIN

The Trials of an Artificial HEART

By Steve Ditlea

The permanent replacement of a failing human heart with an implanted mechanical device has long been one of medicine's most elusive goals. Last year this quest entered a crucial new phase as doctors at several U.S. hospitals began the initial clinical trials of a grapefruit-size plastic-and-titanium machine called the AbioCor. Developed by Abiomed, a company based in Danvers, Mass., the AbioCor is the first replacement heart to be completely enclosed within a patient's body. Earlier devices such as the Jarvik-7, which gained worldwide notoriety in the 1980s, awkwardly tethered patients to an air compressor. In contrast, the AbioCor does not require tubes or wires piercing the skin. In July 2001 Robert L. Tools, a 59-year-old former Marine whose heart had become too weak to pump effectively, became the first recipient of this artificial heart.

Over the next nine months, surgeons replaced the failing hearts of six more patients with the AbioCor. But the initial trials have had mixed results. As of press time, five of the seven patients had died: two within a day of the implantation procedure, one within two months, and two within five months. (Tools died last November.) One of the two survivors has lived for more than eight months with the device, the other for more than six months. Because all the patients were seriously ill to begin with—only people deemed likely to die within a month were eligible for implantation—Abiomed officials argue that the artificial heart is proving its worth. The company has acknowledged, however, that a flaw in the device's attachments to the body might have led to the formation of the blood clots that caused strokes in three of the patients.

With the clinical trials only a year old, it is obviously too early to say whether the AbioCor will be a breakthrough or a disappointment. If the U.S. Food and Drug Administration decides that the device shows promise, it may allow Abiomed to implant its artificial heart in patients who are not as severely ill as those in the initial group. Company officials hope that eventually the rate of survival after implantation will surpass the rate after heart transplants (about 75 percent of the recipients of donor hearts are still alive five years after the transplant). Fewer than 2,500 donor hearts become available every year in the U.S., whereas more than 4,000 Americans are on waiting lists for transplants; for many of those patients, AbioCor could be a lifesaver.

But the artificial heart is competing against less radical treatments, one of which has already proved quite successful. Doctors have been able to restore adequate cardiac function in thousands of patients by attaching a pump to the left ventricle, the chamber most likely to fail. These ventricular-assist devices were originally intended as a short-term therapy for people awaiting transplants, but recent studies show that the pumps can keep patients alive for two years or more. Meanwhile other studies have overturned generations of medical wisdom by suggesting that the human heart can repair itself by generating new muscle tissue. Researchers are now racing to de-

velop therapies using stem cells that could help the heart heal.

Heart History

THE ORIGINS of the artificial heart go back half a century. In 1957 Willem J. Kolff (inventor of the dialysis machine) and Tetsuzo Akutsu of the Cleveland Clinic replaced the heart of a dog with a polyvinyl chloride device driven by an air pump. The animal survived for 90 minutes. Seven years later President Lyndon B. Johnson established an artificial-heart program at the National Institutes of Health. In 1969 Denton A. Cooley of the Texas Heart Institute in Houston implanted an artificial heart into a person for the first time, but only as an emergency measure. The device was intended as a bridge to transplant—it kept the patient alive for 64 hours until a human heart could be found for him. (The patient received the transplant but died two and a half days later.) The next artificial-heart implant was not attempted until 1981. The patient lived for 55 hours with the bridge-to-transplant device before receiving a human heart.

Then came the most publicized clinical trials in modern medicine: cardiac surgeon William DeVries's four permanent implants of the Jarvik-7 artificial heart. When DeVries performed the first cardiac replacement in 1982 at the University of Utah Medical Center, patient Barney B. Clark became an instant celebrity. His medical status was reported almost daily. Reporters tried to sneak into the intensive care unit in laundry baskets or disguised as physicians. By the time Clark died 112 days later—from multiple organ failure after suffering numerous infections—the media had provided a detailed chronicle of the medical problems and discomfort he had experienced.

Nearly two years later DeVries performed his next Jarvik-7 implant, this time at Norton Audubon Hospital in Louisville, Ky., on patient William Schroeder. Schroeder survived on the

Overview/*AbioCor Heart*

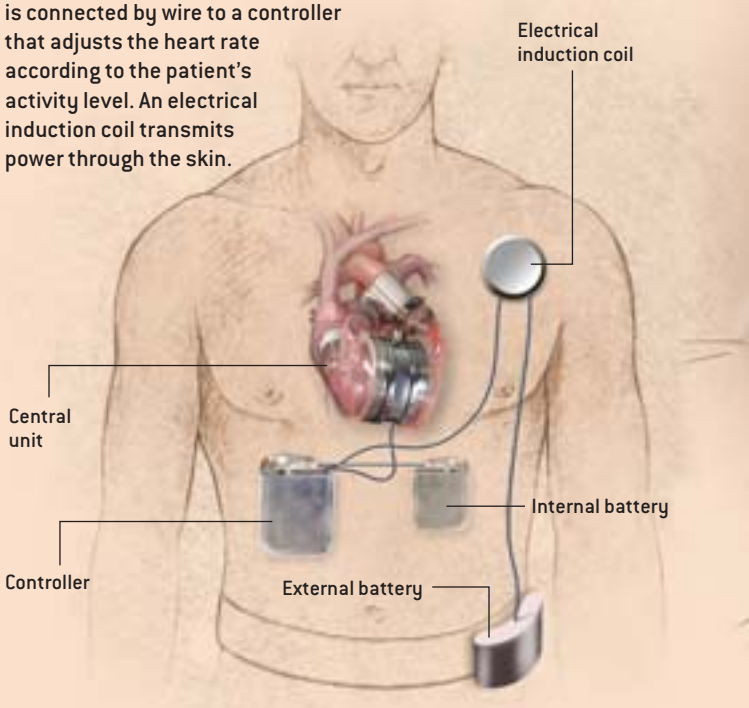
- The goal of implanting a permanent mechanical substitute for a failing human heart was all but abandoned after controversial attempts in the 1980s. The clinical trials of the AbioCor, a new artificial heart designed to be completely enclosed in a patient's body, began in July 2001.
- The trials have had mixed results so far. Of the seven severely ill patients who received the AbioCor, two died within a day of the implantation, one within two months, and two within five months. Although the artificial heart did not cause infections, three patients suffered strokes
.
- If the survival rate of the AbioCor improves, it could eventually become an alternative for people on the long waiting lists for heart transplants. But the device may have to compete with less radical treatments such as ventricular-assist devices and therapies using stem cells.

LIKE A HUMAN HEART, the AbioCor has chambers for pumping blood on its left and right sides. Oxygenated blood from the lungs flows into and out of the left chamber, and oxygen-depleted blood from the body flows into and out of the right chamber. Between the chambers is the mechanical equivalent of the heart's walls: a hermetically sealed mechanism that generates the pumping motions.

At the center of this mechanism, an electric motor turns a miniaturized centrifugal pump at 5,000 to 9,000 rotations a minute. The pump propels a viscous hydraulic fluid; a second electric motor turns a gating valve that allows the fluid to alternately fill and empty from the two outer sections of the pumping mechanism. As fluid fills the left section, its plastic membrane bulges outward, pushing blood out of the AbioCor's left chamber. At the same time, hydraulic fluid empties from the right section and its membrane deflates, allowing blood to flow into the device's right chamber.

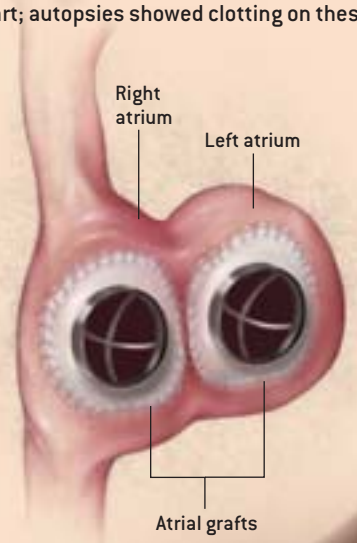
The AbioCor's four valves are made of plastic and configured like natural heart valves. The inflow conduits are connected to the left and right atria of the excised heart, and the outflow conduits are fitted to the arteries. The device weighs about one kilogram and consumes about 20 watts of power. The internal battery, electrical induction coil and controller module add another kilogram to the implanted system. Lithium-ion batteries worn on the patient's belt continuously recharge the internal battery using the induction coil. A bedside console can also be used as a power source and monitoring system. —*S.D.*

THE CENTRAL UNIT of the AbioCor is connected by wire to a controller that adjusts the heart rate according to the patient's activity level. An electrical induction coil transmits power through the skin.



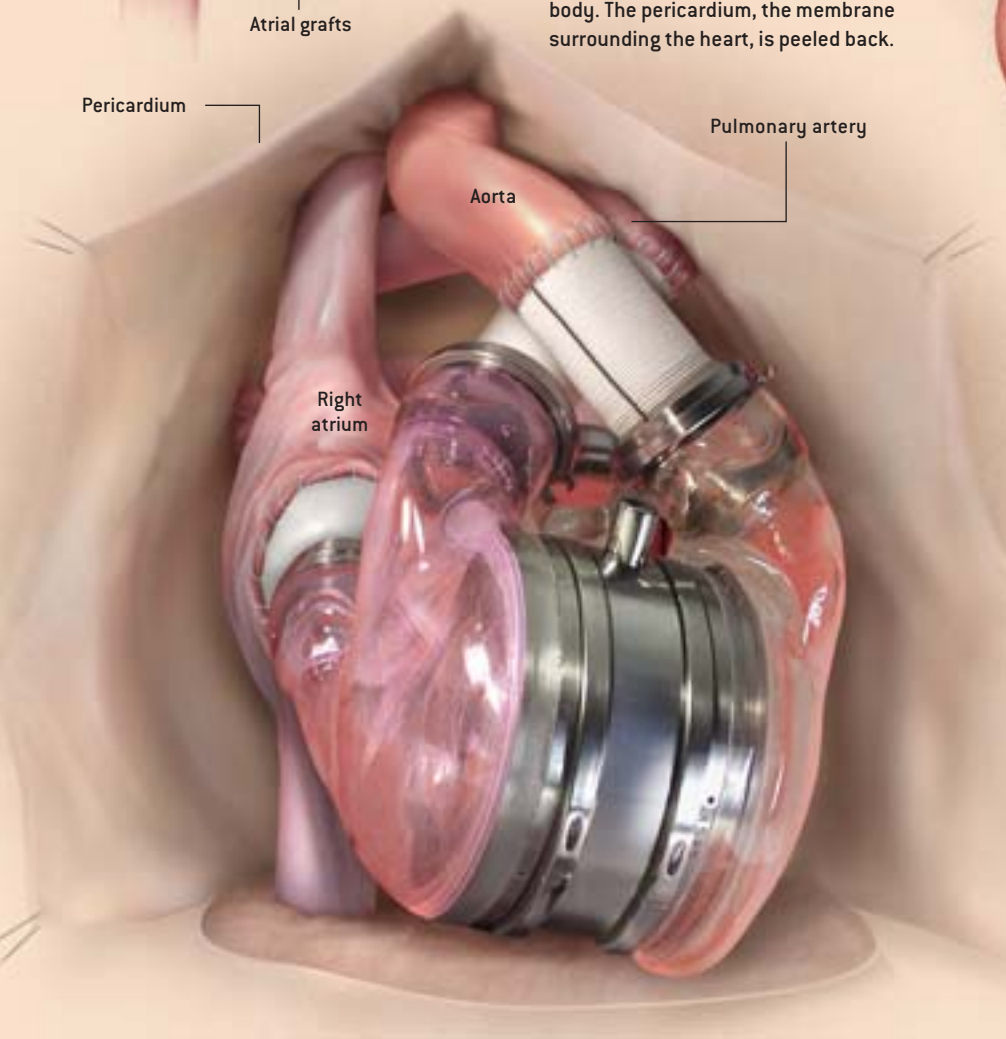
HOW THE ABIOCOR WORKS

THE ABIOCOR is attached to the remnants of the right and left atria of the patient's excised heart. The grafts used in the first six patients had plastic struts designed to keep the atrial walls apart; autopsies showed clotting on these struts.

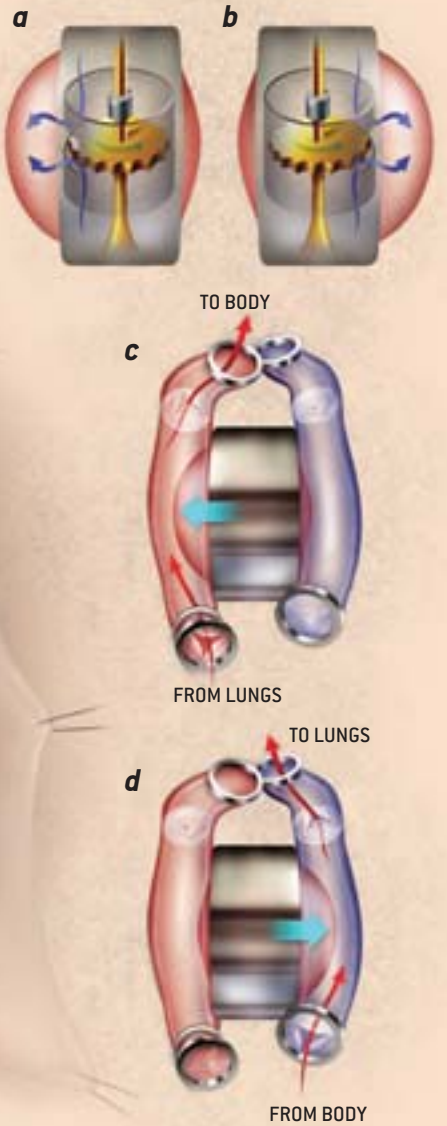


DETAIL OF ATRIAL GRAFT

IN THIS ARTIST'S rendering, the AbioCor is shown after implantation in the patient's body. The pericardium, the membrane surrounding the heart, is peeled back.



THE ABIOCOR'S pumping mechanism mimics the beating of a human heart by propelling hydraulic fluid back and forth. (The diagrams below show the device from the rear perspective.) A centrifugal pump turns continuously in one direction while a gating valve alternately shunts the hydraulic fluid to the left and right (*a* and *b*). When the fluid flows to the left, it pushes a plastic membrane into the AbioCor's left chamber, pumping oxygenated blood to the body (*c*). When the fluid flows to the right, it pushes a membrane into the right chamber, pumping oxygen-depleted blood toward the lungs (*d*).



KEITH KASNOT

ETHICS OF THE HEART

The AbioCor trials revive some troubling questions

DURING THE CLINICAL TRIALS of the Jarvik-7 artificial heart, medical ethicists voiced concern about the suffering of the patients and the intense media coverage that descended on them. Now those issues have surfaced anew with the human testing of the AbioCor. So far ethicists give mixed grades to Abiomed (the maker of the device), the doctors and the press.

"The core ethical issues for the patient remain the same," says Arthur Caplan, director of the Center for Bioethics at the University of Pennsylvania School of Medicine. "First, can you get truly informed consent from a desperate, dying person? Dying is extremely coercive. There's very little you can't get a dying person to consent to." In Abiomed's favor, he rates the firm's 13-page consent form as "very strong" in terms of disclosing risks, and he commends the company's funding of independent patient advocates to inform patients and their families. But Caplan wonders whether the right patients are enrolled in the trials: "I've argued that for some treatments it doesn't make sense to test first in the most severely ill, because you have an impossible time sorting out what's caused by the illness and what's caused by the device."

George J. Annas, a professor at the Boston University School of Public Health, contends that the consent procedure for the AbioCor "should be much more detailed about how you're going to die. No one's going to live for a long time on one of these. You have to plan for death. How is it going happen? Who's going to make the decision and under what circumstances?" In two cases during the clinical trials, family members agreed to shut off the AbioCor's power, overriding its alarms, so a terminally failing patient could die.

Another source of controversy has been Abiomed's policy of limiting the release of information from the trials. For example, company officials will not announce a patient's identity until 30 days after an implantation (leaks at the hospital, however, have sometimes forced them to do so sooner). Although the policy has prevented a repeat of the media frenzy surrounding the Jarvik-7 trials, some ethicists have emphasized the need for full disclosure of the medical problems encountered during the human testing. Renee Fox, a social sciences professor at the University of Pennsylvania, notes that Abiomed's reporting of negative developments has been timely, for the most part. But, she adds, "there has been a tendency by the company and the physicians to interpret adverse events as not due to the implanted heart. In each case there has been an attempt to say that this is due to the underlying disease state of the patient rather than any harm that the device may have done."

Ethicists point out that journalists have erred, too, by writing overoptimistic stories about the AbioCor. It was a hopeful cover story in Newsweek that convinced Robert L. Tools to volunteer for the first implant. Says Ronald Munson, a professor of philosophy of science and medicine at the University of Missouri at St. Louis, "The press shouldn't evangelize a medical procedure." —S.D.

artificial heart for 620 days, the longest of anyone to date, but it took a tremendous toll on him: strokes, infections, fever and a year of being fed through a tube. The third Jarvik-7 recipient lived for 488 days, and the fourth died after just 10 days. Although several hospitals successfully used a slightly smaller version of the Jarvik-7 as a bridge-to-transplant device for hundreds of patients, most medical professionals abandoned the idea of a permanent artificial heart.

But an engineer named David Lederman believed that the concept still held promise. Lederman had worked on developing an artificial heart at the medical research subsidiary of Avco, an aerospace company, and in 1981 he founded Abiomed. He and his colleagues closely followed the clinical trials of the Jarvik-7 and considered ways to improve it. The external air compressor that powered the device was bulky and noisy. Infectious bacteria could easily lodge where the tubing pierced the patient's skin. And inside the heart itself were surface discontinuities where platelets and white blood cells could coagulate into a thrombus, a solid clot that could circulate in the blood and lodge in the brain, causing a stroke.

In 1988 the National Heart, Lung and Blood Institute at the NIH decided to cut off support for replacement-heart research and instead channel funds to ventricular-assist pumps. Lederman went to Washington along with representatives from other research teams to lobby against the change. They convinced a group of senators from their home states to help restore NIH support, resuscitating research programs at two universities (Utah and Pennsylvania State) and two companies (Nimbus in Rancho Cordova, Calif., and Abiomed). Today Abiomed is the last artificial-heart developer left from that group. The company has received nearly $20 million in federal research grants. Its government funding ended in 2000, but that same year Abiomed raised $96 million in a stock offering.

Lederman and his colleagues are doggedly pursuing a medical technology whose time others believe may have already come and gone. In the conference room at Abiomed's headquarters in an office park north of Boston, Lederman attributes his firm's tenacity to its team of researchers: "No one else had the commitment to say there is no alternative to success. This is important stuff. I take pride in the fact that we took it so seriously." It is also evident that for Lederman this is a personal matter: in 1980 his father died suddenly of a heart attack.

Designing AbioCor

THE ABIOCOR is not powered by an air compressor as the Jarvik-7 was. Hidden behind the device's central band of metal is the heart of this heart: a pair of electric motors driving a pump-and-valve system. This pumping mechanism propels hydraulic fluid back and forth, causing a pair of plastic membranes to beat like the inner walls of a human heart [*see box on pages 3 and 4*].

But this innovation was only the start. To be truly self-contained, the device needed a small, implantable controller that

could vary the heart rate to match the patient's activity level. The controller developed by Abiomed is the size of a small paperback; implanted in the patient's abdomen, it is connected to the artificial heart by wire. Sensors inside the heart measure the pressure of the blood filling the right chamber—the blood returning to the heart from the body—and the controller adjusts the heart rate accordingly. The rate can range from 80 to 150 beats a minute. If the clinical trials show that this control system is adequate, it could be shrunk down to a single microchip that would fit on the AbioCor's central unit.

Abiomed also developed a way to power the artificial heart's motors without the use of skin-penetrating wires, which can leave the patient prone to infections. An internal battery implanted in the patient's abdomen can hold enough charge to sustain the heart for 20 minutes. This battery is continuously recharged through electromagnetic induction—the same process used in electric toothbrushes. The internal battery is wired to a passive electrical transfer coil under the patient's skin. Another coil outside the patient's skin, wired to an external battery, transmits power through the skin tissue with minimal radiation and heat. The patient can wear the external battery on a belt, along with a separate monitor that alerts the patient if the battery's charge runs low.

A major concern was to design the AbioCor so that it could pump blood without creating clots. When Lederman had worked for Avco, he had conducted four years of research on the interaction between blood and synthetic materials, studying the reaction rates of various coagulation processes. Essentially the AbioCor minimizes clotting by making sure that the blood cells do not have time to stick together. Blood flows swiftly through the device, and there are no areas where pooling can occur. All the surfaces of the device that are in contact with blood are made of Angioflex, a biologically inert polyurethane plastic. The contact surfaces are also extremely smooth because clots can form on irregular surfaces. Says Lederman, "We had to make a system that was totally seamless."

Trial and Error

AFTER TESTING its artificial heart in calves and pigs, Abiomed received permission from the FDA in January 2001 to begin clinical trials in humans. The FDA would determine the success of the trials by reviewing the patients' survival rates and quality of life, as measured by standard assessment tests. Only patients who were ineligible for a heart transplant could volunteer for the implantation. The size of the AbioCor also ruled out certain patients: the device can fit inside the chests of only half of adult men and 18 percent of adult women. (Abiomed is developing a smaller, second-generation heart that would fit most men and women.) For each procedure, Abiomed agreed to pay for the device and its support. Hospitals and doctors participating in the trials would donate facilities and care. The total cost of each implantation and subsequent treatment: more than $1 million.

On July 2, 2001, the first AbioCor was implanted in Robert L. Tools at Jewish Hospital in Louisville, Ky., by surgeons Laman A. Gray, Jr., and Robert D. Dowling in a seven-hour operation. Tools had been suffering from diabetes and kidney failure as well as congestive heart failure. Before the heart replacement, he could barely raise his head. After the procedure, Tools experienced internal bleeding and lung problems, but within two months his kidney function had returned to normal and he had enough strength to be taken on occasional outings from the hospital. His doctors hoped he would be able to go home by Christmas. Tools's bleeding problems persisted, however, making it difficult for doctors to administer the anticoagulant drugs intended to prevent clot formation. On November 11 he suffered a severe stroke that paralyzed the right side of his body. He died 19 days later from complications following gastrointestinal bleeding.

The second recipient of the AbioCor, a 71-year-old retired businessman named Tom Christerson, has fared much better so far. Surgeons at Jewish Hospital implanted the device in Christerson on September 13, 2001. After a steady recovery, he left the hospital in March to take up residence in a nearby hotel, where he and his family could learn how to tend to the artificial heart on their own. The next month he returned to his home in Central City, Ky. In the following weeks, Christerson continued his physical therapy and visited Jewish Hospital for weekly checkups. His car was wired so that he could use it as a power source for his artificial heart.

At the Texas Heart Institute, O. H. "Bud" Frazier—the surgeon who has the record for performing the most heart transplants—implanted the AbioCor into two patients. One lived with the device for more than four months before dying of complications from a stroke; the other died within a day of the implantation, succumbing to uncontrolled bleeding after spending 20 hours on the operating table. Implantations have also been performed at the University of California at Los Angeles Medical Center and Hahnemann University Hospital in Philadelphia. The Los Angeles patient lived for a little less than two months before heart support was withdrawn following multiple organ failure. The Philadelphia patient, 51-year-old James Quinn, received the AbioCor on November 5, 2001. Although he suffered a mild stroke in December, the next month he was discharged from the hospital to a nearby hotel. This past February, however, he was readmitted to the hospital with breathing difficulties. Doctors treated him for pneumonia, which became life-threatening because his lungs were already weakened by chronic emphysema and pulmonary hypertension. Quinn was placed on a ventilator to help him breathe, but his recovery was slow. By mid-May, though, his condition was improving, and doctors began to wean him from the ventilator.

In January, Abiomed reported preliminary findings from the clinical trials at a press conference. Lederman noted that the artificial heart had continued to function under conditions that could have damaged or destroyed a natural heart, such as a severe lack of oxygen in the blood and a fever of 107 degrees Fahrenheit. Also, no patient had suffered an infection related to the device. But Abiomed acknowledged a design flaw in the artificial heart's connections to the body. The AbioCor is attached to remnants of the atria of the patient's excised heart; autopsies on two patients had shown clotting on the plastic struts

HEART HELPERS

Ventricular-assist devices emerge as an alternative to heart replacement

IN NOVEMBER 2001, soon after human testing of the AbioCor began, researchers reported that another clinical trial had demonstrated the benefits of a less drastic treatment for heart failure. The left ventricular assist device (LVAD)—a pump implanted in the chest or abdomen and attached to the heart's left ventricle, the chamber that pumps oxygenated blood to the body—had been developed as a short-term therapy for patients awaiting heart transplants. But the trial showed that LVADs can keep patients alive for two years or more, and the Food and Drug Administration is expected to approve the devices for long-term use.

The study evaluated 68 patients with implants of the HeartMate, the most widely used LVAD, and 61 patients who received medical therapy, including potent cardiac drugs. After a year, more than half of those with LVADs were still alive, compared with only one quarter of those on medical therapy. At two years, the survival rates were 23 percent for the LVAD group and 8 percent for the medical group. The longest stint on the HeartMate is now more than three years; the longest survivor of the medical group died after 798 days. "There are still 21 patients ongoing with the devices," notes Eric Rose, surgeon in chief at Columbia Presbyterian Medical Center in New York City and principal investigator for the trial. "This sets a new benchmark for treating the disease."

The HeartMate, made by Thoratec in Pleasanton, Calif., is far from perfect. Many of the implanted test subjects suffered serious infections because the device is connected to an external battery by a skin-piercing tube. Other HeartMate patients died from mechanical malfunctions such as motor failure. But Thoratec has already improved on the current version of the device and is developing second- and third-generation systems designed to last eight and 15 years, respectively.

Another LVAD, called the LionHeart, made by Arrow International in Reading, Pa., is a fully implantable system with no skin-piercing tubes or wires. Now in clinical trials, the LionHeart uses an electrical induction coil like the AbioCor's to transmit power through the skin. The MicroMed DeBakey VAD is also fully implantable, but it propels blood in a steady flow rather than pumping it like a natural heart. Proponents of this technology tout its efficiency and reliability; critics argue that a pulsating heartbeat is needed to keep blood vessels clear. Cardiac pioneer Michael E. DeBakey, who performed the first successful coronary bypass in 1964, developed the device in collaboration with one of his patients, David Saucier, a NASA engineer who had had heart transplant surgery.

Robert K. Jarvik, inventor of the Jarvik-7 artificial heart and now CEO of New York City–based Jarvik Heart, has introduced the Jarvik 2000, the only assist device small enough to be lodged inside the left ventricle. Like the DeBakey VAD, the Jarvik 2000 pumps blood in a steady flow. The device is currently in trials for bridge-to-transplant use and has been implanted in some patients for long-term use as well. Jarvik believes the device could help a less severely damaged heart to repair itself, perhaps in combination with stem cell treatments. Another potential combination therapy might be the use of LVADs with the steroid clenbuterol to strengthen the heart. In a test reported last year, Magdi Yacoub of Harefield Hospital in London administered clenbuterol to 17 patients with implanted LVADs. In five of the patients, the hearts recovered enough to allow the removal of the LVADs. —S.D.

of thimble-size "cages" that were intended to maintain the separation of the remaining atrial walls [*see illustration on page 4*]. Because these clots could cause strokes, Abiomed declared that it would no longer use the plastic cages when implanting the AbioCor. The cages were needed to test the device in calves but are unnecessary in humans.

In early April, Abiomed announced that it would not be able to meet its original schedule of implanting the AbioCor in 15 volunteers by the end of June. The company said that it wanted to devote further study to its first six cases. But a week later doctors at Louisville's Jewish Hospital performed another implantation, the first using an AbioCor without the plastic cages. The artificial heart functioned properly, but the 61-year-old patient died within hours of the procedure after a clot lodged in his lungs. According to Laman Gray, who performed the operation with colleague Robert Dowling, the clot did not originate in the AbioCor.

The surgeons who have worked with the AbioCor remain convinced of the device's potential, despite the recent setbacks. Frazier of the Texas Heart Institute believes the formation of clots in the AbioCor's plastic cages was a complication that could not have been anticipated. "Fortunately, this one can be corrected," he says. "It's not something inherently wrong in the device." Gray concurs: "In my opinion, it's very well designed and is not thrombogenic at all. The problem has been on the inflow cage. I'm truly amazed at how well it has done in initial clinical trials." (Both surgeons consulted on the AbioCor's design and were responsible for much of its testing in animals.)

But not everyone is as sanguine as Frazier and Gray. "Total heart replacement by mechanical devices raises a number of questions that have not been addressed in this small group of patients," says Claude Lenfant, director of the National Heart, Lung and Blood Institute. "What quality of life can a total-heart-replacement patient expect? Will there be meaningful clinical benefits to the patient? Is the cost of this therapy acceptable to society?" And Robert K. Jarvik, the developer of the Jarvik-7 device that made headlines 20 years ago, now argues that permanent artificial hearts are too risky. "Cutting out the heart is practically never a good idea," he says. "It was not known in 1982 that a heart can improve a lot if you support it in certain very common disease states. That's why you should cut out the heart only in the most extreme situations."

As the abiocor trials continue, the most crucial objective will be reducing the incidence of strokes. Doctors had originally hoped

to guard against this risk by prescribing low levels of anticoagulant drugs, but some of the test subjects were so severely ill that they could not tolerate even these dosages. Because these patients had medical conditions that made them susceptible to internal bleeding, determining the best dosage of anticoagulants became a delicate balancing act: giving too much might cause the patient to bleed to death, and giving too little might cause a stroke.

Heart of the Matter

DESPITE THE NEED for more refinement, Lederman is satisfied with the clinical results to date. The initial goal of the trials was to show that AbioCor could keep the patients alive for at least 60 days, and four of them surpassed that mark. Says Lederman, "If most of the next patients go the way the first ones have gone but without unacceptable complications such as strokes, we plan to ask the FDA to authorize clinical use of the system for patients who are on their last breath. We think we have a convincing argument that we can give patients with less than 30 days to live many months of quality life." But some medical ethicists have questioned this approach, saying that people at death's door might consent to any procedure, no matter what the consequences [*see box on page 5*].

And then there is the issue of how to define an acceptable quality of life. In 1981 Jarvik wrote that for the artificial heart to achieve its goal "it must be forgettable"—that is, the device should be so unobtrusive and reliable that patients would be able to ignore it [see "The Total Artificial Heart," by Robert K. Jarvik; SCIENTIFIC AMERICAN, January 1981]. Does the AbioCor meet that standard? Tools's wife, Carol, says that her husband was aware that his old heartbeat had been replaced by the AbioCor's low, steady whir. "Sometimes he'd lie there, and he would listen to it," she says. "But other times he would forget it.... [He] always knew it was there, because he still had to power it. It's not like replacing a hip." Still, she believes that the quality of life during his last months was good: "He had a chance to live quite well, although unfortunately, it was shorter than we would have liked." She adds, "He never had any regrets about it." SA

Steve Ditlea is a freelance journalist based in Spuyten Duyvil, N.Y. He has been covering technology since 1978.

MORE TO EXPLORE

More information about Abiomed, the manufacturer of the AbioCor, is available at **www.abiomed.com**

The Web site of the Implantable Artificial Heart Project at Jewish Hospital in Louisville, Ky., is **www.heartpioneers.com**

The Texas Heart Institute in Houston: **www.tmc.edu/thi**

The National Heart, Lung and Blood Institute at the National Institutes of Health: **www.nhlbi.nih.gov/index.htm**

MENDING BROKEN HEARTS

Stem cells may prove to be the best medicine for injured hearts

EVERY SO OFTEN, unexpected findings turn scientific wisdom upside down. Two studies recently published in the New England Journal of Medicine have refuted the long-held notion that the human heart cannot repair itself after a heart attack or other injury. The research indicates that new muscle cells can indeed grow in adult hearts and that they may arise from stem cells, the undifferentiated building blocks of the body. The discovery may pave the way for therapies that encourage natural healing.

Research teams at the New York Medical College (NYMC) in Valhalla, N.Y., and the University of Udine in Italy conducted the iconoclastic experiments. The first study found chemical markers indicating new growth of muscle cells in heart samples taken from patients who had died four to 12 days after a myocardial infarction (the medical term for a heart attack). The second study, which involved the postmortem examination of female hearts transplanted into men, showed the presence of stem cells with Y chromosomes in the donated hearts. Although these stem cells could have migrated from the male recipient's bone marrow, they could have also come from the cardiac remnant to which the female heart was attached.

"Our paper suggests the possibility that cardiac stem cells may exist," says Piero Anversa, director of the Cardio-vascular Research Institute at the NYMC. "We need to determine all the characteristics that prove that we are dealing with a primitive cell in the heart. And then we need to see whether we can mobilize these cells in areas of heart damage to promote repair."

Other medical researchers are pursuing regenerative cardiac therapies with stem cells taken from other parts of the body. Philippe Menasché, professor of cardiovascular surgery at the Bichat-Claude Bernard Hospital in Paris, has injected primitive muscle cells from patients' legs into damaged areas of their hearts during cardiac bypass surgery. Initial results from the clinical trials have been encouraging, showing thickening of heart muscle walls with functional tissue. But Menasché is cautious about therapeutic outcomes. "At best, these cells may help enhance other treatments," he says. "Imagining that you'll be able to completely regenerate an infarcted heart is probably unrealistic."

But some biotechnology firms are entertaining even wilder hopes. Advanced Cell Technology, the Worcester, Mass.–based company that gained notoriety last year with its human cloning experiments, has already turned stem cells into beating heart cells and is trying to create transplantable patches for repairing larger areas of damage. "Eventually we want to engineer a full heart," says Robert Lanza, the company's vice president for medical and scientific development. The task would require generating cardiac muscle and blood vessel tissue as well as fabricating a dissolvable biological scaffolding material for building the heart. How far off is a biological artificial heart? According to Lanza, "We could produce a functioning heart in 10 years, with clinical trials in maybe 15 years."

—S.D.

Originally published in October 2000

Operating on a Beating Heart

Coronary bypass surgery can be a lifesaving operation. Two new surgical techniques should make the procedure safer and less expensive

by Cornelius Borst

After climbing just one flight of stairs, Mr. Patnaki must rest before he ascends to the next story. He feels as though an elephant has stepped on his chest. Such pain results from blockages in Mr. Patnaki's coronary arteries, the vessels that supply oxygen-rich blood to the muscles of the heart. He needs coronary artery bypass surgery but cannot afford the operation and the lengthy hospital stay required. (In the U.S., for example, the surgery and hospitalization cost around $45,000; in Europe, about half this amount.)

Mrs. Wales is an elderly lady crippled by attacks of chest pain after just the slightest movement. Getting up and putting on her clothes takes at least an hour. She badly needs a coronary bypass. Fortunately, she lives near a cardiac care facility, and her medical insurance will pay for the procedure. Yet Mrs. Wales has lung problems and kidney disease, and she recently suffered a stroke. The cardiac surgeon considers it too dangerous to perform a bypass operation on her.

Mr. Brennick runs his own software business from an office at home. He needs triple bypass surgery but fears that the operation will put him out of business by diminishing his programming skills. Heart operations can sometimes impair a patient's brain function, and Mr. Brennick is not willing to take this chance. (Mr. Patnaki, Mrs. Wales and Mr. Brennick represent composite portraits based on numerous patients.)

Coronary bypass surgery is common—about 800,000 people undergo the procedure every year worldwide. But the operation is expensive and risky. To reroute the flow of blood around blockages in coronary arteries, surgeons must graft other vessels (taken from the patient's chest and leg) onto the diseased vessel, past the obstructions. Before doing so, however, they must open the chest (called "cracking" the chest, because the sternum must be split with a saw and the chest cavity spread open). They must then stop the heart, typically for around an hour. A surgeon simply cannot suture a vessel onto the heart accurately while it is still beating.

During the time the heart is stopped, the patient must be put on a heart-lung machine, which artificially circulates blood and supplies the body's tissues with oxygen until doctors restart the heart. This sophisticated machine ushered in the era of modern cardiac surgery some 40 years ago. Yet to this day, the artificial circulation provided by the heart-lung machine remains associated with serious complications, particularly in elderly or debilitated patients. It is the major cause of the long postoperative hospital stay (typically between six and eight days) and often results in a two- or three-month convalescence period at home. Furthermore, people may recover slowly from having had their chest cracked, and they are susceptible to certain infections, including pneumonia, as they recuperate.

In the mid-1990s two surgical techniques emerged that could signal a revolution in coronary bypass surgery. Researchers, including myself, began examining whether the heart-lung machine could be discarded by having doctors actually operate on a beating heart. Other teams have been investigating methods for performing endoscopic surgery on the heart—an operation that requires little more than a few keyhole-size incisions in the chest. I expect that over the next decade, coronary bypass surgery will become dramatically safer and less expensive thanks to these new technologies.

The chest pain experienced by Mr. Patnaki, Mrs. Wales and Mr. Brennick results from atherosclerosis—commonly known as hardening of the arteries—inside the major coronary arteries. Over time, substances such as cholesterol can build up in arterial walls, eventually narrowing these passageways. The disease progresses gradually, but in 19 percent of U.S. men between the ages of 30 and 35, the most important coronary artery has already closed by at least 40 percent. By around middle age, people might notice a bit of chest pain when they exert themselves because the coronary blood flow can no longer keep up with the extra amount required during vigorous activity. A clogged vessel may be likened to a garden hose that won't spray after someone has stepped on it.

People are often crippled by the chest pain of atherosclerosis, and millions around the world have been stricken with this devastating disease. Genetic factors play a role in its development, but diet and lifestyle are also important. Although my emphasis—both in this article and in my research—is on improving therapeutic procedures to treat coronary heart disease, I want to stress that its prevention, through encouraging proper diet, exercise and not smoking, must be the medical community's primary focus.

Once a patient's chest pain has been diagnosed as a symptom of atherosclerosis, drugs may be recommended. Other patients opt for angioplasty, a procedure in which a cardiologist

inserts a small, sausage-shaped balloon into the obstructed artery; inflating the balloon reopens the vessel by stretching the diseased wall. In addition, the cardiologist might position a tiny metal structure, or stent, inside the vessel to keep it open. But in some cases, when the cardiologist foresees that the artery will renarrow soon after angioplasty, a bypass is the best option for restoring adequate blood flow to the heart. Coronary bypass surgery usually involves grafting between three and five vessels onto the arteries of the heart. For each bypass graft, surgeons must spend up to 20 minutes carefully placing more than a dozen tiny stitches through both the graft vessel and the coronary artery.

The need to use a heart-lung machine is one of the greatest sources of complications during cardiac surgery. To connect a patient to the device, the doctor must insert tubes in the inflow and outflow vessels of the heart, close off the aorta with a clamp and introduce a cardioplegic solution into the coronary arteries, which stops the heart from beating. This complex procedure can dislodge particles of atherosclerotic plaque from the wall of the aorta. Such debris, if it reaches the brain, can cause a stroke. In addition, the heart-lung machine upsets the body's natural defense system, frequently resulting in fever, organ damage and blood loss; after the operation, it can also leave a patient temporarily unable to breathe without the aid of a ventilator. Finally, when the heart does resume beating, it often shows signs of impaired function: a patient may suffer low blood pressure, reduced blood flow through the body and reduced urine production. In rare cases, the patient cannot be weaned from the heart-lung machine without a mechanical pump to maintain acceptable blood pressure.

Several studies have quantified these hazards. In particular, the likelihood of death soon after coronary bypass surgery increases with age. In the U.S., for example, it rises from a 1.1 percent chance between the ages of 20 and 50 to 7.2 percent between ages 81 and 90. One out of three patients suffers at least one operative complication. A 1997 report on more than 100,000 U.S. health insurance records revealed the dangers posed to bypass patients 65 and older: 4 percent died in the hospital; 4 percent were discharged to a nursing home; and 10 percent were discharged after at least two weeks in the hospital. Memory and attention loss as well as physical weakness and emotional depression often prevent patients from returning to normal activities for at least two or three months.

The practical implications of these potential risks vary. The possibility that a patient will require an extended stay in the hospital, perhaps in the intensive care unit on a ventilator, raises the odds that the final bill will be too high for someone like Mr. Patnaki. People who have a history of stroke, for instance, are more likely to have another one during the operation—which is why Mrs. Wales's physician recommended that she avoid bypass surgery. And the specter of possible memory loss scares away candidates like Mr. Brennick.

For the past 15 years, my research has centered on devising better ways to treat coronary artery disease. By using a mechanical device to stabilize only the clogged vessel, not the entire heart, I believe my colleagues and I may have developed an improved and less expensive surgical therapy for this common disease.

In March 1993 in Palm Coast, Fla., at a workshop for physicians and researchers interested in the use of lasers in medicine and biology, I listened intently to Richard Satava, then a U.S. Army physician. He described a military initiative to design robots that would be remotely controlled by doctors to perform emergency surgery in the battlefield. Satava's photograph showing a prototype robot prompted me to think of using robots to operate on a beating heart inside a closed chest.

While exploring a robotic approach to the surgery, I began to consider the feasibility of operating on a beating heart without such complex and expensive equipment.

The "Octopus"

In the spring of 1994 my colleague at the Heart Lung Institute in Utrecht, cardiac surgeon Erik W. L. Jansen, and I attempted to reproduce an approach to beating-heart surgery developed independently in the 1980s by Federico J. Benetti of the Cardiovascular Surgical Center of Buenos Aires and Enio Buffolo of the Paulista School of Medicine of the Federal University of São Paulo. Benetti and Buffolo had each reported their experiences with human patients; Jansen and I operated first on pigs.

In their work, the two South American doctors immobilized a small region of the heart's surface, which then allowed them to suture the coronary artery bypass successfully. They secured the region of interest with the help of a number of stabilizing sutures placed in tissue adjacent to the bypass site and through the use of pressure, applied by an assistant with a stable hand, who held a large surgical clamp. By restraining only part of the beating heart—just a few square centimeters—they hardly impeded its overall pumping action. Other surgeons, however, found it difficult to master this elegant, simple and cheap approach, and Benetti and Buffolo initially had few followers.

One day in May 1994 in Utrecht, during an experimental operation on a pig, I served as the assistant to the surgeon, charged with holding the clamp steady. Unfortunately, we failed to fully arrest the region of the heart where we wanted to place a bypass graft. But the failure inspired me. Unsteady tissue sutures and the human hand could be replaced by one rigid mechanical gadget to stabilize the heart. Exhilarating weeks followed, in which Jansen was able to construct with ease perfect bypasses on a pig's beating heart with the aid of prototype cardiac stabilizers crafted by technician Rik Mansvelt Beck.

Shortly thereafter my Utrecht colleague Paul Gründeman joined our team, and we invented the Octopus cardiac stabilizer—an instrument that can immobilize any small area on the surface of a beating heart. The name originated from the fact that we use suction cups to attach the instrument to the heart and from "Octopussy," one of the laboratory pigs (all our animals were named after characters in James Bond movies). We first used the Octopus during bypass surgery on a human patient in September 1995. By mid-2000, more than 50,000 people had been treated with the Octopus worldwide (more than 400 of them here in Utrecht; in this select group of patients, the mortality rate, both during the operation and for 30 days afterward, is zero).

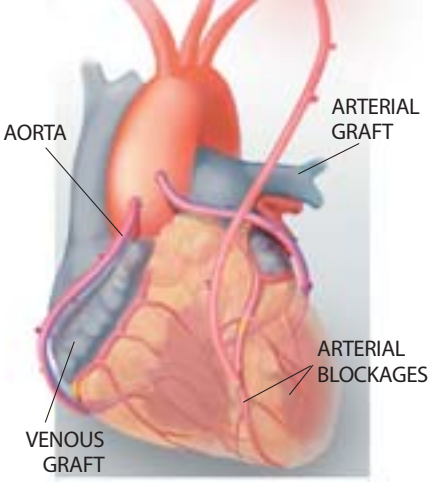
As is often the case in medical research, other investigators independently began developing mechanical stabilization devices around this time. In contrast to the Octopus, which holds onto the heart by suction, most of the other devices rely on pressure and friction—they resemble a large surgical clamp pressing on the heart. Currently there are some 13 different types of mechanical stabilizers available to cardiac sur-

geons. In 1994 fewer than 0.1 percent of coronary operations worldwide were performed without the aid of a heart-lung machine. In 1999 this number was about 10 percent. This year we expect it to rise to around 15 percent and by 2005 to more than 50 percent. At hospitals that lack sophisticated facilities with heart-lung machines—especially those in the developing world—the ability to perform beating-heart surgery will make coronary procedures available to patients for the first time.

Around this same time, Benetti, the surgeon from Argentina, gave the beating-heart approach another boost. He pioneered an operation involving a limited eight-centimeter incision be- tween the ribs on the left side of the chest, which could be used in patients who needed only one bypass graft to the most important coronary artery on the front of the heart. Although this procedure still requires surgeons to separate adjacent ribs, it is significantly less damaging than cracking open the entire chest.

A number of other surgeons quickly recognized the potential advantages of this technique for beating-heart surgery, notably Valavanur Subramanian at Lenox Hill Hospital in New York City and Michael Mack at Columbia Hospital in Dallas. In November 1994 Subramanian showed a video presentation of his technique at a workshop in Rome; as a result, the limited-incision, beating-heart surgery spread quickly through Europe. In addition, Antonio M. Calafiore at the San Camillo de Lellis Hospital in Chieti, Italy, subsequently reported such good results in a large number of patients that beating-heart surgery began to attract worldwide attention. By the start of the first international workshop on minimally invasive coronary surgery, held in September 1995 in Utrecht, several thousand patients had undergone beating-heart surgery.

For the time being, beating-heart surgery will not fully replace traditional bypass surgery. For many candidates, the conventional operation will remain the better choice. But we continue to refine our method, expanding the types of cases for which it can be used. For example, when someone needs a bypass performed on the back of the heart (a common scenario), beating-heart surgery is often difficult. To reach the back of the heart, the surgeon must lift it partly out of the chest. This maneuver, when performed on an active heart, significantly deforms the organ, reduces the amount of blood it can pump and typically leads to a dangerous drop in blood pressure.



GRAFTING BYPASSES onto the heart typically involves attaching between three and five vessels to existing arteries so that blood flow through the bypasses will circumvent blockages. Surgeons can use either arterial grafts (arteries redirected from the vicinity of the heart) or venous grafts (vein segments taken from the leg).

In the past few years, however, researchers have discovered a number of simple measures that can be taken to avoid this hazard. In my laboratory, Gründeman has shown that tilting the operating table 15 to 20 degrees down, so that the head is lower than the chest, helps to prevent a serious drop in blood pressure. At the Real Hospital Português in Recife, Brazil, Ricardo Lima found another elegant way to expose the back of the heart without compromising blood pressure too much. Most surgeons have now adopted his technique of using the pericardial sac surrounding the heart to lift the organ partly out of the chest.

By mid-2000, close to 200,000 patients had undergone beating-heart bypass surgery with the aid of a mechanical stabilizer. The first round of follow-up studies that we and many other centers conducted indicated that these people experienced fewer complications during surgery, required fewer blood transfusions, remained on an artificial respirator or in intensive care for less time, and left the hospital and returned to normal activities sooner than patients who had undergone traditional cardiac surgery. In addition, preliminary reports for single bypass procedures show that the overall cost was lower by about one third. Virtually all these studies, however, involved carefully selected patients. Thus, the results may not represent the general coronary surgery population. My colleagues and I await definitive results on the risks and benefits of beating-heart surgery that will be available once randomized clinical trials end. The Octopus trial in the Netherlands should conclude in late 2001.

Keyhole Surgery

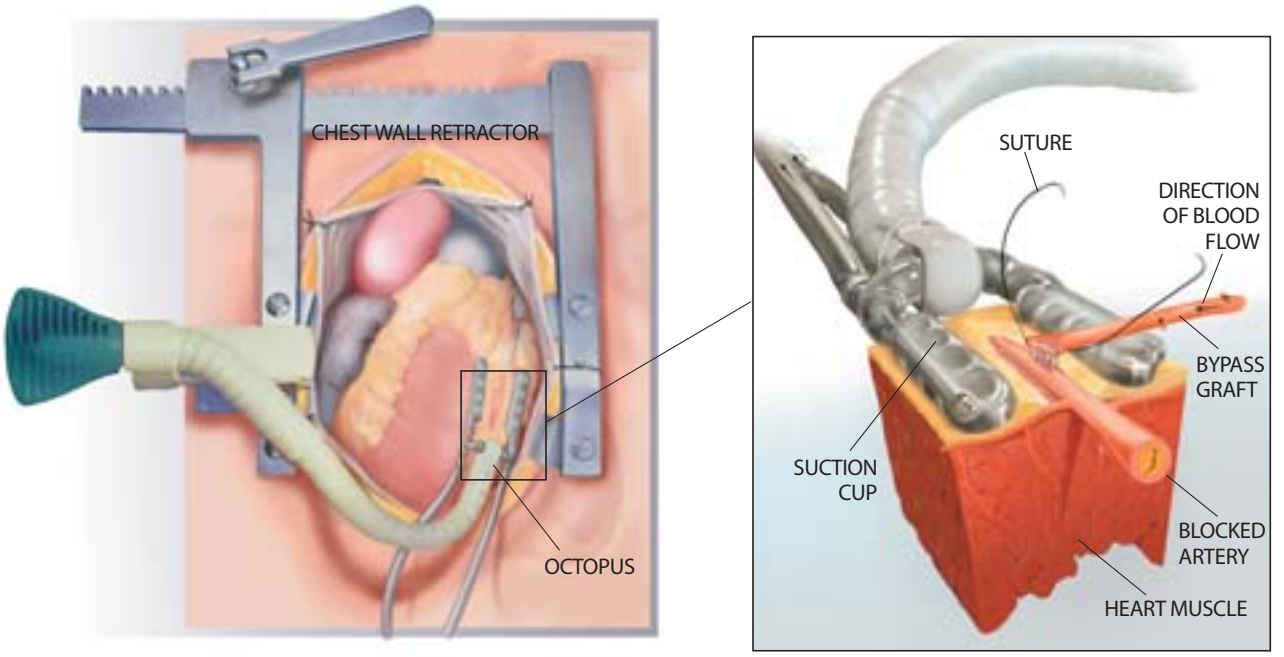
The crucial advantage of beating-heart surgery is that the heart-lung machine can be turned off. Unfortunately, though, the other major drawback to conventional bypass surgery—the need to open the chest widely—remains. But this should not always be the case. In abdominal surgery, for example, physicians can perform entire operations, such as removing the gallbladder, through small, keyhole-size incisions, thanks to endoscopic surgery. In this technique, doctors insert a rigid tube connected to a miniature video camera (the endoscope) through one incision and the required surgical instruments through two other incisions; a video feed from the endoscope guides the surgeons' movements. So why not operate on the heart in a minimally invasive way, through one-centimeter openings between the ribs?

Researchers at Stanford University took just such a leap in 1991. The Stanford initiative led to the founding of the company Heartport, now in Redwood City, Calif., dedicated to performing closed-chest endoscopic cardiac surgery on a stopped heart with the patient hooked up to a heart-lung machine.

To connect a Heartport patient to the heart-lung machine and to stop the heart without opening the chest, various tubes and catheters required for the task had to be manipulated from the groin area. This procedure did not go smoothly in all patients. Furthermore, the actual bypass suturing proved even more demanding. Because of the limitations of conventional endoscopic surgical instruments and the tight maneuvering space in the closed chest, these initial attempts to operate on the heart endoscopically had to be abandoned after just three patients. Only by making larger incisions (between six and nine centimeters) could surgeons reliably suture grafts to the coronary arteries. By mid-2000, more than 6,000 coronary patients had been treated in this manner.

Ideally, cardiac surgeons would like to perform a truly minimally invasive bypass operation: closed-chest, beating-

CAROL DONNER (*illustration*)



OCTOPUS HEART STABILIZER immobilizes an area on the surface of the beating heart so that surgeons can accurately suture a bypass graft. The Octopus, invented by the author and his colleagues, uses suction to take hold of a small region of the heart; tightening the blue knob anchors the Octopus to the metal device used to retract the chest wall (*left*). Although the heart continues to beat almost normally, the graft site (*right*) remains virtually still, allowing the surgeon to suture a bypass to the blocked artery.

heart coronary surgery. To avoid the restrictions of conventional endoscopic instruments, researchers—proceeding with great caution—have begun to use robotic endoscopic surgery systems for such operations. In these systems, the surgical instruments are not controlled directly by a surgeon's hands but instead by a remotely operated robot. Doctors can see inside the chest cavity in three dimensions, and their hand motions at the computer console are accurately translated to the surgical instruments inside the chest. Indeed, the computer automatically filters these motions to remove natural tremor and thus actually augments precision.

The first surgeons to take advantage of robotic equipment for closed-chest coronary surgery (but with a heart-lung machine) were Friedrich Mohr, Volkmar Falk and Anno Diegeler of the Heart Center of Leipzig University, and Alain Carpentier and Didier Loulmet of the Broussais Hospital in Paris. Working in 1998, in a renewed attempt to apply the original Heartport arrested-heart approach, these doctors combined Heartport with the so-called da Vinci robotic endoscopic surgery system, which was developed by Intuitive Surgical in Mountain View, Calif.

In September 1999, at the University of Western Ontario Health Center in London, Ontario, Douglas Boyd utilized the Zeus robotic surgical system, which was developed by Computer Motion in Goleta, Calif., to perform the first computer-assisted, closed-chest, beating-heart surgery. But in contrast to the two hours that a single bypass, limited-incision operation on a beating heart usually requires, this first procedure lasted most of the day. By mid-2000, however, surgeons at five centers—in Munich, Leipzig, Dresden, London, Ontario, and London, England—had reduced operating-room time to between three and five hours for some 25 successful closed-chest, beating-heart, single-bypass operations.

Robotic techniques such as those required for a closed-chest operation are likely to become an integral part of the operating room. As the technology advances, surgical residents might one day be able to practice endoscopic coronary surgery just as pilots practice flying aircraft, and physicians might be able to rehearse upcoming operations. Other innovations may further facilitate the surgical treatment of coronary heart disease. For example, a "snap" connector in development may allow surgeons to attach a bypass rapidly without sutures.

Ultimately, the coronary bypass operation may very well become extinct. In the meantime, however, improving coronary surgery while keeping the cost reasonable remains an important goal—particularly because such advancements could make surgical interventions against coronary heart disease available worldwide to every patient who needs them. But regardless of new developments in surgical techniques, prevention of coronary heart disease must remain at the top of the medical agenda. SA

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Further Information

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CAROL DONNER

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Surgical Treatment of Cardiac Arrhythmias

To save the life of a doomed patient, the author and his colleagues developed a now standard surgical procedure for correcting lethally fast heartbeats in many people susceptible to them

by Alden H. Harken

In 1978 a vice president of a bank in Philadelphia collapsed at work when his heart began to beat dangerously fast. Fortunately, his co-workers were able to administer cardiopulmonary resuscitation immediately, keeping him alive until emergency medical workers arrived. He was soon brought to the Hospital of the University of Pennsylvania, where I was a junior member of the surgical faculty.

Little did either of us know that within weeks of this episode we would participate together in making a small piece of surgical history. Desperate to prevent the banker's imminent death, my colleagues and I devised a new surgical treatment to correct the underlying disturbance that caused his heart to malfunction. Since then, hundreds of other patients have been aided by this therapy. At the same time, further research has expanded insight into why our treatment strategy, born of necessity, proved so useful.

I well remember our initial evaluation of the banker's medical condition because we were in for a surprise. When he first appeared at the hospital, we suspected he had suffered a heart attack (myocardial infarction): the death of cardiac muscle after blockage of an artery feeding that tissue. But tests told a different story. Indeed, the muscle was in good shape, except for a small area that had been damaged during a heart attack several years before.

His heart had malfunctioned now because it became suddenly and lethally unstable electrically. The electrical wiring system that regulates the heartbeat induces the cardiac muscle to contract and thus push blood into the arterial circulation some 72 times a minute. The man's muscle had begun to receive much more frequent signals, leading to abnormally fast pumping. If the heart beats too rapidly, its interior chambers do not have time to fill with blood. Be-

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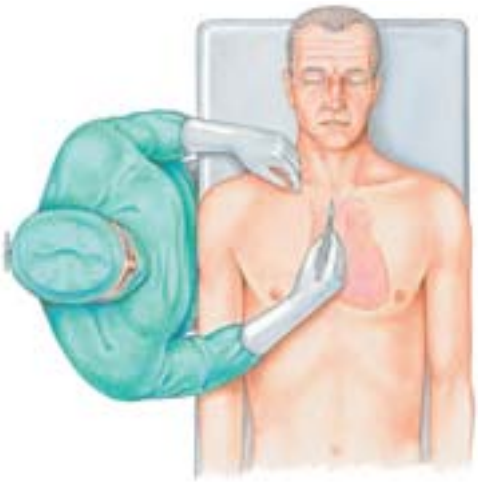

LIFESAVING OPERATION involves excising flap of diseased muscle (lined area in image at right), about three square centimeters in area and several millimeters thick, from the inner surface of a patient's heart. When successful, the surgery halts propagation of impulses through a pathway known as a reentrant circuit, which may arise months or years after a heart attack and can fatally disturb normal cardiac rhythms. The surgeon has entered the left ventricle through an incision (broken line in inset) in dead scar tissue (shaded area in inset) left by the heart attack. Clamps hold back the edges of the incision.

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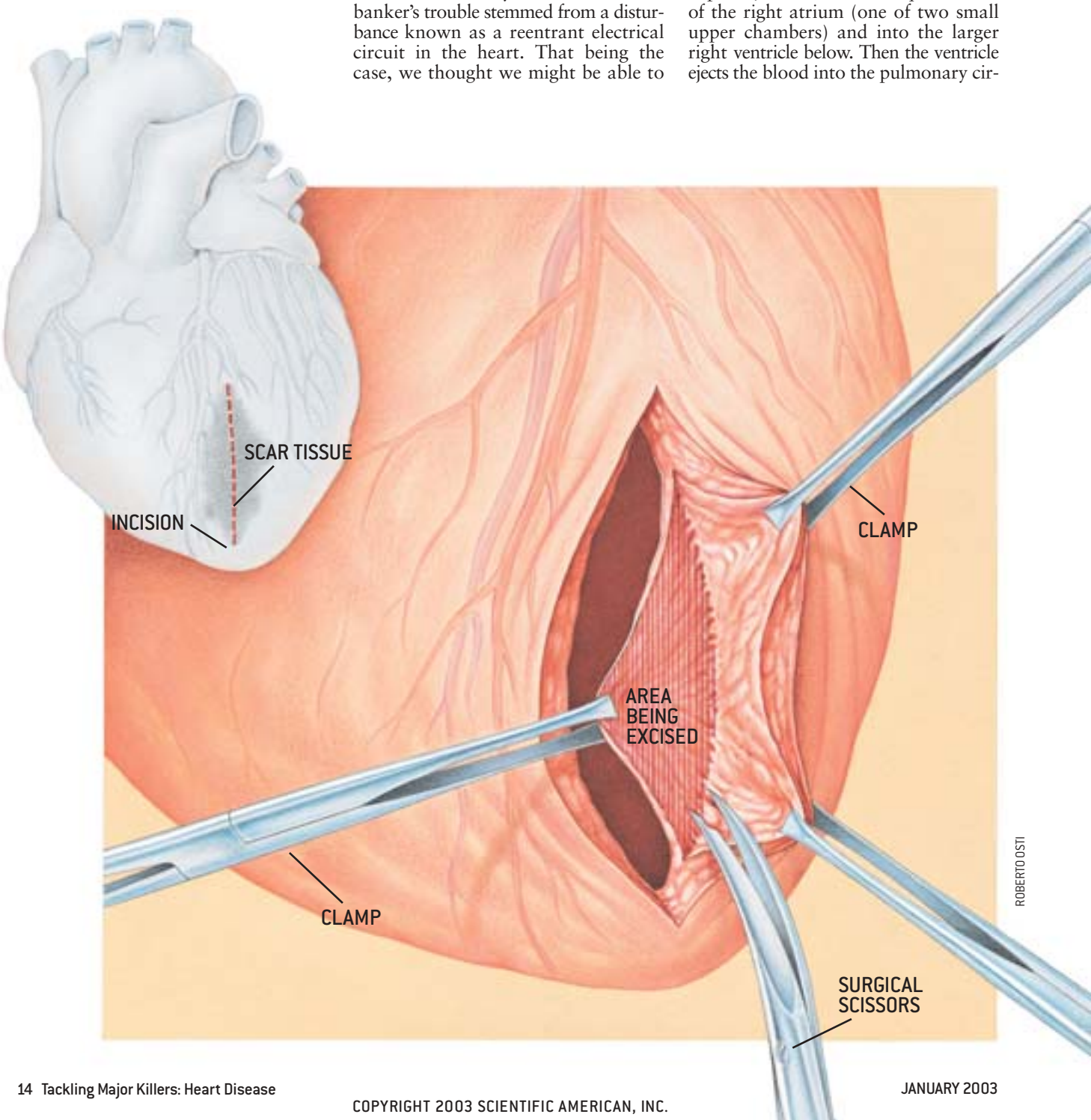
cause the organ cannot eject something it does not receive, delivery of blood to the body's tissues, including to the cardiac muscle itself, can drop precipitously, causing the heart to stop. Although we had originally expected to find evidence of a new heart attack, we were also aware that the banker's electrical derangement was not unique. Six years earlier Hein J. J. Wellens, then at the University of Limburg in the Netherlands, observed that excessively fast pumping occurred in certain patients months or years after a heart attack.

We understood as well that medications designed to prevent arrhythmias, or abnormal heartbeats, could restore proper functioning in some people, and so we tried every type available. Each failed. In a span of three weeks at the hospital, the banker seriously extended his metaphysical line of credit, suffering three additional cardiac arrests. To let him leave under those conditions would most assuredly have been fatal—and he knew it.

At the time, I was privileged to be working with Mark E. Josephson and Leonard N. Horowitz, who specialized in diagnosing cardiac electrical abnormalities. They concluded that the banker's trouble stemmed from a disturbance known as a reentrant electrical circuit in the heart. That being the case, we thought we might be able to interrupt the circuit surgically.

To follow our logic, it helps to know a bit about how the heart's electrical system controls cardiac activity. The heart, which is divided into four chambers, is essentially a ball of muscle (myocardium) lined by conduction tissue: unique fibers that form a kind of internal nervous system. These special fibers convey electrical impulses swiftly to the entire cardiac muscle.

In response to the impulses, the muscle contracts—first at the top of the heart and slightly thereafter at the bottom. As contraction begins, oxygen-depleted, venous blood is squeezed out of the right atrium (one of two small upper chambers) and into the larger right ventricle below. Then the ventricle ejects the blood into the pulmonary cir-



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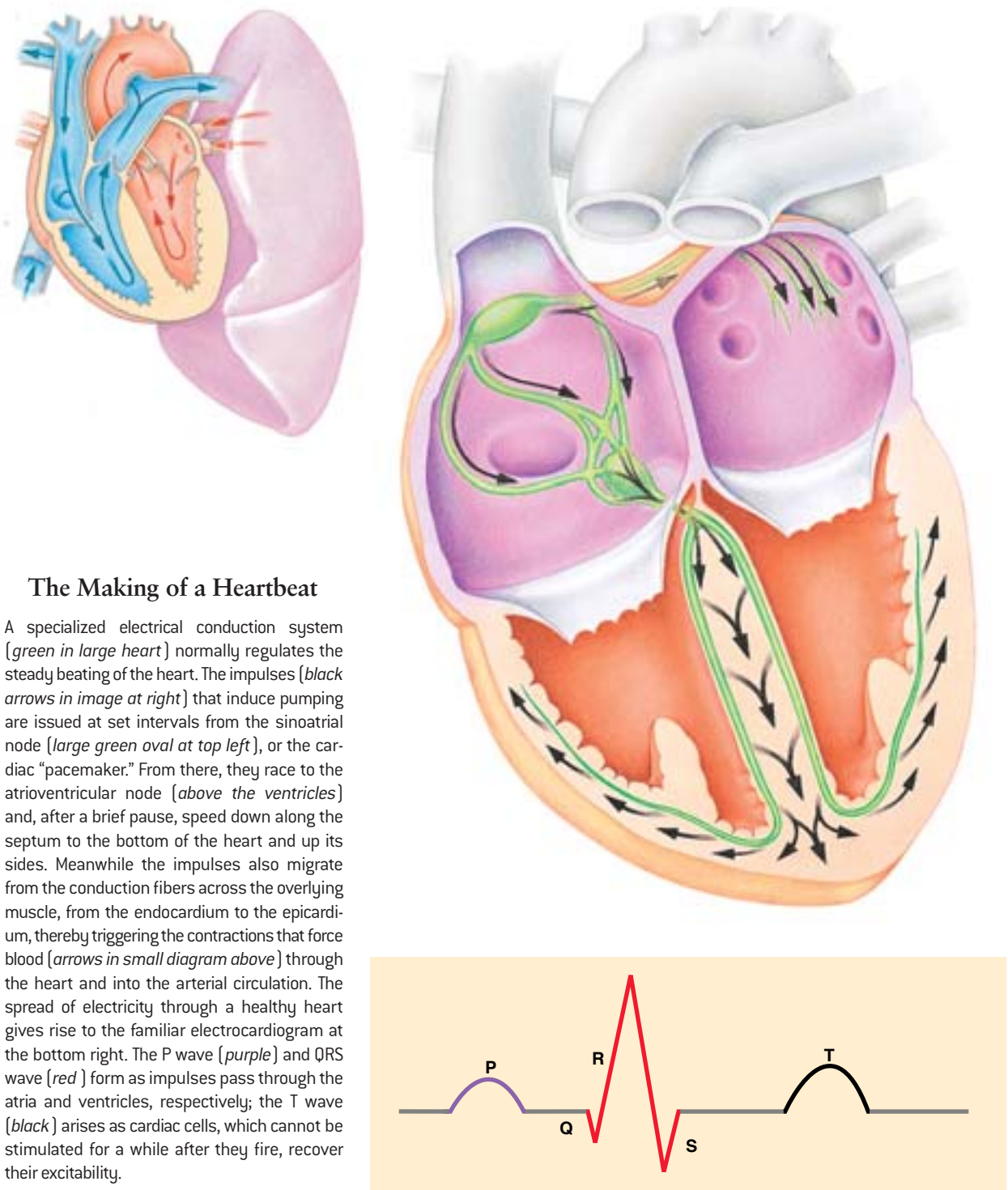
culation, which resupplies oxygen and delivers the blood to the left side of the heart. In parallel with the events on the right, the muscle pumps newly oxygenated blood from the left atrium into the left ventricle and, from there, out to the aorta, which distributes it to every part of the body.

The signal giving rise to these machinations emanates from a cluster of conduction tissue cells collectively known as the sinoatrial node. This node, located at the top of the right atrium, establishes the tempo of the heartbeat; hence, it is often referred to as the cardiac pace-maker. It sets the tempo simply because it issues impulses more frequently than do other cardiac regions, once about every 830 milliseconds. If something provoked another part of the heart to fire at a faster rate, as occurred in the banker, it would become the new pacemaker. Although the sinoatrial node can respond to signals from outside the heart, it usually becomes active spontaneously. In other words, it is on "automatic pilot," a capability known as automaticity.

Such automaticity stems from the unique leakiness of the membrane encasing nodal cells. As is true of the mem-



The Making of a Heartbeat

A specialized electrical conduction system (*green in large heart*) normally regulates the steady beating of the heart. The impulses (*black arrows in image at right*) that induce pumping are issued at set intervals from the sinoatrial node (*large green oval at top left*), or the cardiac "pacemaker." From there, they race to the atrioventricular node (*above the ventricles*) and, after a brief pause, speed down along the septum to the bottom of the heart and up its sides. Meanwhile the impulses also migrate from the conduction fibers across the overlying muscle, from the endocardium to the epicardium, thereby triggering the contractions that force blood (*arrows in small diagram above*) through the heart and into the arterial circulation. The spread of electricity through a healthy heart gives rise to the familiar electrocardiogram at the bottom right. The P wave (*purple*) and QRS wave (*red*) form as impulses pass through the atria and ventricles, respectively; the T wave (*black*) arises as cardiac cells, which cannot be stimulated for a while after they fire, recover their excitability.

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brane surrounding muscle cells and neurons, the nodal cell membrane is studded with pumps that transport ions into and out of the cell. The net result of this exchange is the creation of an electrical potential, or unequal charge distribution, across the membrane. Yet unlike muscle and nerve cells, which maintain their resting potential until they are jogged by an outside stimulus, nodal cells allow certain ions to leak back out of the cells. This outflow reduces the membrane potential to a critical value.

At that point, the membrane permits a flood of other ions to rush back into the cells. This onslaught momentarily depolarizes the cells (eliminates the membrane potential) and actually reverses the membrane polarity. Such depolarization constitutes an impulse. After the impulse is generated, cells repolarize and prepare for firing anew.

Impulses born at a cell in the sinoatrial node typically speed instantly through the rest of the node; from there, they course through the entire heart in the span of 160 to 200 milliseconds. Traveling along conduction fibers, they first race across both atria and then regroup at the atrioventricular node, a cellular cluster centrally located atop the ventricles. After a pause, they course down the ventricles along a conduction cable that divides into two branches known as conduction bundles; these further ramify to form arbors of thinner projections called Purkinje fibers. One arborized bundle serves each ventricle, sending signals first along the surface of the septum (a wall dividing the two ventricles) to the tip of the heart (the apex) and, from there, up along the inner surface of the external (lateral) walls to the top of the ventricle.

As impulses from the conduction fibers reach muscle, they activate the overlying cells. Muscle cells, too, are capable of relaying impulses, albeit more slowly than do conduction fibers. The cells of the endocardium (the inner surface of the wall) depolarize first and relay the impulses through the thickness of the muscle to the outer surface (the epicardium). Depolarization, in turn, triggers contraction.

Josephson and Horowitz suggested that diseased cells had distorted this normal flow of electricity in the banker's heart. After a heart attack, many cells surrounding the resulting scar (the group of cells killed by lack of blood delivery) continue to live but are abnormal electrically; they may conduct impulses unusually slowly or fire when they would typically be silent.

These diseased areas, my co-workers indicated, might perturb smooth signaling by forming a reentrant circuit in the muscle: a pathway of electrical conduction through which impulses can cycle repeatedly without dying out. In our patient's case, the circuit was thought to be in the left ventricle, where his heart attack, in common with most others, occurred. (Activation of reentrant circuits some time after a heart attack is now believed to take place in a sizable number, perhaps 10 percent, of the roughly 1.2 million Americans who suffer heart attacks every year.)

Passage of impulses through a reentrant circuit can be envisioned by imagining a wave of impulses encountering, say, the bottom of an oval scar in the left ventricle. On reaching the scar, the wave would split in two, to detour around both sides of the dead area. If diseased cells somehow interrupted impulses propagating along one of those branches, impulses might still flow up along the opposite branch and over the top of the oval. Then they might traverse the previously blocked path and return to the beginning of the circuit—a region we call the origin.

If this circuit were negotiated slowly enough, the origin would have repolarized and become responsive once again to stimulation. (Between the time cells depolarize and repolarize, they are generally refractory, or incapable of responding to new impulses.) In that case, the impulses could reexcite the origin, sending impulses back into the diseased circuit and also out to the rest of the ventricular muscle.

Despite the slow conduction, the impulses could complete the circuit in a shorter time than the interval between normal heartbeats. Hence, persistent cycling could enable the origin of the circuit to become the new pacemaker and to provoke sustained ventricular tachycardia: excessively rapid pumping by the ventricles.

We knew that continuous passage through reentrant circuits could occur in humans because Wellens had established that fact in the 1970s. Fortunately for us, he also introduced a procedure for determining whether a quiescent circuit lurks in a patient who survives a life-threatening episode of tachycardia and whether any existing drugs can prevent renewed activation of the pathway. A physician threads an electrode known as a pacing catheter into the heart and issues a series of specifically timed impulses. Initiation of sustained premature heartbeats confirms that a patient harbors a reentrant pathway. (In contrast, impulses delivered to a healthy heart would yield only single contractions that would not be repeated.) Next, the individual is given an antiarrhythmic drug. If paced stimuli now fail to trigger sustained tachycardia, the finding implies the drug should be helpful.

When Josephson and Horowitz performed the procedure on the banker, they found they could indeed induce persistent tachycardia and that, sadly, no antiarrhythmic medications could aid him. I met with the two of them soon afterward in their tiny, windowless catheterization laboratory. Knowing our patient carried a life-threatening electrical pathway inside his heart, we began wondering if we might prevent its activation by surgically removing all or part of the culprit circuit, especially the origin. We realized the plan could fail, or that by removing the tissue, we might actually create other problems. But we were out of options.

Before proceeding, we had to develop a way to locate the renegade pacemaker. We hoped we might find it by analyzing signals reaching an electrode placed directly on the inner or outer surface of the heart. More specifically, we planned to induce sustained tachycardia with a pacing electrode. During each heartbeat, we would measure electric currents produced at a single site (consisting of a small cluster of cells) along the diseased border of the heart attack scar. We would start at a position arbitrarily designated as 12 o'clock and proceed around the "clock face" back to the beginning.

We would delineate the circuit by comparing the time of electrical activation in each region against that seen in healthy tissue. Regions that generated currents before the healthy tissue did would be revealed as belonging to the circuit; the area that became excited earliest would be the pacemaker. We could not rely on standard electrocardiography for this purpose because it lacked the specificity we needed. Familiar electrocardiogram tracings, made by attaching electrodes to the skin, reflect the summed activity of many thousands of cells in the heart; they cannot identify the precise swatch of muscle that is depolarized at any given moment.

Our general approach made sense, but no one had ever attempted to "map" the flow of signals in the living, pumping chambers of the human heart by recording directly from the organ's surface. We had no idea whether we could obtain decipherable results. The next day

I was scheduled to remove a cancerous lung from a different patient. He kindly agreed to let us try to detect signals directly from the outside of his heart. To our delight, we could clearly discern when a wave of impulses crossed any point on the muscle.

I was now ready to discuss our proposed strategy with the banker. Not knowing whether the origin of the circuit—the zone of earliest activation—was closer to the inside or outside of the cardiac muscle, we intended to map both the inner and outer surfaces. We planned to reach the interior by opening the heart through the existing scar. (Cutting into healthy tissue would, after all, destroy new tissue unnecessarily.) If we found the troublesome region, we proposed to remove it surgically. To keep blood moving through the patient's body during the operation, we should have to attach him to a heart-lung machine. This device diverts unoxygenated blood into an artificial lung. Blood containing oxygen is then pumped back into the arterial circulation via the aorta.

People often call physicians "courageous," but it was our patient who was brave. After I described our therapeutic strategy in great detail, he posed the dreaded question: "How many times have you done this before?" I told him, "Never." Then he asked how many times anyone had performed the operation previously. I informed him it was untried. Despite these unsettling answers, he gave me a confident smile and said, "Go ahead."

The next morning we were able to pinpoint and excise the region of earliest activity, which turned out to reside on the inside surface. (Today we know that virtually all reentrant pathways weave through cells in or close to the endocardium.) Our patient not only resumed banking but also went on to become the county tax assessor. I lost track of him a few years ago, but as of a decade after our treatment, he had suffered no further arrhythmias.

Not everyone who has the surgery is as lucky as the banker was, however. Of all the patients who undergo the procedure after surviving an episode of persistent tachycardia, approximately 9 percent succumb either during the operation or within a month after it. On the other hand, 80 percent of surgically treated patients live for at least a year without recurrence of tachycardia, and 60 percent survive for five years or more. The candidates most likely to do well are those whose heart muscle is damaged least.

In addition to assembling survival statistics, we have discovered since 1978 that reentrant pathways need not be as large as we originally thought. Those occurring at a microscopic level can be equally pernicious. In fact, microanatomic reentrant circuits seem to be the most common form of all.

The notion that microcircuits could exist was first suggested in the early 1970s by another surgeon: James L. Cox, then at Duke University. He argued that a small bit of mottled tissue, consisting of diseased cells interspersed with islands of dead cells, could set up the conditions needed to establish reentrant tachycardia. In such a microscopic circuit, impulses that encounter a divided pathway at an entryway to a mottled patch would split and travel along both routes.

As is true of larger, "macro" reentrant circuits, impulses propagating along one branch would encounter a one-way blockade. At the same time, impulses flowing along the other branch would meander through a maze of diseased cells and return along the previously blocked lane.

If conduction through the diseased tissue were su ciently slow, the impulses would come back to the entryway, or origin of the circuit, after that site was no longer refractory. Excitation of the site would then stimulate the ventricular muscle to contract and, at the same time, would send the impulses back into the microcircuit again and again. Instead of traveling along the circumference of a scar, then, a reentrant circuit could trace a recursive path through a more localized maze of cells in the diseased boundary between a heart attack scar and fully healthy tissue.

Two of my colleagues, Glenn J. R. Whitman and Michael A. Grosso, decided to test this idea in the early 1980s. They were able to create small heterogeneous zones consisting of mixed dead and living but diseased cells in the ventricles of test animals. These animals, not previously susceptible to the electrical induction of self-sustaining tachycardia, became highly prone to it.

Whitman and Grosso assumed that if the mottled tissue were at fault, killing all the cells in the patch should restore appropriate electrical activity in the heart. Instead of wandering through a dangerous maze, impulses encountering the homogeneous patch of killed tissue would either be extinguished or zoom around it through adjacent healthy cells. Sure enough, when the mottled patches were destroyed, the predisposition to arrhythmia vanished.

These findings revealed that mottling could set the stage for reentrant tachycardia. They also provided the hindsight needed to explain why a different surgical treatment tested by us and others in various patients had not worked well. Believing that the scar itself was somehow responsible for the electrical disturbances, we had previously removed only the dead tissue. Whitman and Grosso's work indicated that this approach was doomed to failure because it left the true culprit—the zone of mixed living and dead cells—in place.

Yet we still faced two significant puzzles, one scientific and one clinical. Why is it that reentrant circuits do not become active every time the heart beats in susceptible patients? In other words, why can people often survive for months or years before deadly disturbances of rhythm arise? We also wondered how we might noninvasively identify patients at risk for reentrant tachycardia before they experienced a potentially life-threatening episode.

The simplistic explanation for why a reentrant circuit does not jump into action with each heartbeat seemed to be that impulses fired by the sinoatrial node cannot cycle repeatedly through the troublesome pathway. At the end of the first cycle, they return to a still refractory starting site. Blocked from reentering the circuit, they go no further. Unfortunately, this explanation did not clarify how persistent cycling does arise. We now think it is triggered when, in a case of exquisite bad luck, an electrically irritable cell lying adjacent to a reentrant pathway fires spontaneously in a narrow window of time between one activation of the sinoatrial and atrioventricular nodes and the next.

We came to this conclusion after reviewing research reported in the late 1970s by our colleagues E. Neil Moore and Joseph F. Spear of the Hospital of the University of Pennsylvania. By impaling cells on tiny, needlelike electrodes, Moore and Spear were able to track changes in the membrane potentials of single, diseased cardiac cells taken from the area surrounding heart attack scars. After healthy cells depolarize, they repolarize smoothly. In the diseased cells, by contrast, the membrane potential fluctuated markedly during the repolarization period.

We presumed that these fluctuations would sometimes progress to premature depolarization, or firing of an impulse. If an irritable cell happened to lie next to a reentrant pathway, it might well insert an impulse into the worrisome channel during the interval between normal heartbeats.

This insertion might activate a reen-

trant circuit, whereas an impulse originating at the sinoatrial node would not, because recent passage of an impulse through a pathway can alter the electrochemical characteristics of that pathway and slow conduction of a subsequent signal. Thus, the impulse delivered by the irritable cell could pass through the circuit more slowly than would a prior signal originating at the sinoatrial node. If delivery of the wayward impulse were timed properly, the impulse propagating through the circuit would return to the entryway at a most devastating moment: after the site regained excitability (and so could relay the impulse onward) but before the sinoatrial node fired for a second time (thereby gaining control of the heartbeat). Hitting a receptive target, the impulse might proceed to run many unimpeded laps around the lethal circuit.

Our second problem—readily identifying patients at risk for reentrant tachycardia—was resolved masterfully by our co-worker Michael B. Simson, a person of many talents. Aside from being a superb cardiologist, he is, as I sometimes say, an enthusiastic sports-car hack and computer driver. Steering his beat-up sports car home one night after sitting in on one of our surgical research meetings, he began to ponder the electrical noise, or seemingly random signals, emanating from the hood of his car. If he simply monitored the currents reaching the hood, he reasoned, the resulting data would be indecipherably chaotic. But if he wanted to track the electrical impulses coming specifically from his distributor, he might well discern them by signal averaging.

In this procedure, he would record the voltage and direction (the electrical vector) of currents flowing toward and away from the hood during particular phases of rotation by his distributor rotor. If he summed the signals obtained by repeated measurements in a given phase, random currents would tend to cancel one another out, leaving a record of only those produced by the rotor. Dividing the result by the number of readings made in a selected phase would give him a measure of the current generated by the distributor in that phase.

It then occurred to Simson that he might apply much the same approach to screen heart attack victims for susceptibility to reentrant tachycardia. Perhaps signal averaging would enable him to detect very slow electrical activity persisting after the normal flow of signals passed through the ventricles. Most of the extra activity he found would reflect impulses propagating belatedly through a potentially dangerous reentrant channel. Put another way, Simson thought he could place electrodes on the skin, as for a standard electrocardiogram, but then record only those currents produced in the 40 milliseconds immediately after formation of the familiar QRS wave seen on electrocardiograms. (The QRS wave reflects the spread of impulses through the ventricles.) Heart cells are generally quiet at that point, giving rise to a flat line on the electrocardiogram tracing. Signal-averaged deviations from this normal pattern would signify slow conduction in a reentrant pathway.

Simson spent that night in his basement building a signal-averaging device. The next day Josephson, Horowitz and I were scheduled to remove tissue that had earlier caused reentrant arrhythmia in one of our patients. Before surgery, Simson attached his new recorder to the patient and noted, as expected, that there was a flurry of electrical activity in the usually quiescent span following ventricular excitation. But was the signal, in fact, an indication of late impulse conduction in a reentrant circuit? The answer would be yes if the fluctuations disappeared after the operation. The surgical procedure went well. Josephson and Horowitz identified the circuit, and I excised the entryway. After surgery, Simson reattached his device to the patient. The post-QRS fluctuations were gone.

We had come a long way since 1978. We had learned why our surgical approach, initially designed by guesswork, is useful. It interrupts the diseased anatomic pathway that, in response to aberrant firing by a nearby cell, gives rise to the repeated flow of impulses through a recursive circuit. Moreover, we had gained the ability to identify noninvasively patients at risk.

At the University of Colorado, where I moved in 1984, we use Simson's screening test routinely. We usually wait two or three months after a heart attack to be sure we are not detecting a predisposition to "automatic" tachycardias. For a week or so after a person has a heart attack, dying cells often fire when they should be silent. This behavior can cause the heart to beat prematurely. If the cell depolarizes repeatedly, the activity could lead to fast beating, and sometimes failure, of the heart. A tendency to automatic tachycardia generally resolves within a few weeks, as the sputtering cells expire.

If a propensity for reentrant tachycardia is discovered after a suitable waiting period, and if medications do not suffice, patients can consider other treatment options. I speak of more than one choice because surgery is no longer the only therapeutic alternative to drugs. A device known as an implantable defibrillator has been available since 1980.

When the heart begins to beat quickly, the machine issues a shock that depolarizes the entire heart instantly, giving the sinoatrial node a chance to resume its pacemaker function.

About half as many patients die from complications of the implantation procedure for the device as from consequences of undergoing our surgery. But, in contrast to the surgery, the device offers only palliation, not a cure. Recipients continue to face episodes of tachycardia and may lose consciousness each time they are shocked back into normal rhythm. Consequently, they cannot drive or engage in other activities where sudden blackouts could be dangerous. If surgery to eliminate a reentrant circuit is deemed the better therapy for a given patient, it can now be obtained at many medical centers.

Overall, it is fair to say that the majority of patients who survive a heart attack are not vulnerable to reentrant arrhythmias. Perhaps half of the small group who are susceptible can be treated with medication. Of those who do not respond to drugs, however, as many as 80 percent are likely to die from their electrical abnormality within a year after their first bout of reentrant tachycardia unless they receive some other therapy. It is reassuring to know that for many of those individuals the courage of a Philadelphia banker has permitted a cure. SA

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Defibrillation: The Spark of Life

In the 50 years since doctors first used electricity to restart the human heart, we have learned much about defibrillators and little about fibrillation

by Mickey S. Eisenberg

The operation had gone well. There was a brief period of fast heart rate, when the ether was given, but that was easily controlled with digitalis. The two-hour surgery had been technically demanding. The 14-year-old boy's congenitally deformed chest allowed respiration only 30 percent of normal. The task of the attending surgeon, Claude S. Beck, was to separate the ribs along the breastbone and repair nature's botched work. Beck relaxed as the easy part began. But as the 15-inch wound was being closed, triumph abruptly turned to crisis: the boy's heart stopped. Beck grabbed a scalpel, sliced through his sutures, enveloped the heart in his hand and rhythmically squeezed. He could feel the heart's ineffective quivering and knew at once that it had gone into the fatal rhythm called ventricular fibrillation. In 1947 no one survived this rhythm disturbance, but that did not deter Beck.

He called for epinephrine and digitalis to be administered and calmly asked for an electrocardiograph and a defibrillator, all the while continuing to massage the boy's heart. It took 35 minutes to obtain an electrocardiogram, which—wavering and totally disorganized—confirmed the distinctive appearance of ventricular fibrillation. Ten minutes later assistants wheeled in an experimental defibrillator from Beck's research lab adjoining the University Hospitals of Cleveland. Beck positioned the machine and placed its two metal paddles directly on the boy's heart. The surgical team watched the heart spasm as 1,500 volts of electricity crossed its muscle fibers. Beck held his breath and hoped.

The goal of a defibrillatory shock is to jolt the heart into a momentary standstill. With the chaotic pattern of contractions interrupted, the cardiac muscle cells have the chance to resume work in an orderly sequence again. The first shock did not work, and Beck began open-heart massage again while calling for additional medications. Twenty-five minutes passed, and Beck ordered a second shock. This time the shock blasted away the fibrillatory waves, and a normal

rhythm ensued. Three hours later the boy responded appropriately to questions and went on to make a full recovery.

Beck realized the significance of this first successful human defibrillation. In the 1940s the nation was in the midst of an epidemic of coronary artery disease—an epidemic that continues today and one that remains the leading cause of death in adults. Beck knew most coronary deaths, especially from sudden cardiac arrest, were triggered by ventricular fibrillation. Ventricular fibrillation is the fatal rhythm in some 65 percent of cardiac arrests. About 3 percent of arrests are caused by ventricular tachycardia (a very fast heart rate), which usually deteriorates into fibrillation, and the remainder is the consequence of an asystolic (flat line) rhythm or a rhythm called pulseless activity (a flaccid heart unable to contract).

The exact cause of ventricular fibrillation is poorly understood. In many instances, it is triggered by a partially or completely occluded coronary artery causing an ischemic—and irritable—area of muscle in the heart. But sometimes the heart goes directly into ventricular fibrillation without an obvious cause. At the instant of fibrillation, the heart pumps no blood, so the pulse ceases and the blood pressure falls to zero. This is called clinical death, and it will turn into irreversible biological death if circulation is not restored within minutes.

Ventricular fibrillation, though it occasionally happens during surgery, most often occurs outside a hospital setting, during routine activities. Of the 350,000 sudden cardiac deaths a year in the U.S., 75 percent happen at home, striking people who are in the prime of their lives.

In 1947 Beck's only option was to reopen the chest and manually compress the heart. Cardiopulmonary resuscitation (CPR), as we know it today, would not be invented until 1960. Beck knew that manually compressing the heart only bought time—electricity was (and remains) the only means for treating ventricular fibrillation. For a decade, Beck had developed and perfected his machine, defibrillating hundreds of dogs, but he needed to demonstrate its lifesaving potential on a human. One case was all he needed. He published a report in the *Journal of the American Medical Association* and immediately proselytized physicians to recognize fibrillation and learn how to use defibrillators.

Beck envisioned being "at the threshold of an enormous potential to save life." He saw the defibrillator as the tool for dealing with, to use his expression, "hearts too good to die"—hearts that would remain undamaged if the defibrillation could occur quickly enough. His expression is apt because a heart that is successfully defibrillated usually has many years of mileage left; a heart that fibrillates is like a million-dollar piece of equipment failing because of a 20-cent fuse.

Fifty years later is a good time to ask whether Beck's vision has been achieved. Did the world embrace his invention? Has its huge potential been realized? What does the future hold?

Beck's defibrillator was a large, ponderous machine. It used alternating current directly from a wall socket and required a bulky and heavy step-up transformer. The voltage, usually 1,000 volts, was applied for a quarter or half of a second. The machine was barely portable, although wheels gave it some mobility. Its biggest drawback was the supposed need to place its metal paddles directly on the ventricles, because not enough was known about how much electricity to use to shock through the chest. But it was a start. From such humble beginnings, defibrillators have grown smaller, smarter and far more sophisticated. As the technology developed, so did the clinical applications.

Shortly after Beck's 1947 report, defibrillators were placed in operating rooms throughout the Western world. But they would remain in operating rooms and have very limited use so long as the chest had to be opened and the paddles placed directly on the heart. This problem was solved in 1956 by Paul M. Zoll of Harvard Medical School, who demonstrated that defibrillation could successfully occur across an intact chest. Now the device could move to the rest of the hospital. Defibrillators began appearing in emergency departments as well as coronary care units.

Because defibrillators were large and inherently stationary and required alternating current to operate, they were confined to hospitals. To leave the hospital, defibrillators had to become portable, and there had to be a way of bringing them to patients where they lived. The obstacles were overcome in 1960 by Bernard Lown of the Harvard School of Public Health and K. William Edmark of the University of Washington. They demonstrated not only that defibrillators could be powered by direct current but also that these DC machines were, in fact, safer because there were fewer postshock complications such as heart blocks or other difficult-to-treat rhythm disturbances. Also, direct current allowed relatively portable batteries to power the device and used capacitors for collecting and concentrating the charge. Although these first-generation battery-powered devices weighed 35 pounds, portable defibrillators could at last enter the community. Now all that was needed was a means to transport them to the patient.

At Royal Victoria Hospital in Belfast, Northern Ireland, two cardiologists saw the mounting toll from coronary artery disease—an almost invisible carnage because it was occurring before their patients were admitted, usually within an hour of symptoms. J. Frank Pantridge and his colleague John S. Geddes reasoned that the only way to reach patients dying from ventricular fibrillation was to go after them directly in their homes. Resurrecting an old ambulance, they established the world's first mobile intensive care unit in 1966. The unit was staffed with a doctor and nurse and equipped with a jerry-rigged defibrillator powered by two 12-volt car batteries.

Success came slowly, but within 18 months they had accumulated enough experience to publish their findings in the international medical journal *Lancet*. Of groundbreaking importance: information on 10 patients with cardiac arrest. All had ventricular fibrillation, and all were resuscitated and admitted to the hospital. Five were subsequently discharged alive.

An Evolving Technology

The concept spread rapidly. By the late 1960s programs to implement mobile intensive care units were established in several cities. The U.S. version replaced the doctor and nurse with specially trained individuals called paramedics. For the first time in history, people dying suddenly in the community were being brought back to life. Paramedic programs delivering advanced emergency care are now found in virtually every urban and suburban area of the U.S. and in many Western countries.

But paramedics and ambulances are not enough. When a person goes into defibrillation, every minute counts, and waiting for an ambulance to arrive eats away at precious time. Clearly, it would be beneficial to have defibrillators in the hands of a still wider group of laypeo-

ple or emergency service personnel.

Up into the 1970s defibrillators were manually operated. The operator—doctor, nurse or paramedic—had to interpret the cardiac rhythm on a small oscilloscope and then, if ventricular fibrillation was present, apply the paddles and shock the patient. To bring defibrillators to a larger audience, the device would have to become easier to use. The next technological evolution provided just that. In the 1980s the defibrillator grew "brains." Computer algorithms, able to detect ventricular fibrillation, were incorporated into standard defibrillators. Such "smart" defibrillators, known as automatic external defibrillators, interpret the patient's rhythm and will deliver a shock only if ventricular fibrillation is present. Using voice-chip technology, automatic external defibrillators, some weighing as little as four pounds, "talk" to the operator and coach him or her through the procedure. Smart defibrillators spread the technology to another level of emergency care, namely, the hundreds of thousands of medical technicians who staff basic ambulance services.

Each new technological breakthrough has seen a corresponding increase in the number of defibrillators and the situations in which they are used. Today there are more than 250,000 defibrillators in the U.S. Some 110,000 are deployed outside hospitals, and perhaps half of those are automatic external defibrillators.

The American Heart Association launched a public-access defibrillation effort in 1994, advocating automatic external defibrillators in the hands of first responders and other public personnel (such as police and security guards). Clearly, we are on the cusp of another surge in defibrillator availability. There is no question that efforts to place more defibrillators in the community and into the hands of public personnel will be useful. But the payoff will be small because most cardiac arrests do not happen in stadiums or shopping malls; they happen in bedrooms and living rooms. In Seattle and King County, Washington, for instance, only 15 percent of cardiac arrests occur in public locations.

The promise for defibrillators will most probably be realized only when they become consumer products and can be purchased at the neighborhood pharmacy. For this to happen, the price must be made affordable, and the Food and Drug Administration would have to allow companies to market defibrillators to consumers. Currently automatic external defibrillators are prescription devices that cost $3,000, although it is likely that mass production (on the scale of one million units a year) could lower the selling price to $350. There is nothing inherently dangerous about an automatic home defibrillator, because the device shocks only for ventricular fibrillation and will not allow a shock to be delivered if the condition is not present. One day consumer automatic external defibrillators may be as common as fire extinguishers in the home.

Small Enough to Implant

The concept of building smaller, more intelligent defibrillators and moving them from the operating room to people's living rooms can be logically carried even further. Why not place the defibrillator in the person's chest? This is exactly what Michel Mirowski of Sinai Hospital of Baltimore did after a tragic personal experience in 1966. His mentor and friend was hospitalized for recurrent heart arrhythmias unresponsive to medications and required constant monitoring and repeated defibrillatory shocks in the coronary care unit. The friend chose not to live his life in the hospital and, against advice, checked himself out. He died days later. Although there was nothing anyone could do then, Mirowski vowed to solve the problem.

Working in a basement laboratory at Sinai and without research funding, Mirowski and his colleague Morton M. Mower set out to miniaturize defibrillators and implant them in the chests of high-risk patients. After prototypes were tested on dogs, the first human implantation occurred in 1980 at Johns Hopkins Hospital. It was a success. Another five years of clinical testing passed before the device received FDA approval.

The first marketable implantable defibrillators were the size of a Walkman and weighed 12 ounces. Because of their size and weight, they had to be placed in a skin pocket in the abdomen with wires and electrodes running to the heart. Open-heart surgery was required because the electrodes had to be sewn directly onto the heart's ventricle. The device constantly monitored the heart's rhythm, and if it detected fibrillation, it charged its capacitors and its battery delivered a shock of 34 joules. The lower energy, compared with 200 or 300 joules for standard external defibrillation, was sufficient because it was applied directly to the heart and did not have to travel through the chest.

Implanting a defibrillator was major surgery, to be undertaken only in the most dire circumstances. But it was a start, and it demonstrated that lives could be saved. From 1985 until today, several generations of implantable cardioverter defibrillators have been developed. Each generation has resulted in a smaller and more sophisticated device. The latest version weighs only three ounces, small enough to be placed under the skin in the upper chest, similar to a pacemaker. The titanium can housing the device serves as one of the electrodes, and a single wire, threaded through a large vein directly into the heart, acts as the other. Thus, open-heart surgery is not needed, and placement is a simple, one-hour outpatient procedure. The most recent designs have a battery life of eight years. They can also store hours of sensing and electrocardiographic information that can then be downloaded through the skin, enabling the cardiologist to diagnose and troubleshoot ongoing problems. Such technology does not come cheap: these defibrillators cost $30,000, plus another $15,000 to $20,000 for implantation. In the U.S., more that 100,000 such devices have been implanted to date. At a projected rate of 30,000 a year, it is a $1-billion-a-year industry.

The Definitive Solution

Claude Beck would be amazed if he could see today's defibrillators. Smart defibrillators and three-ounce devices implanted in patients are advances inconceivable in 1947. But have these 50 years of development achieved defibrillation's promise for saving lives? The answer is a resounding no. Despite hundreds of emergency medical service programs and thousands of paramedics trained in defibrillation, only a tiny proportion of cardiac arrest victims are saved every year in the U.S. The small number (at best a few thousand) is not higher because defibrillation occurs too late. A strategy based on rushing defibrillators to collapsed individuals is destined to achieve minimal success.

The sad reality is that we do not understand the cause of fibrillation and cannot predict it, and therefore we cannot put defibrillators in the hands, and chests, of everyone who might benefit

from them. (Twenty percent of ventricular fibrillation cases occur in people who have not been diagnosed with heart disease.) We can only speculate that its triggers include ischemia (insufficient blood to part of the heart muscle, making it irritable); electrolyte abnormalities; autonomic imbalances, caused by abnormal surges in hormones such as adrenaline; drugs; and inherited disorders.

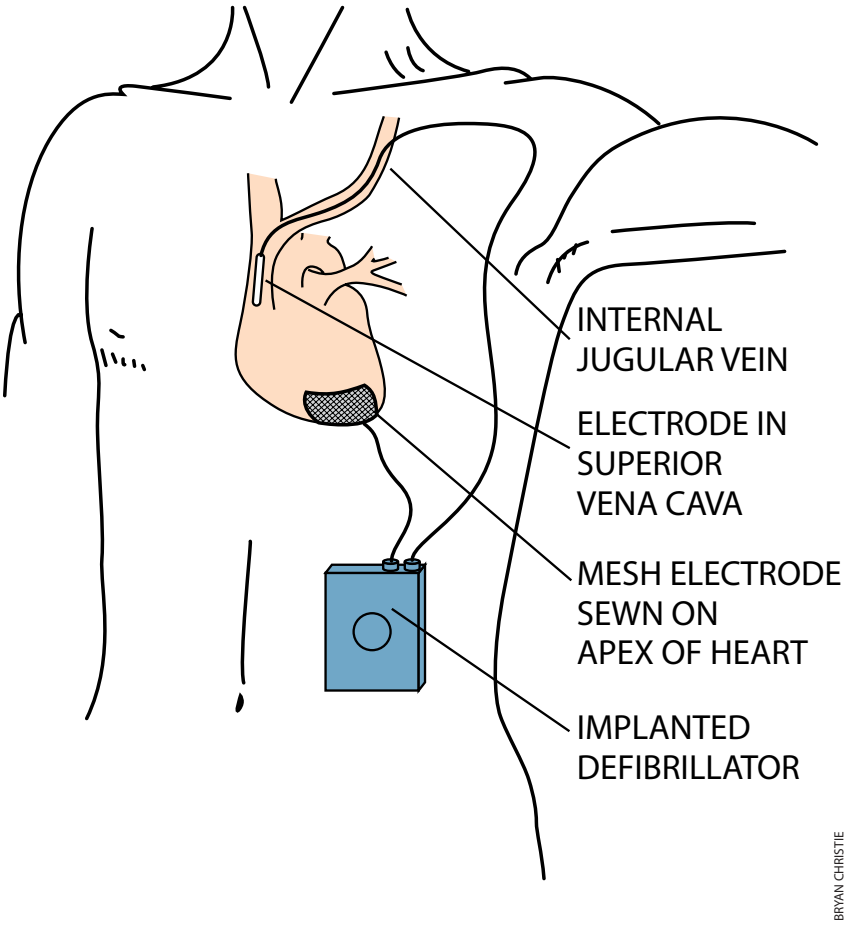
In fact, we know very little about why defibrillation works in the first place. It is believed that the electrical shock simultaneously depolarizes every muscle fiber in the heart, allowing its internal timing mechanism to reset and return to normal. In a way, it is like rebooting a computer that has suddenly and mysteriously seized. Not only can we not predict it, but we also cannot prevent it. Whether the future brings widespread availability of consumer automatic external defibrillators or liberalized indications for implantable devices, it is important to realize that the only definitive solution to the problem of ventricular fibrillation lies in prevention.

For now, rapid defibrillation offers the only hope for victims of sudden cardiac death. Defibrillators seem to epitomize medical high technology and offer thousands of patients the promise of extended life. Yet within that promise lies a paradox first described by essayist and physician Lewis Thomas. What we think of as high technology—in this case, defibrillation—is really low technology, because we have only a rudimentary understanding of the disease.

The highest level of medical technology is the least expensive and comes about only with a good understanding of the disease—vaccination, for example. The lowest level is very expensive and results from treatment of the ravages of the disease rather than its prevention. We can miniaturize defibrillators and place them in people's chests. But we do not yet know what causes the heart suddenly to fibrillate. And we cannot yet define the harbingers of ventricular fibrillation.

Fifty years have witnessed astounding technological and clinical progress in defibrillation. Yet the problem of ventricular fibrillation still looms as the leading cause of death in adults. I would have to say Beck's vision is only 50 percent achieved. When home defibrillators are approved, perhaps the enormous potential of defibrillation will finally be attained.

But this will be a false victory. The true victory will occur when we understand ventricular fibrillation and can prevent its occurrence. Wouldn't it be nice one day to view a defibrillator as an outdated piece of low technology? SA



THE EARLIEST IMPLANTABLE defibrillators (*above*) were relatively bulky affairs of 12 ounces implanted in the abdomen, with electrodes running directly to the apex of the heart and the superior vena cava.

The Author

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If You Don't Have a Defibrillator

by Carl E. Bartecchi

Cardiopulmonary resuscitation, commonly known as CPR, can save the lives of victims of ventricular fibrillation and its common predecessor, ventricular tachycardia. Nationwide, however, the technique successfully salvages fewer than 5 percent of out-of-hospital cardiac arrests. The reasons are sobering. The elderly, who need it most often, are least likely to have CPR training. Bystanders are unlikely to respond because of concern for their own health in this era of AIDS, hepatitis and drug-resistant tuberculosis. Also, although cardiac arrest tends to occur in the home, most family members of cardiac patients remain unfamiliar with CPR techniques. And the hyperacute atmosphere surrounding cardiac arrest does not lend itself to the clear, methodical process taught in CPR courses.

There is an alternative to CPR that is simple and easily learned, especially by the elderly. It features maneuvers that can be performed quickly—during the four- to six-minute window of opportunity for restoring circulation and oxygenation. As with basic CPR, one should not expect these steps to be successful in a high percentage of cases. The nature of cardiac arrest itself, together with age and underlying problems, may make saving the victim impossible. Yet simply doing *something* can sometimes save a life. Chest compressions alone, for example, can keep a person alive for a few minutes until trained medical help arrives. The important lesson to remember is to do something and to do it fast.

What to Do

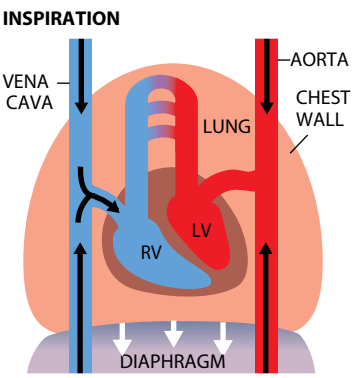
When an individual suddenly collapses, first quickly check for pulse or heartbeat. If one is present, raise the victim's legs two feet above the plane of the reclining body (to augment fluid return to the central circulation); then, call for medical assistance.

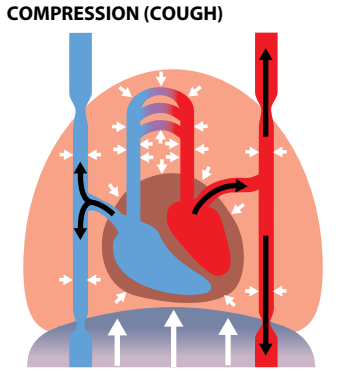
If there is no pulse, immediately suspect cardiac arrest. Check the airway for obstruction and clear it. Because most victims resuscitated from cardiac arrest have ventricular tachycardia or ventricular fibrillation, assume that is the problem and follow one of these two procedures:

Cough

If the victim is conscious and capable, he or she should be encouraged to cough vigorously once or twice. Forceful coughs have been shown to transmit a small amount of current to the heart capable of terminating these catastrophic dysrhythmias and allowing for an effective cardiac rhythm to be reestablished. This maneuver is especially suited for self-administration; a patient with known cardiac disease who suddenly feels palpitations in the chest followed by lightheadedness and the feeling of impending loss of consciousness could do little harm by bringing forth one or two vigorous coughs.

ILLUSTRATIONS BY DANA BURNS-PIZER





During the cough's inspiratory phase, the downward movement of the diaphragm facilitates the return of blood from the body to the heart's right ventricle and even oxygenates the blood flowing through the lungs at that time. During the expiratory phase, contraction of the abdominal muscles forces the diaphragm into the chest cavity, generating high pressures that are applied to the heart and its associated large blood vessels, which in turn propels blood through the open heart valves to the brain and other organs.

Regular, repeated, forceful coughs—at a rate of up to 60 per minute—can be as effective as classical CPR in providing blood flow to critical organs, thus supplementing the stricken heart. Cough CPR has proved effective for approximately 90 seconds, although isolated cases for up to five minutes have been reported. The only problem is that the patient is certain to develop fatigue. But cough CPR can buy time.

Thump

If the patient is not capable of coughing, one or two thumps to the midchest can be given with a clenched fist within no more than one minute of collapse. The thump should be applied from six to eight inches above the chest and directed at an area about two thirds of the distance down the breastbone. Should the first blow not result in a pulse, a second, stronger blow should be given immediately. The thump can also be self-administered.

It is not known how the thump procedure works, although it is suspected that the thump causes a mechanoelectrical stimulus that terminates the undesirable rhythm disturbance.

CARL E. BARTECCHI is clinical professor in the department of medicine at the University of Colorado Health Sciences Center.

Originally published in May 2002

ATHEROSCLEROSIS: THE NEW VIEW

It causes chest pain, heart attack and stroke, leading to more deaths every year than cancer. The long-held conception of how the disease develops turns out to be wrong

By Peter Libby

JEFF JOHNSON *Hybrid Medical Animation*

ATHEROSCLEROSIS in an artery feeding the heart can set the stage for a heart attack.

AS RECENTLY AS FIVE YEARS AGO, most physicians would have confidently described atherosclerosis as a straight plumbing problem: Fat-laden gunk gradually builds up on the surface of passive artery walls. If a deposit (plaque) grows large enough, it eventually closes off an affected "pipe," preventing blood from reaching its intended tissue. After a while the blood-starved tissue dies. When a part of the cardiac muscle or the brain succumbs, a heart attack or stroke occurs.

Few believe that tidy explanation anymore. Investigations begun more than 20 years ago have now demonstrated that arteries bear little resemblance to inanimate pipes. They contain living cells that communicate constantly with one another and their environment. These cells participate in the development and growth of atherosclerotic deposits, which arise in, not on, vessel walls. Further, relatively few of the deposits expand so much that they shrink the bloodstream to a pinpoint. Most heart attacks and many strokes stem instead from less obtrusive plaques that rupture suddenly, triggering the emergence of a blood clot, or thrombus, that blocks blood flow.

The research has, moreover, established a key role for inflammation in atherosclerosis. This process—the same one that causes infected cuts to become red, swollen, hot and painful—underlies all phases of the disorder, from the creation of plaques to their growth and rupture. When microbial invaders threaten to hurt us, inflammation (literally meaning "on fire") helps to ward off infection. In the case of atherosclerosis, though, the inflammation proves harmful. In other words, our own defenses bombard us with friendly fire, just as happens in more famously inflammatory conditions, such as rheumatoid arthritis.

This revised conception suggests new ideas for detecting and treating atherosclerosis. It also resolves some disturbing mysteries—notably, why many heart attacks strike without warning and why certain therapies meant to avert heart attacks frequently fail. Society sorely needs advances in prevention, detection and therapy of atherosclerosis. Contrary to public perception, the heart attacks and strokes that result from this condition exceed cancer as a cause of death in industrial nations and are growing more prevalent in developing countries as well.

Overview/*Atherosclerosis*

- Scientists now agree that inflammation fuels the development and progression of atherosclerosis: the dangerous accumulation of fat-laden deposits, or plaques, in the arteries. The old view—that fat builds up on passive artery walls—is no longer tenable.
- Inflammation can also cause certain plaques to rupture. Blood clots tend to form over ruptured plaques and can then occlude arteries, leading to such atherosclerotic complications as heart attack and stroke.
- Excess low-density lipoprotein (LDL), or "bad cholesterol," in the blood can trigger arterial inflammation. And cholesterol-lowering therapies—already cornerstones of treatment for atherosclerosis—can reduce it. Strategies that interfere with inflammation in other ways are under study as well.
- A blood test that detects ongoing inflammation might prove useful as an adjunct to the cholesterol tests that doctors now employ to assess risk for heart attack and stroke.

Igniting Trouble

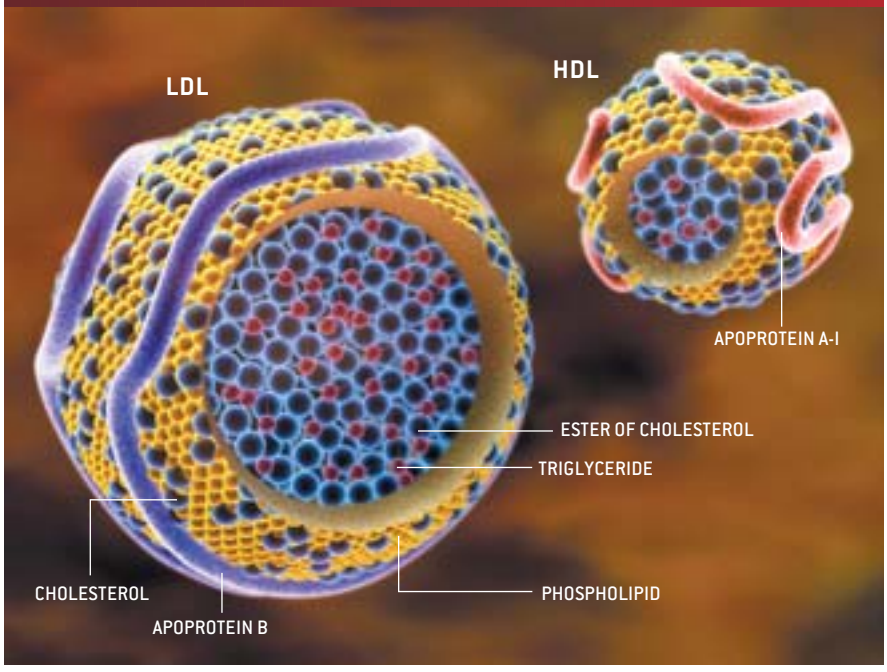
LACKING TOOLS to describe interactions among cells and molecules, the ancients who first defined inflammation had to focus on what they could see and feel. Today we know that the outward signs reflect a pitched struggle playing out on a microscopic battlefield. After sensing (rightly or wrongly) that a microbial attack has begun, certain white blood cells—the immune system's frontline warriors—convene in the apparently threatened tissue. There they secrete an array of chemicals intended to limit any infection. These chemicals include oxidants (able to dam-

NEW ROLES FOR FAMILIAR ACTORS

POPULAR DESCRIPTIONS of atherosclerosis correctly cast low-density lipoprotein (LDL) as "bad" and high-density lipoprotein (HDL) as "good." Yet these particles (*shown in cutaway views*) fulfill their roles in more ways than scientists once thought.

Lipoproteins transport cholesterol in the bloodstream. LDLs truck it from the liver and intestines to various tissues, which use it to repair membranes or produce steroids. HDLs haul cholesterol to the liver for excretion or recycling. The classic view of how atherosclerosis develops implies that excess LDL promotes the condition by accumulating on vessel walls. More recent work shows that it accumulates *within* vessel walls, where its components become oxidized and altered in other ways; the altered components then incite an inflammatory response that progressively—and dangerously—alters arteries.

Physicians also generally explain HDL's protective effects as deriving from its removal of cholesterol from arteries. HDL certainly does that, but new findings indicate it can also combat atherosclerosis by interfering with LDL oxidation. —*P.L.*



age invaders) and signaling molecules, such as small proteins called cytokines, that orchestrate the activities of defensive cells. Researchers therefore document an inflammatory response by identifying inflammatory cells or mediators of their activities in a tissue.

The clearest picture of inflammation's role in the onset of atherosclerosis comes from investigations into low-density lipoprotein, a.k.a. bad cholesterol. LDL particles, composed of fatty molecules (lipids) and protein, transport cholesterol (another lipid) from their source in the liver and intestines to other organs. Scientists have long known that although the body needs LDL and cholesterol, excessive amounts promote atherosclerosis. Until recently, however, no one could explain how a surplus leads to plaque formation.

Experiments on cultured cells and animals now indicate that the trouble begins when LDLs from the blood collect in the intima, the part of the arterial wall closest to the bloodstream [*see illustration on next two pages*]. At reasonable concentrations in the blood, LDLs can pass in and out of the intima, which consists mainly of the endothelial cells that line vessel walls, the underlying extracellular matrix (connective tissue), and a smattering of smooth muscle cells (matrix producers). But in excess, LDLs tend to become stuck in the matrix.

As the LDLs accumulate, their lipids undergo oxidation (similar to the processes that rust pipes and spoil butter) and their proteins undergo both oxidation and glycation (binding by sugars). Cells in the vessel wall seem to interpret the changes as a danger sign, and they call for reinforcements from the body's defense system.

In particular, endothelial cells display adhesion molecules on their blood-facing surface. These molecules latch like Velcro onto quiescent inflammatory cells known as monocytes, which normally circulate in the blood. This interaction causes the cells to drop from the circulation and to roll along and attach to the artery wall. The modified LDLs also spur the endothelial cells and smooth muscle cells of the intima to secrete chemicals called chemokines, which attract monocytes. Much as hounds track the scent of their prey, the monocytes squeeze between endothelial cells and follow the chemical trail to the intima.

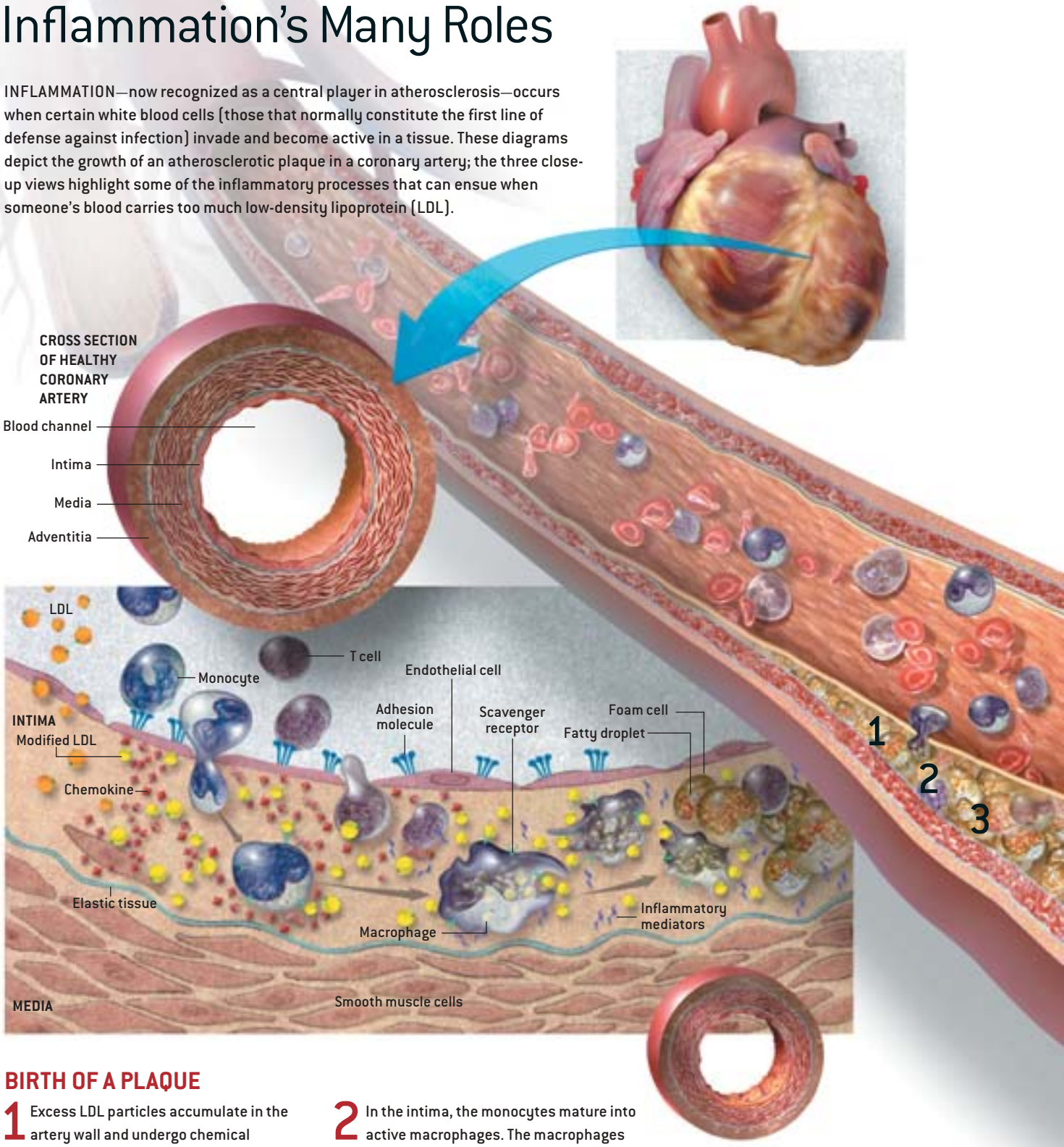
Chemokines and other substances elaborated by the endothelial and smooth muscle cells then induce the monocytes to multiply and mature into active macrophages: fully armed warriors, ready to unleash their various weapons against the body's enemies. These warriors also set about clearing perceived invaders from the vessel wall. Reacting to proteins emitted by stimulated endothelial and intimal smooth muscle cells, the macrophages decorate their surface with molecules called scavenger receptors, which capture modified LDL particles and help the macrophages ingest them. The macrophages ultimately become so packed with fatty droplets that they look foamy when viewed under a microscope. Indeed, pathologists refer to the fat-filled macrophages as foam cells.

Just as monocytes follow adhesion molecules and chemokines into the intima, so do T lymphocytes, white blood cells that represent a different branch of the immune system. These lymphocytes also release cytokines that amplify inflammatory activities in artery walls. Together the foamy macrophages and a lesser number of T lymphocytes compose the so-called fatty streak, a precursor of the

MEDICINE HORSE *Hybrid Medical Animation*

Inflammation's Many Roles

INFLAMMATION—now recognized as a central player in atherosclerosis—occurs when certain white blood cells (those that normally constitute the first line of defense against infection) invade and become active in a tissue. These diagrams depict the growth of an atherosclerotic plaque in a coronary artery; the three close-up views highlight some of the inflammatory processes that can ensue when someone's blood carries too much low-density lipoprotein (LDL).



BIRTH OF A PLAQUE

1 Excess LDL particles accumulate in the artery wall and undergo chemical alterations. The modified LDLs then stimulate endothelial cells to display adhesion molecules, which latch onto monocytes (central players in inflammation) and T cells (other immune system cells) in the blood. The endothelial cells also secrete "chemokines," which lure the snared cells into the intima.

2 In the intima, the monocytes mature into active macrophages. The macrophages and T cells produce many inflammatory mediators, including cytokines (best known for carrying signals between immune system cells) and factors that promote cell division. The macrophages also display so-called scavenger receptors, which help them ingest modified LDLs.

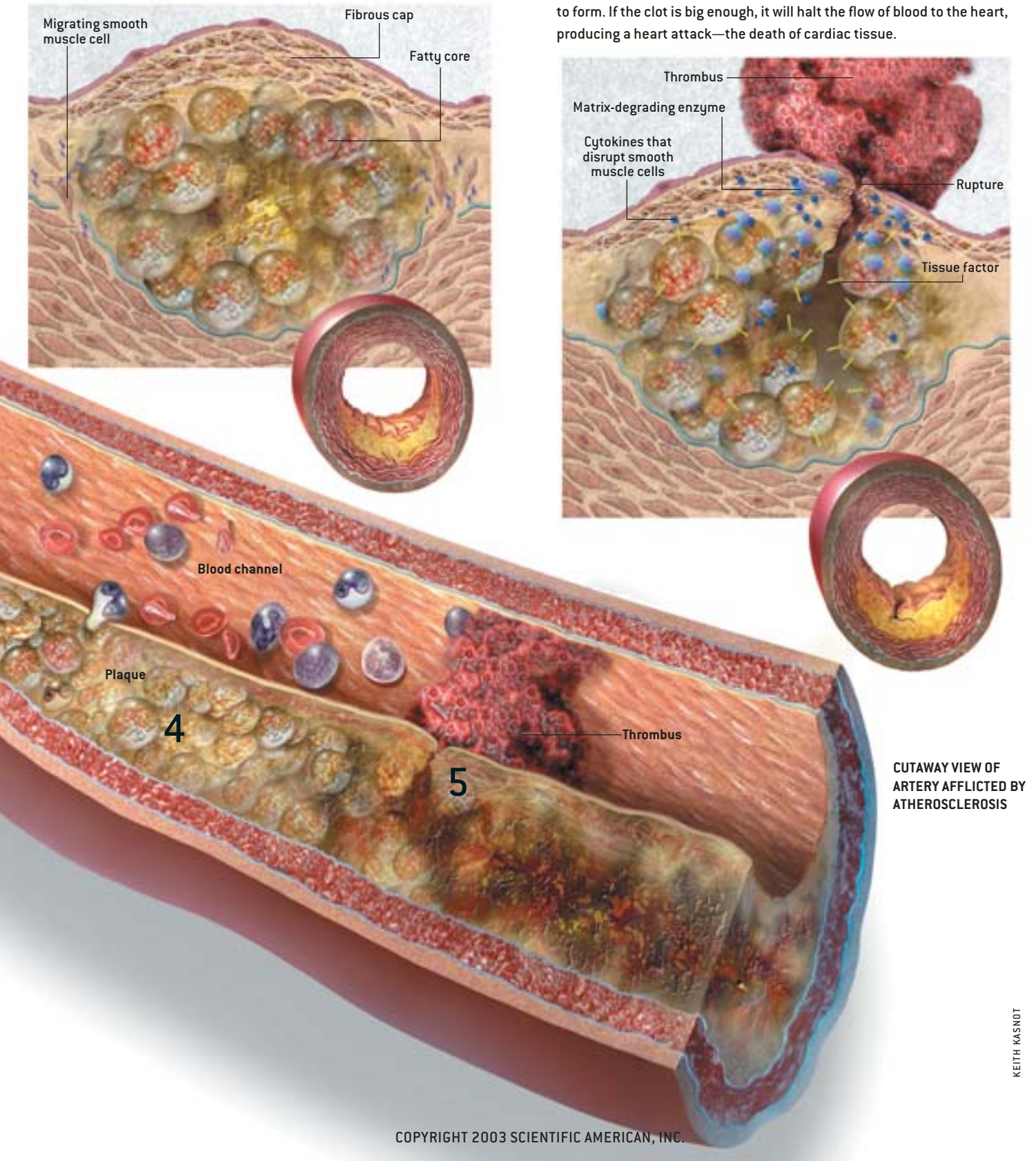
3 The macrophages feast on LDLs, becoming filled with fatty droplets. These frothy-looking, fat-laden macrophages (called foam cells) and the T cells constitute the fatty streak, the earliest form of atherosclerotic plaque.

PLAQUE PROGRESSION

4 Inflammatory molecules can promote further growth of the plaque and formation of a fibrous cap over the lipid core. The cap develops when the molecules induce smooth muscle cells of the media to migrate to the top of the intima, multiply and produce a tough, fibrous matrix that glues the cells together. The cap adds to the size of the plaque but also walls it off safely from the blood.

PLAQUE RUPTURE

5 Later, inflammatory substances secreted by foam cells can dangerously weaken the cap by digesting matrix molecules and damaging smooth muscle cells, which then fail to repair the cap. Meanwhile the foam cells may display tissue factor, a potent clot promoter. If the weakened plaque ruptures, tissue factor will interact with clot-promoting elements in the blood, causing a thrombus, or clot, to form. If the clot is big enough, it will halt the flow of blood to the heart, producing a heart attack—the death of cardiac tissue.



CUTAWAY VIEW OF ARTERY AFFLICTED BY ATHEROSCLEROSIS

KEITH KASNOT

complex plaques that later disfigure arteries. Disturbingly, many Americans harbor nascent plaques as early as their teens.

Fueling Plaque Growth

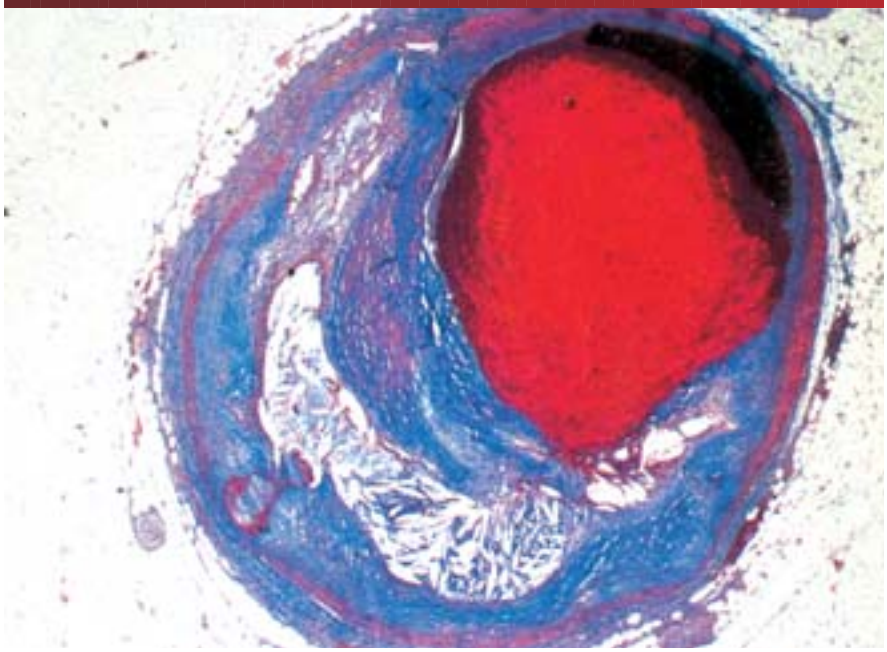
WHEN AN INFLAMMATORY response in, say, a scraped knee successfully blocks an infection, macrophages release molecules that facilitate healing. A "healing" process also accompanies the more chronic, low-level kind of inflammation that operates in atherosclerosis. Instead of restoring artery walls to their original state, though, the process perversely remodels—changes the character of—the wall, eventually generating a bigger, more complicated plaque.

In recent years, biologists have learned that macrophages, endothelial cells and smooth muscle cells of the inflamed intima secrete factors that prod smooth muscle cells of the media (the tissue under the intima) to migrate to the top of the intima, replicate and synthesize components of the extracellular matrix. The cells and matrix molecules coalesce into a fibrous covering overlying the original atherosclerotic zone. As this "cap" matures, the zone underneath generally changes somewhat. Most obviously, some fraction of the foam cells die, releasing lipids. For this reason, pathologists denote the region under the cap as the lipid or necrotic core.

Surprisingly, atherosclerotic plaques expand outward during much of their existence, rather than impinging on an artery's blood-carrying channel. This pattern preserves blood flow for quite some time, often for decades. When the plaques do push inward, they restrict the blood channel—a condition called stenosis. Stenosis can impede blood delivery to tissues, especially at moments of greater need, when the arteries would usually expand. When a person exercises or experiences stress, for instance, blood flow through a compromised heart artery can fail to match the increased demand, causing angina pectoris: a feeling of tightness, squeezing or pressure usually under the breastbone. Narrowing in other arteries can cause painful cramping of the calves or buttocks during exertion, symptoms known as intermittent claudication.

AN INSIDE VIEW

THE BLOOD CLOT, or thrombus (*red*), captured in this micrograph has formed at the site of an atherosclerotic plaque in a coronary artery and has occluded the vessel. Some clots dissolve before they cause a heart attack or stroke, but they can foster trouble in another way—by stimulating plaque expansion.



M. J. DAVIES/OXFORD UNIVERSITY PRESS/HARVEY MILLER PUBLISHERS

Causing Crises

SOMETIMES A PLAQUE grows so large that it virtually halts blood flow in an artery and generates a heart attack or stroke. Yet only about 15 percent of heart attacks happen in this way. By carefully examining vessel walls of people who died from heart attacks, pathologists have demonstrated that most attacks occur after a plaque's fibrous cap breaks open, prompting a blood clot to develop over the break. The plaques most likely to fracture possess a thinned cap, a large lipid pool and many macrophages, and their vulnerability stems, as in earlier stages of atherosclerosis, from inflammation.

The integrity of the fibrous covering depends largely on steel-strong collagen fibers made by smooth muscle cells. When something causes inflammation to flare in a relatively quiet plaque, mediators of the process can compromise the cap in at least two ways. My laboratory has shown that these inflammatory mediators can stimulate macrophages to secrete enzymes that degrade collagen, and they can inhibit smooth muscle cells from extruding the fresh collagen required to repair and maintain the cap.

Clots form when blood seeps through a fissure in the cap and encounters a lipid core teeming with proteins able to facilitate blood coagulation. For example, molecules on T cells in the plaques spur foam cells to manufacture high levels of tissue factor, a potent clot inducer. Circulating blood itself contains precursors of the proteins involved in the cascade of reactions responsible for clot formation. When blood meets tissue factor and other coagulation promoters in a plaque's core, the clotting precursors jump into action. Our bodies produce substances that can prevent a clot from materializing or can degrade it before it causes a heart attack or stroke, but inflamed plaques release chemicals that impede the innate clot-busting machinery.

If a clot does get cleared naturally or with the aid of drugs, the healing process may kick in once again, restoring the cap but also further enlarging the plaque by

forming scar tissue. Indeed, considerable evidence suggests that plaques grow in fits and starts, as triggers of inflammation come and go and as clots emerge and dissolve but leave scars.

The new picture of atherosclerosis explains why many heart attacks seem to come from out of the blue: the plaques that rupture do not necessarily protrude very far into the blood channel and so may not cause angina or appear prominently on images of the channel. The new view also clarifies why therapies that focus on widening the blood passage in semioccluded arteries (balloon angioplasty or insertion of wire-cage stents) or on surgically creating a bypass can ease angina yet frequently fail to prevent a future heart attack. In such cases, the danger may lurk elsewhere, where a plaque causes less narrowing but is more prone to rupturing. Sadly, even when stenosis *is* the problem, treated arteries often become reoccluded fairly rapidly—apparently in part because the treatments can elicit a robust inflammatory response.

Beyond Bad Cholesterol

ALTHOUGH LDL frequently sparks the sequence of events I have outlined, scientists have identified several other factors that unequivocally increase a person's risk for atherosclerosis or its complications. Many of these risk factors, and a few still under study, exhibit intriguing inflammatory properties. Before I describe some of those features, I must first point out that LDL probably plays an even larger role in initiating and perpetuating atherosclerosis than is generally recognized.

A much repeated statistic says that half of all patients who have angina or have had a heart attack do not have above-average LDL levels—a finding frequently interpreted to mean that in such individuals, LDL exerts no influence on the atherosclerosis at the root of those disorders. But typical LDL levels in Western society exceed by far the body's needs and can actually promote arterial disease.

Indeed, in response to new data correlating heart health with lipoprotein levels, public health experts have progressively refined the definition of "healthy" LDL levels. Guidelines released last year by an expert panel convened in cooperation with the National Institutes of Health now explicitly label LDL-cholesterol levels below 100 milligrams per deciliter of blood (mg/dL) as optimal. They also suggest considering drug treatment earlier than before—at 130 mg/dL instead of 160—for certain people with multiple risk factors. For adults with a relatively low risk of heart disease, the guidelines recommend (as before) initiating "lifestyle changes"—diet and exercise—at 160 mg/dL and considering drug treatment at 190 mg/dL.

Investigators have yet to explore the connections between other risk factors and inflammation with the intensity accorded to LDL, but they have uncovered suggestive links. Diabetes, for instance, elevates glucose levels in the blood; this sugar can enhance the glycation, and thus the inflammatory properties, of LDL. Smoking causes oxidants to form and might hasten the oxidation of LDL's constituents, thereby fostering arterial inflammation even in individuals with average LDL levels. Obesity contributes to diabetes and vascular inflammation. High blood pressure may not exert direct inflammatory effects, but a hormone partly responsible for much human hypertension—angiotensin II—appears to incite inflammation as well; elevated levels of this hormone, then, might give rise to hypertension and atherosclerosis simultaneously.

Conversely, high-density lipoprotein (HDL) seems beneficial; as levels of this "good cholesterol" decline, the likelihood of suffering a heart attack goes up. Accordingly, to fine-tune estimates of cardiovascular risk, many physicians today measure not only levels of LDL in the blood but also the level of HDL and the ratio of LDL (or LDL plus its various relatives) to HDL. HDL may achieve its beneficial effects in part by reducing inflammation: along with cholesterol, it can transport antioxidant enzymes able to break down oxidized lipids.

Given inflammation's usual responsibility in the body—blocking and eliminating infectious agents—biologists have naturally looked at whether arterial infections might contribute to inflammation in the arteries. Recent work suggests that atherosclerosis can develop in the absence of infection. Nevertheless, circumstantial evidence suggests that certain microorganisms, such as herpesviruses or the bacterium *Chlamydia pneumonia* (a frequent cause of respiratory infections), could well induce or aggravate atherosclerosis at times. *C. pneumonia,* for instance, appears in many atherosclerotic plaques, and its constituents can evoke inflammatory responses by macrophages and by vascular endothelial and smooth muscle cells.

Infections might also act from a distance, in what I call an echo effect. When the body fights infections, inflammatory mediators can escape into the blood and travel to distant sites. These substances can, in theory, stimulate the white cells in atherosclerotic plaques, thereby prompt-

The ancients who first **DEFINED INFLAMMATION** had to focus on what they could see and feel. Today we know that the outward signs reflect a pitched struggle playing out on a **MICROSCOPIC BATTLEFIELD**.

THE AUTHOR

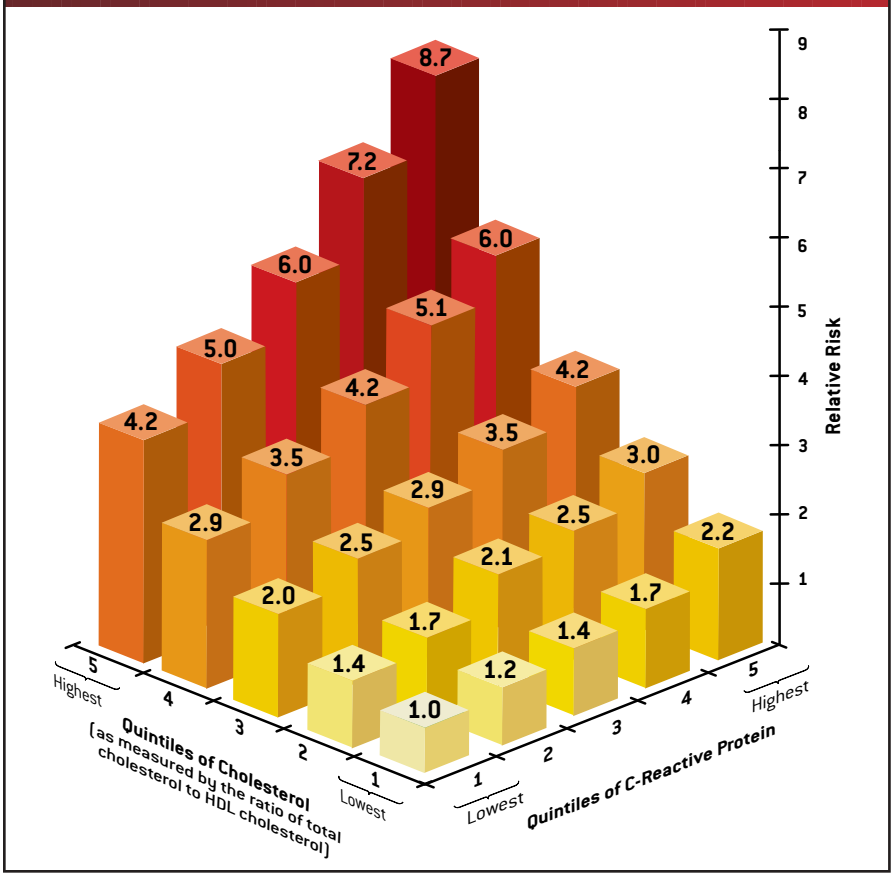
PETER LIBBY, who earned his M.D. from the University of California, San Diego, is chief of cardiovascular medicine at Brigham and Women's Hospital, Mallinckrodt Professor of Medicine at Harvard Medical School, and co-editor of the sixth edition of *Heart Disease,* a classic cardiology textbook (see "More to Explore," on page 55). He regards "lifestyle modification as the cornerstone of cardiovascular prevention" and practices what he preaches by running recreationally, albeit, he says, more avidly than swiftly.

A TELLING TEST

IN DECIDING WHETHER a patient requires therapy to prevent an atherosclerosis-related heart attack or stroke, physicians usually rely heavily on measurements of cholesterol in the person's blood. But that approach misses a great many vulnerable individuals. Several studies suggest that measuring blood concentrations of C-reactive protein—a marker of inflammation—could add useful information. Indeed, in one recent report, Paul M. Ridker of Brigham and Women's Hospital demonstrated that examining both C-reactive protein levels (which cannot be predicted from cholesterol measures) and cholesterol levels provides a more accurate indication of risk than assessing cholesterol alone (*graph*).

Ridker grouped cholesterol levels in the general adult population into five progressively rising ranges (quintiles) and, separately, divided C-reactive protein levels into quintiles as well. Then he determined the relative risk faced by people having different combinations of cholesterol and C-reactive protein values. That is, he assigned a danger level of "one" to individuals whose cholesterol and C-reactive values both fell in the lowest quintile (*front corner*) and calculated how much that risk multiplied in adults having other permutations of cholesterol and C-reactive protein measurements.

He found that high C-reactive protein values signify markedly elevated risk for heart attack or stroke even in individuals with seemingly reassuring cholesterol values. For instance, people with average (third-quintile) cholesterol levels and the highest C-reactive protein levels face much the same peril as those who have the highest cholesterol and lowest C-reactive protein levels. And subjects having the highest values for both cholesterol and C-reactive protein confronted the greatest risk of all. Encouraged by such results, researchers now hope to undertake a large study assessing whether basing treatment decisions on combined C-reactive protein and cholesterol testing will save lives. —*P.L.*



ing plaque growth or rupture. Clinical trials to see whether limited courses of antibiotics will prevent recurrent heart attacks are under way. A recently completed trial suggests, however, that antibiotics do not forestall recurrences in heart attack survivors.

Reducing Danger

INFLAMMATION'S essential role in atherosclerosis implies that anti-inflammatory medicines might slow this disease, and some (including aspirin) are already in use or under study. But logic and the investigations conducted so far suggest a need to look elsewhere as well.

Aspirin belongs to the class of drugs called NSAIDs (nonsteroidal anti-inflammatory drugs), a group that also claims such popular painkillers as ibuprofen and naproxen. Like other NSAIDs, aspirin can block the formation of certain lipid mediators of inflammation, including the prostaglandins, which generate pain and fever. Strong data from well-performed clinical trials indicate that aspirin shields against heart attacks and, in some patients, against mini strokes (technically, transient ischemic attacks, or TIAs). But the low doses that afford this protection probably reduce the clotting propensity of blood instead of quieting inflammation.

Scientists have little clinical data relating to the effects of other NSAIDs on atherosclerosis, and some evidence suggests that selective inhibitors of the prostaglandin-producing enzyme COX-2 might actually enhance thrombus development in some patients. Cortisone and related steroids could prove too toxic for long-term use, and no data support their utility in reducing atherosclerotic complications.

Even if anti-inflammatory drugs proved effective, they might have to be given for years on end to keep atherosclerosis at bay. That prospect worries me, because ongoing interference with inflammation could come at too high a price: increased risk of infection. One day someone could devise a way to halt the chronic, destructive inflammation of atherosclerosis without undermining overall immunity. But I suspect that a more practical strategy would concentrate on defusing the triggers at the root of arterial inflammation.

NINA FINKEL; SOURCE: "HIGH-SENSITIVITY C-REACTIVE PROTEIN: POTENTIAL ADJUNCT FOR GLOBAL RISK ASSESSMENT IN THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE," BY PAUL M. RIDKER IN *CIRCULATION*, VOL. 103, PAGES 1813–1818; APRIL 3, 2001

Fortunately, some means are at hand already. A heart-healthy diet, regular exercise and, for obese individuals, weight loss can reduce the risk of a heart attack and combat diabetes. In addition, since 1994 several impeccably designed and executed clinical trials have established beyond a doubt that lipid-lowering drugs can reduce the likelihood of atherosclerotic complications and can prolong life seemingly across the board—that is, in individuals with a broad range of risk levels. Researchers have not yet nailed down the mechanism behind the success of the lipid-lowering drugs, which do not seem to reduce arterial stenosis substantially. But studies of cells, whole animals and humans suggest that lipid lowering (as might be expected from the foregoing discussion) might help by limiting inflammation, thereby minimizing plaque buildup and make existing plaques less likely to rupture.

Recent analyses of the statins (widely prescribed lipid-controlling drugs) support this notion. They confirm that the drugs can decrease inflammation in patients. Experiments on isolated cells and laboratory animals indicate as well that the drugs' anti-inflammatory effects may not depend entirely on changing the concentrations of lipids in the blood. Statins—which decrease the levels of LDL and related bad lipids by increasing their disposal in the body—also limit the availability of chemicals that enable cells to respond to inflammatory mediators.

Experimental drugs that aim at other risk factors for heart disease and stroke might exert useful anti-inflammatory effects as well. Agents that raise levels of HDL or limit the action of angiotensin II come to mind. But treatment with antioxidant vitamins has proved disappointing.

No matter how good a drug is, it will be of no value if it sits unused on pharmacy shelves. Doctors need better ways of detecting dangerous atherosclerosis in the large fraction of people whose lipid levels look too good to justify treatment. Recent findings suggest that blood tests combining lipid testing with monitoring of a substance called C-reactive protein might improve detection.

Toward Early Detection

THE PRESENCE of C-reactive protein in the blood signifies that inflammation is occurring somewhere in the body; highly elevated levels, even in the presence of LDL values too low to prompt treatment under current guidelines, indicate an increased risk of heart attack or stroke. What is more, in at least one study, delivery of statins to people with below-average LDL concentrations but high C-reactive protein levels reduced the incidence of heart attack relative to the rate in a matched group of patients who received no treatment. Such results need to be confirmed in a much larger trial before doctors can confidently treat patients on the basis of the combined test, although some physicians already incorporate tests of C-reactive protein in their practices.

Noninvasive methods for specifically identifying vulnerable plaques might also help pinpoint individuals who lack strong warning signs of risk for heart attack or stroke but who nonetheless are destined for disaster. Ideas include measuring the heat of blood vessels (because heat should accompany inflammation) and altering existing imaging technologies, such as MRI or CT scans, to improve their ability to visualize material inside vessel walls. Geneticists, meanwhile, hunt for gene variants that render some people more vulnerable to chronic inflammation and to atherosclerosis and its complications, so that individuals most prone to these disorders can seek more aggressive monitoring and treatment.

For most of human history, inflammation's ability to ward off infection outweighed its drawbacks. Today, as we live longer, exercise less, eat too much and smoke, many of us suffer from inflammation's dark side—including its ability to contribute to atherosclerosis and other chronic disorders. Scientists continue to pursue a deeper understanding of inflammation's role in atherosclerosis and to decipher the devilishly intricate interactions that ignite and drive the inflammatory processes in the arteries. These insights should enable us to make further inroads against a disease of growing worldwide importance that causes extensive disability and takes far too many lives. SA

THE NEW PICTURE of atherosclerosis explains why many heart attacks come from out of the blue: the plaques that rupture do not necessarily protrude very far into the blood channel and so **MAY NOT CAUSE ANGINA**.

MORE TO EXPLORE

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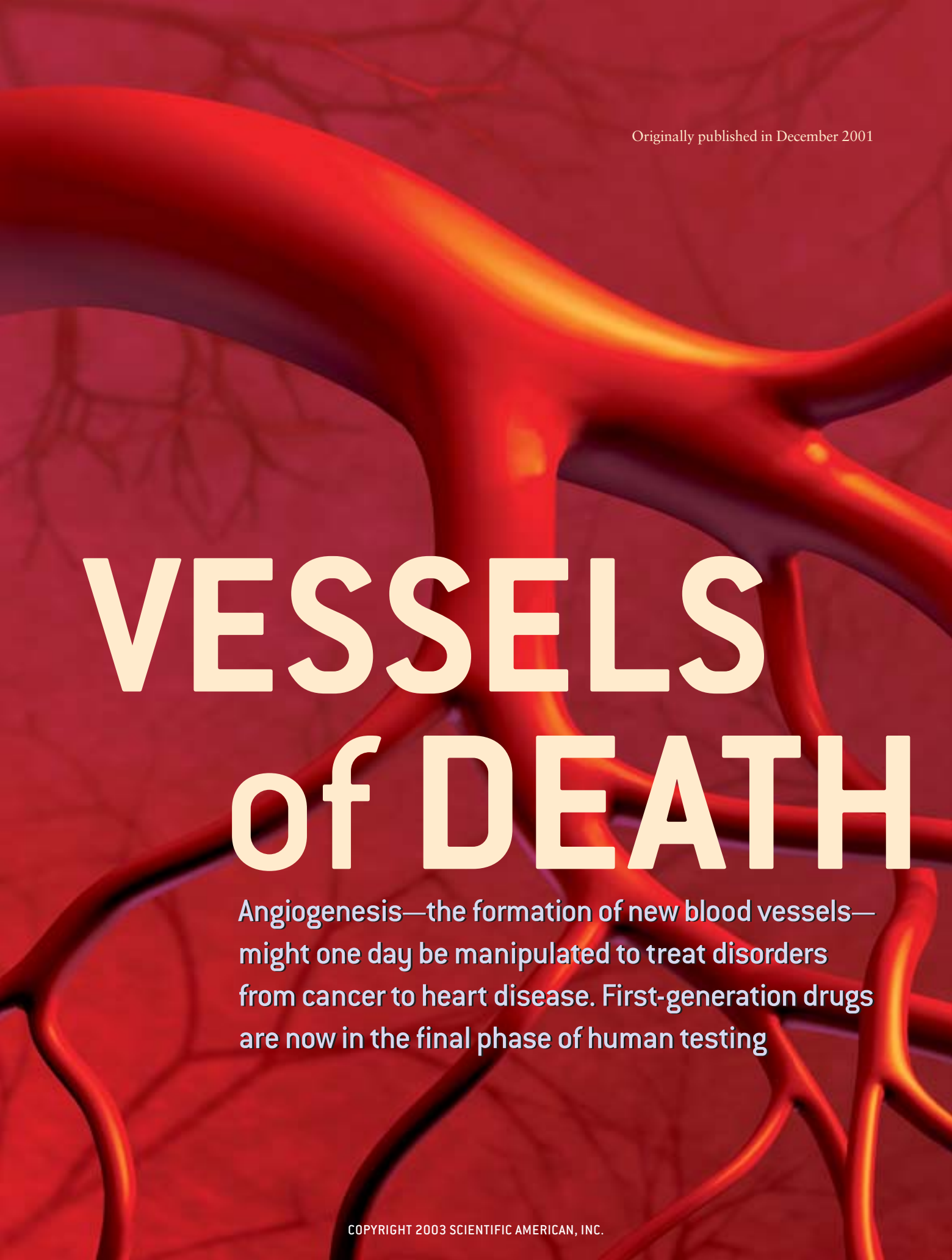

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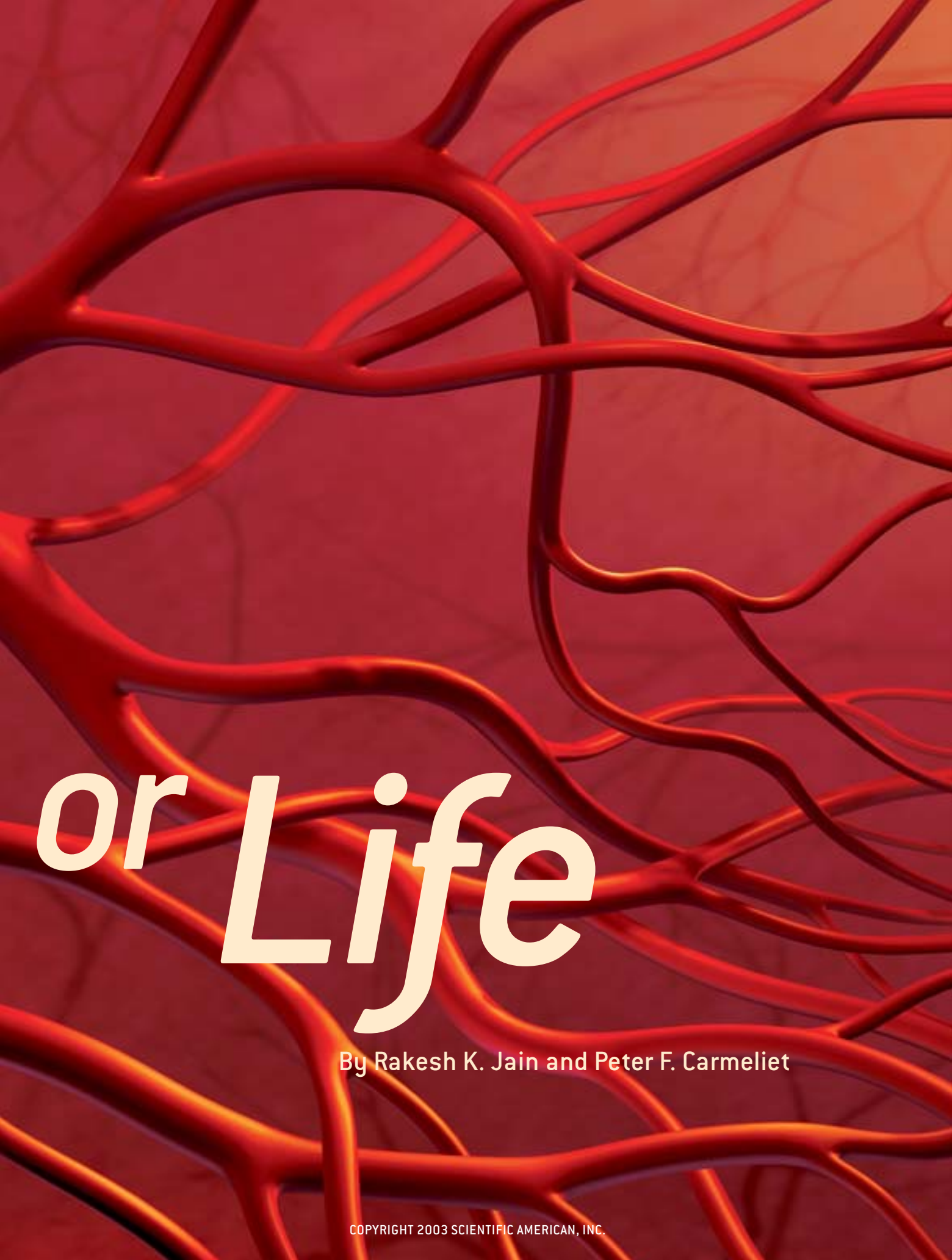
VESSELS of DEATH

Angiogenesis—the formation of new blood vessels—might one day be manipulated to treat disorders from cancer to heart disease. First-generation drugs are now in the final phase of human testing



or Life

By Rakesh K. Jain and Peter F. Carmeliet

They snake through our bodies, literally conveying our life's blood, their courses visible through our skin only as faint bluish tracks or ropy cords. We hardly give them a thought until we cut ourselves or visit a clinic to donate blood. But blood vessels play surprisingly central roles in many serious chronic disorders.

New growth of the body's smallest vessels, for instance, enables cancers to enlarge and spread and contributes to the blindness that can accompany diabetes. Conversely, lack of small vessel, or capillary, production can contribute to other ills, such as tissue death in cardiac muscle after a heart attack. Accordingly, we and other scientists are working to understand the mechanisms that underlie abnormal vessel growth. This effort will help us develop and optimize drugs that block vessel growth—or improve vessel function.

The study of small vessel growth—a phenomenon referred to generally as angiogenesis—has such potential for providing new therapies that it has been the subject of countless news stories and has received enthusiastic interest from the pharmaceutical and biotechnology industries. Indeed, dozens of companies are now pursuing angiogenesis-related therapies, and approximately 20 compounds that either induce or block vessel formation are being tested in humans. Although such drugs can potentially treat a broad range of disorders [*see box on page 39*], many of the compounds now under investigation inhibit angiogenesis and target cancer. We will therefore focus the bulk of our discussion on those agents. Intriguingly, animal tests show that inhibitors of vessel growth can boost the effectiveness of traditional cancer treatments (chemotherapy and radiation). Preliminary studies also hint that the agents might one day be delivered as a preventive measure to block malignancies from arising in the first place in people at risk for cancer.

Results from the first human tests of several compounds that block blood vessel growth were announced earlier this

Overview/*Angiogenesis*

- More than 20 compounds that manipulate angiogenesis—either by stimulating new blood vessel growth or by blocking it—are now in human tests against a range of disorders, from cancer to heart disease.
- Angiogenesis inhibitors are generally safe and less toxic than chemotherapeutic drugs, but they are unlikely to treat cancer effectively on their own. Instead physicians will probably use angiogenesis inhibitors in conjunction with standard cancer treatments such as surgery, chemotherapy and radiation.
- The blood vessels of tumors are abnormal. Surprisingly, angiogenesis inhibitors appear to "normalize" tumor vessels before they kill them. This normalization can help anticancer agents reach tumors more effectively.

HURD STUDIOS (*preceding pages*)

year. Some observers were disappointed because few of the patients, who had cancer, showed improvement. But those tests were designed solely to assess whether the compounds are safe and nontoxic, which they appear to be. Human tests of efficacy are under way and will be a much better judge of whether angiogenesis inhibitors can live up to their very great promise.

The Genesis of Angiogenesis

THE TERM "angiogenesis" technically refers to the branching and extension of existing capillaries, whose walls consist of just one layer of so-called endothelial cells. In its normal guise, angiogenesis helps to repair injured tissues. In females it also builds the lining of the uterus each month before menstruation and forms the placenta after fertilization. The development of blood vessels is governed by a balance of naturally occurring proangiogenic and antiangiogenic factors. Angiogenesis is switched on by growth factors such as vascular endothelial growth factor (VEGF) and is turned off by inhibitors such as thrombospondin. When the regulation of this balance is disturbed, as occurs during tumor growth, vessels form at inappropriate times and places.

Cancer researchers became interested in angiogenesis factors in 1968, when the first hints emerged that tumors might release such substances to foster their own progression. Two independent research teams—Melvin Greenblatt of the University of Southern California, working with Phillipe Shubik of the University of Chicago, and Robert L. Ehrmann and Mogens Knoth of Harvard Medical School—showed that burgeoning tumors release a then unidentified substance that induces existing blood vessels to grow into them. Such proliferation promotes tumor growth because it ensures a rich supply of blood loaded with oxygen and nutrients. In 1971 Judah Folkman of Harvard proposed that interfering with this factor might be a way to kill tumors, by starving them of a blood supply. What is more, Folkman later posited that blocking the factor could slow cancer's spread, a process called metastasis, because cancer cells must enter blood vessels to travel to other parts of the body.

Nipping New Blood Vessels in the Bud

CURRENT TESTS of angiogenesis inhibitors against cancer employ several different strategies. Chief among these is interfering with the action of VEGF. This molecule, which was initially named vascular permeability factor when it was discovered in 1983 by Harold F. Dvorak and his colleagues at Harvard, appears to be the most prevalent proangiogenic factor identified to date. Scientists gained a tool for better understanding the function of VEGF in 1989, when Napoleone Ferrara of Genentech and his co-workers isolated the gene encoding the molecule. In 1996 groups led by Ferrara and one of us (Carmeliet) independently demonstrated the critical role of VEGF in vessel formation by generating mice that lacked one of the normal two copies of the VEGF gene. The mice, which made half the usual amount of VEGF, died in the womb from insufficient and abnormally organized blood vessels.

Researchers are exploring a number of ways to neutralize VEGF's angiogenic activity in patients. These include immune system proteins called antibodies that can bind specifically to and disable VEGF; soluble forms of the cellular receptors for VEGF, to act as decoys that sop up the growth factor before it can bind to cells; and small molecules that can enter cells and block the growth messages that VEGF sends into an endothelial cell's interior after binding to receptors at the surface. The compounds under study also include factors, such as interferons, that decrease the production of VEGF and substances, such as so-called metalloproteinase inhibitors, that block the release of VEGF from storage depots in the extracellular matrix, the "glue" that binds cells together to create tissues.

Although halving the amount of VEGF is lethal to mouse embryos, wiping out cancers in humans with such therapies will probably require the complete neutralization of all the VEGF protein present in a tumor, and that might be difficult to do. VEGF is a potent agent, and trace amounts could protect the endothelial cells from death. But even after all the VEGF is neutralized, a tumor could rely on other proangiogenic factors, such as basic fibroblast growth factor or interleukin-8.

Another widely studied approach for inhibiting angiogenesis in cancer patients is administering or increasing the natural production of antiangiogenic factors. The idea for this therapy emerged when Folkman learned that Noel Bouck of Northwestern University had identified a naturally occurring inhibitor—thrombospondin—in 1989. Surgeons already knew that removing a patient's primary tumor in some cases accelerated the growth of other, smaller tumors—almost as if the primary tumor had secreted something that kept the smaller tumors in check. They have never questioned the necessity of removing the primary tumor in most cases, because such tumors often obstruct the normal functions of organs and tissues, and leaving them in place would provide a source of cancerous cells for yet more metastases. But discovery of a natural angiogenesis inhibitor suggested to Folkman that the primary tumor's secretions might be harnessed as cancer drugs to suppress the growth of both primary and small metastases.

With this concept in mind, Folkman and his colleagues discovered two more of these naturally occurring antiangiogenic substances—angiostatin and endostatin—in 1994 and 1997, respectively. These inhibitors have received a great deal of attention. This is in part because of studies by Folkman's group showing that they can eradicate tumors in mice. A front-page story

THE AUTHORS

RAKESH K. JAIN and *PETER F. CARMELIET* bring complementary backgrounds to the study of angiogenesis. Jain, who is now the Andrew Werk Cook Professor of Tumor Biology at Harvard Medical School and director of the Edwin L. Steele Laboratory at Massachusetts General Hospital, started his career as a chemical engineer. He held posts at Columbia University and at Carnegie Mellon University before joining Harvard in 1991. Carmeliet is a professor of medicine at the University of Leuven in Belgium, where he also serves as adjunct director of the Center for Transgene Technology and Gene Therapy at the Flanders Interuniversity Institute of Biotechnology. He received his M.D. from Leuven in 1984 and his Ph.D. from the same institution in 1989.

Therapeutic Angiogenesis

When making more blood vessels is good for the body

It's easy to understand how restricting the growth of new blood vessels could help kill tumors, but fostering vessel growth—a strategy termed therapeutic angiogenesis—could be useful against other disorders.

Researchers around the world are now evaluating whether the angiogenic substances they are trying to block to treat cancer might help heart attack patients—or those at risk for heart attack—grow new blood vessels in the heart. Those factors might also be used to treat people with vascular disorders in their feet and legs.

A heart attack, properly called a myocardial infarction, occurs when a blood clot forms in one of the arteries that feeds the heart muscle, preventing part of the heart from receiving oxygen and nutrients, a condition known as ischemia. Unless the clot is dissolved or dislodged rapidly, the patch of heart muscle can die. In addition, many diabetics suffer from a lack of circulation in their extremities caused by occluded blood vessels; some require amputations.

Therapeutic angiogenesis can involve directly administering a vessel growth–promoting substance, such as vascular endothelial growth factor (VEGF). It can also be accomplished using gene therapy, administering to a patient genetically engineered viruses, cells or pieces of DNA that carry the gene encoding VEGF or another angiogenic factor.

Therapeutic angiogenesis with VEGF or fibroblast growth factor (FGF) has been explored for the past 10 years. In 1991 scientists led by Stephen H. Epstein of the National Institutes of Health studied the effects of FGF on the heart vessels of animals. A year later Paul Friedmann and his co-workers at Baystate Medical Center in Springfield, Mass., showed that FGF injections could prompt angiogenesis in the hind limbs of rabbits. In the mid-1990s several groups—including those led by Epstein, Michael Simons of Harvard Medical School, Jeffrey M. Isner of St. Elizabeth's Medical Center in Boston and Ronald G. Crystal of Cornell University Medical School in New York City—demonstrated that therapy involving angiogenic factors or the genes that encode them could stimulate angiogenesis in the hearts and limbs of animals.

Clinical trials aimed at evaluating the safety and efficacy of angiogenic factors in patients are now under way. Carmeliet and others are also testing the therapeutic potential of other promising molecules, such as placental growth factor, a relative of VEGF. Creating functional blood vessels appears to be a formidable challenge, however. Researchers are trying to find the best combinations of such proangiogenic agents as well as the optimal dose, administration schedule and delivery route for the drugs. They are also evaluating whether transplants of endothelial stem cells—the precursors of the endothelial cells that make up blood vessels—can augment the regeneration of blood vessels. Such stem cells can be isolated from the bone marrow of adults.

But potential risks accompany the promise of proangiogenic therapy. Therapeutic angiogenesis could increase a patient's risk of cancer by allowing tiny tumors that had been dormant in the body to gain a blood supply and grow. In addition, because the atherosclerotic plaques that underlie heart disease require their own blood supply as they become larger, therapeutic angiogenesis could backfire as a treatment for cardiac disease by stimulating the growth of plaques that had caused the individual's heart attack in the first place.

Human studies to evaluate the likelihood of these dire scenarios have only recently begun. We hope one day to be able to use genetic tests to evaluate a patient's natural balance of proangiogenic and antiangiogenic factors before beginning to treat them with proangiogenic drugs.

This information might also help us understand whether myocardial ischemia results from the insufficient production of angiogenic factors or from the excess production of angiogenic inhibitors. The results will undoubtedly aid in the development of more directed strategies for therapeutic angiogenesis.

—R.K.J. and P.F.C.

heralding such successes in 1998 in the *New York Times* increased the visibility of the entire field of angiogenesis.

Clinical trials of angiostatin and endostatin are currently in early stages (experiments involving small numbers of patients to evaluate a potential drug's safety). Preliminary results reported at this year's American Society of Clinical Oncology conference, which were alluded to earlier, indicate that endostatin is safe and causes no side effects. We await the outcome of the various clinical trials of these and other angiogenesis inhibitors in the coming years.

Going after Established Blood Vessels

THE TWO APPROACHES described thus far interfere with the formation of new blood vessels. But what about preexisting vessels in a tumor? Is it possible to target those without disrupting the established vessels in healthy tissues and organs (an approach termed antivascular therapy)?

Luckily, it turns out that the blood vessels of tumors are abnormal. Not only are they structurally disorganized, tortuous, dilated and leaky, but the cells that compose them display certain molecules on their surfaces from a class known as integrins that are absent or barely detectable in mature vessels. Biologists have recently produced small proteins, called RGD peptides, that preferentially recognize the integrins on tumor vessels. These peptides can be linked to cell-killing drugs to target such therapeutic agents to tumors without damaging other tissues. They could also be used to clog the vessels that feed the tumor, by delivering molecules that cause blood clots to form.

But it might not be so easy for any drug to zero in on all a given tumor's blood vessels. The individual cells that make up even a single tumor vessel can vary widely. Studies in one of our labs (Jain's) have found that 15 percent of the blood vessels in human colon cancers are mosaic: some have a particular protein on their surfaces, whereas others do not. If the proteins targeted by new drugs turn out to differ from one tumor to the next or to vary within a tumor during the course of its growth or treatment, this heterogeneity will make it difficult to get therapies that target blood vessels to work on their own.

Combine and Conquer

MOST LIKELY, surgery or radiation—or both—will continue to be used to attempt to eliminate the original tumor. Today chemotherapy is often administered before or after such therapy to shrink tumors and mop up undetectable malignant cells remaining in the body. Antiangiogenic drugs could well be combined with any of the other approaches to improve the success rate.

Following the pioneering studies of Beverly Teicher of Harvard in the 1990s, several groups have shown the benefits of such a combined approach. Recently Folkman, Robert Kerbel of the University of Toronto and Jain's group have found that combined therapy can produce long-term cures in mice.

Interestingly, antiangiogenic therapy appears to boost the effectiveness of traditional cancer treatments. This is surprising because chemotherapeutic agents depend on blood vessels to reach a tumor, and radiation kills only those cells that have an adequate supply of oxygen (it turns oxygen into toxic free radicals). Logic suggests that by compromising the blood supply of tumors, antiangiogenic therapy would interfere with the effectiveness of these standard treatments. But scientists have demonstrated that the delivery of chemotherapy—as well as nutrients and oxygen—improves during the course of some antiangiogenic therapies.

Indeed, researchers led by Jain have shown that antiangiogenic factors can "normalize" tumor vasculature before killing it by pruning excess, inefficient vessels while leaving efficient vessels temporarily intact. In studies of mice, the researchers found that angiogenesis inhibitors decreased the diameters of tumor

ANGIOGENESIS INHIBITORS NEARING THE MARKET

These potential therapies for cancer are in phase III testing, the last stage before Food and Drug Administration approval. Angiostatin and endostatin are in earlier phases of evaluation. Similar compounds are also in trials against the eye disease macular degeneration.

PRODUCT	DEVELOPER	DESCRIPTION	DISEASE TARGET
Avastin	Genentech	Monoclonal antibody that disables vascular endothelial growth factor (VEGF), a promoter of angiogenesis	Breast and colorectal cancer
BMS275291	Bristol-Myers Squibb	Synthetic compound having multiple effects	Nonsmall cell lung cancer
Interferon alpha	Roche, Schering	Protein that inhibits release of growth factors such as VEGF	Various tumors
Marimastat	British Biotech	Synthetic compound having multiple effects	Breast and prostate cancer
Neovastat	Aeterna	Naturally occurring inhibitor with a range of properties	Nonsmall cell lung and renal cancer
SU5416	Sugen	Synthetic compound that blocks the receptor for VEGF	Colorectal cancer
Thalidomide	Celgene	Organic molecule whose specific mechanism of action is unknown	Renal cancer and multiple myeloma

blood vessels and made them less leaky, so they began to resemble normal vessels. If such studies pan out in humans, however, physicians will need to work out the optimal dosage and timing of administration.

As is true for many drugs, future generations of antiangiogenic agents are likely to be more effective than the first generation. To optimize future drugs, researchers will need to modify their investigation methods. Most preclinical studies, performed before a drug can be tested in people, are carried out on tumors that are artificially grown under the skin of animals such as mice. But few human tumors arise beneath the skin. To get a more realistic idea of whether a given cancer drug will work in people, researchers will need to study animals with spontaneously occurring tumors growing in more natural sites.

Another limitation of preclinical studies is that they are time-intensive and costly, so researchers usually halt them when tumors begin to shrink but before they can be sure a treatment being tested will actually eradicate the cancers. Because tumors can recur from even a very small number of surviving cancer cells, scientists should follow treated animals for longer periods to better determine the promise of new drug candidates. In addition, investigators tend to begin administering experimental drugs to animals before tumors are fully established, at a time when the cancers are vulnerable—possibly tilting the scales in the drug's favor. Animal tumors also tend to grow more quickly than those in people, and drugs that kill such fast-growing cancers might not be effective against slower-growing human tumors.

Researchers also need to study combinations of antiangiogenic drugs. Cancer cells are masters of evasion. Each tumor produces different combinations of angiogenic molecules that may vary or broaden as they grow. Administering an antiangiogenic drug that blocks only one molecule, such as VEGF, can simply prompt tumors to use another proangiogenic substance to attract a blood supply. In the end, optimal antiangiogenic therapy might consist of a cocktail of several angiogenesis inhibitors.

An Ounce of Prevention

IF ANGIOGENESIS INHIBITORS fulfill their early promise against cancer, patients will probably need to take them for a long time. The drugs might also be administered as cancer preventatives to people with a high risk of particular cancers—an approach initially suggested in 1976 by Pietro M. Gullino of the National Cancer Institute. Consequently, they must be shown to be safe over the long term. (The drug interferon, an indirect antiangiogenic agent, has been given for years with no side effects to pediatric patients with hemangiomas—benign blood vessel tumors.) The existing human trials will not address this question; they are designed to evaluate safety for just a few months. Animal studies hint that some antiangiogenic compounds might not be safe enough for the long-term administration required to prevent growth or relapse of cancer. Mice that have been genetically manipulated to reduce their production of VEGF can develop neurological defects after a prolonged period, for example, as shown in experiments by Carmeliet.

Insufficient angiogenesis can also impair the heart's recovery from ischemia, tissue starvation stemming from a poor supply of blood. During a heart attack, a blood clot lodges in an artery that supplies the heart muscle, killing a part of the organ. Indeed, researchers are testing agents that spur angiogenesis as treatments for ischemic heart disease. Accordingly, antiangiogenic cancer treatments might increase a patient's risk of ischemic heart disease. As with any therapy, then, physicians and patients will have to carefully weigh the risks and benefits of using angiogenesis inhibitors.

Nevertheless, the burgeoning understanding of angiogenesis has changed our thinking about how to attack cancer. Current treatment with radiation and chemotherapy halts many cancers, but too often the existing treatments bring about only a temporary symptom-free period before the tumor shows up again, spreads throughout the body and kills. Part of the problem is that physicians and pathologists lack reliable, sensitive, cheap and easy-to-use tests that can identify characteristics about each patient's cancer that indicate the best treatment strategy. Genetic analyses of tumors and patients promise to improve the accuracy of diagnoses as well as the efficacy and safety of treatments in the future, but we suspect that within the next 10 or 20 years, better visualization of abnormal vessel structure and function will help as well.

Antiangiogenic approaches have already shown benefit in patients with hemangiomas. As knowledge of tumor angiogenesis progresses, cancers may be detected through elevated levels of angiogenic molecules in the blood—long before clinical symptoms. Physicians may begin to examine patients regularly using molecular tests and new imaging techniques to determine an individual's profile of proangiogenic and antiangiogenic factors.

Based on such tests, doctors will be able to devise treatment plans that, along with other therapies, incorporate a mix of angiogenesis inhibitors appropriate for that individual's tumor. Tests that detect the presence of abnormal vessels will allow doctors to detect possible relapses at an early, potentially treatable stage. Perhaps, as safe oral antiangiogenic drugs are developed and become available, cancer patients will be able to take "a pill a day to keep the cancer away." If so, forms of cancer that are currently untreatable will be reduced to chronic health problems similar to hypertension or diabetes, and many more people will be able to live long, satisfying lives. SA

MORE TO EXPLORE

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The National Cancer Institute Web site provides updates on cancer trials that are using angiogenesis inhibitors: **www.cancertrials.nci.nih.gov**