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Questions, comments or requests for more information:

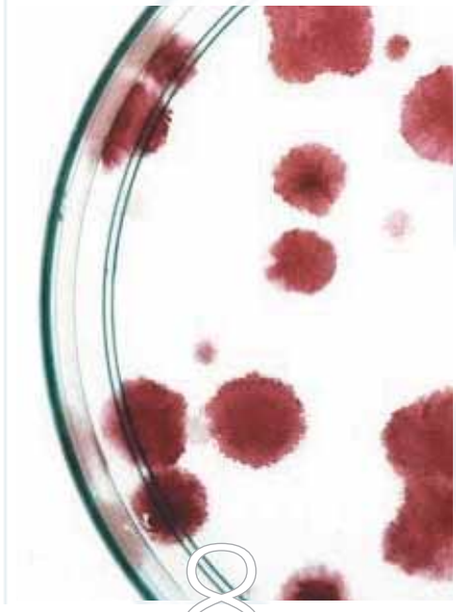
E-mail:
clevelandclinicmagazine@ccf.org

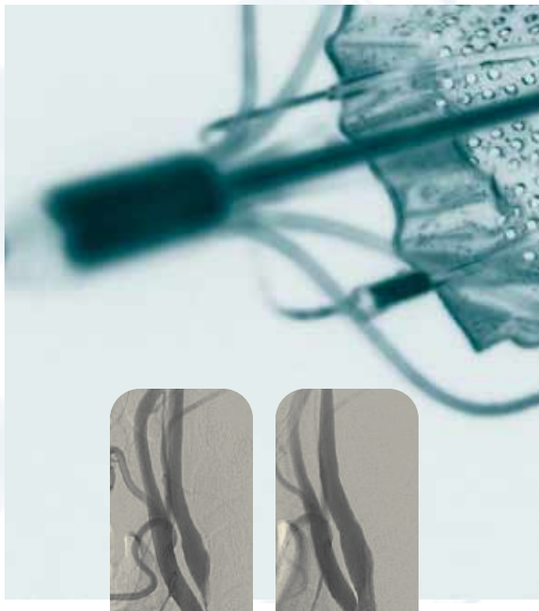
Mail:
Managing Editor
Cleveland Clinic Magazine
The Cleveland Clinic/W14
9500 Euclid Avenue
Cleveland, OH 44195

Phone:
216/445-4908

Web:
Please visit our Web site at
www.clevelandclinic.org

ON THE COVER: Cordis® Nitinol Carotid Precise Stent (*Photo: S. Travarca*)





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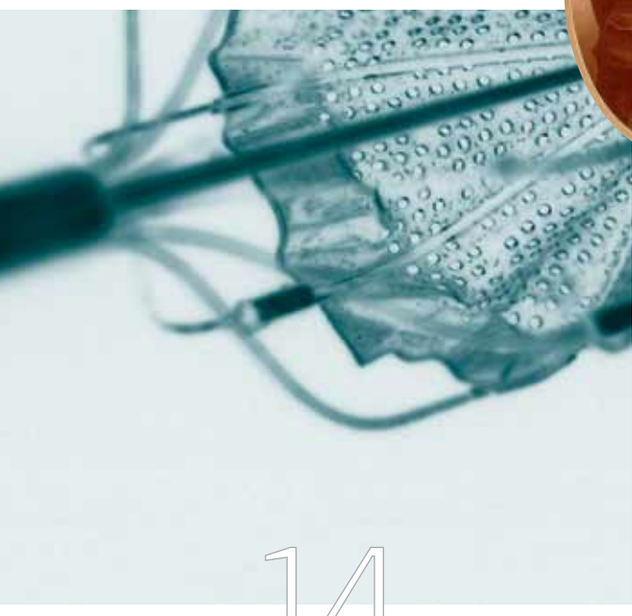

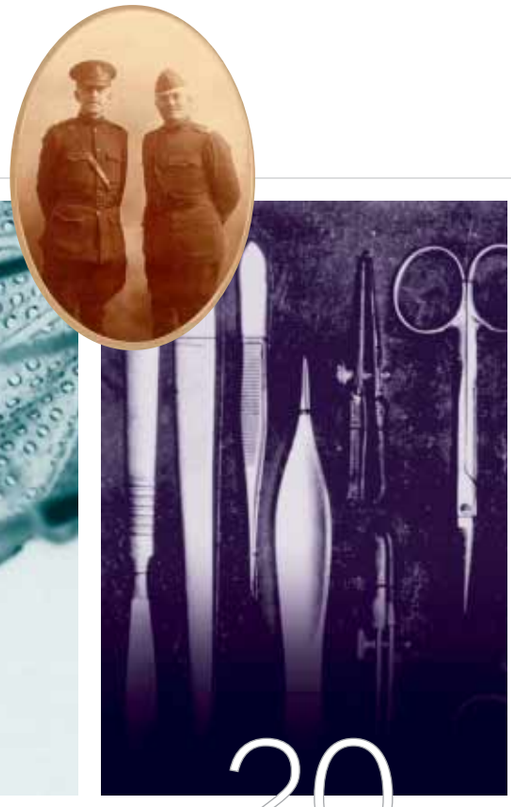

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By Natalie Manco
as told to *Cleveland Clinic Magazine*

NEVER HAVE AN UNSATISFIED PATIENT

Change is certain, a British historian observed; progress is not. Hospitals and academic health care centers finally appreciate that great customer service is not optional; it's basic.

A handful of American companies whose names are synonymous with customer service (e.g., Lexis, Nordstrom and Disney) has become even greater by exceeding their users' optimistic expectations.

For these companies, the core value is, "Respect for the customer. Respect for the employee. Respect for suppliers and other business partners. Respect for the community."

Outstanding service is a strategy that can achieve outstanding benefits. These benefits include personnel satisfaction, customer loyalty, improved retention and a stronger positive image in the community.

The Cleveland Clinic has launched the most widespread service initiative in the history of American medicine. We call it World Class Service. It involves every member of our comprehensive Cleveland Clinic staff. It involves greater attention to every aspect of service: our working environment, collegiality and patient interaction. World Class Service advances our achievements in medicine.

Everyone who works in The Cleveland Clinic is informed of the values and precepts of World Class Service and is inspired to practice them on a daily basis. The singular purpose of The Cleveland Clinic is to benefit humanity through the efficient, effective and ethical practice of medicine, by advancing scientific investigation and medical education, by maintaining the highest standard of quality and by honoring creativity and innovation. Each member of the organization is a guardian of this enterprise and is responsible for assuring that The Cleveland Clinic is synonymous with the finest health care in the world.

World Class Service involves patient and staff surveys. We've surveyed our physicians and employees to assess baseline attitudes, and we have solicited ideas about how to make The Cleveland Clinic a better place. The results have been astounding. More than 9,000 ideas were offered in the past ten months. We review and answer each and every one. More than 16 percent of these ideas have already been implemented.

These measures all add value to medicine, because when employees are happier, patients are more satisfied.

The responsibility of modern medical care is to treat patients, families and visitors the way we would like to be treated. How we act, and what we do and say to our patients makes all the difference. Our obligation is to communicate more effectively with our patients. The principles include:

1. ACKNOWLEDGEMENT
Connecting with the patient through a smile or greeting and making the patient the total focus of attention.

2. INTRODUCTION
Proper introduction of all caregivers.

3. INFORMATION
Explaining the rationale of testing or procedures.

4. EXPLANATION
Providing the patient with a full disclosure of treatment, results and prognosis. Answering all questions.

5. GRATITUDE

The words of founder Dr. William E. Lower are as true today as they were 60 years ago: "A patient is the most important person; the patient is not someone to argue or match wits with; a patient is not dependent on us – we are dependent on them; a patient is not an interruption of our work – it is the purpose of it; the patient is not outside our business – they are our business; and, the patient is a person and not a statistic."

For years, I've been saying that there should be a sign over the door of every hospital that says, "Never have an unsatisfied patient." Now, through the ongoing process of World Class Service, that motto is reality.

Floyd D. Loop, M.D.
Chairman and Chief Executive Officer

In the Pink After Pain

Richard Mehocic knows about discomfort. He survived the tropical heat of the Philippines in World War II and endured the biting cold of winter while fixing machines for a stone quarry in Pennsylvania. But he wasn't prepared for the throbbing ache in his hands that wouldn't go away.

Though some chronic pain is usually associated with a specific cause, such as a herniated disc, diseased joint, nerve disorder, or bone fracture, Mehocic's pain seemed to come out of nowhere — the pain that, month after month, robbed him of the ability to enjoy digging in the garden, clutching a fishing rod or squeezing the trigger of his hunting rifle.

"One winter, a few years ago, it suddenly became hard for me to keep my hands warm," says the 77-year-old Mehocic. "My fingers would turn white, then blue, and then start to ache."

Though a local physician attributed his problem to poor circulation, probably due to hardening of the blood vessels in Mehocic's fingers, the problem remained. The restricted blood flow not only deprived his fingers of warmth, but also inhibited his body's normal repair route for healing damaged tissue. As a result, over the months the skin on his fingers became cracked, ulcerated, infected and increasingly painful.

"It became hard to use my hands for much of anything," says Mehocic, who hurt too much even to dig in the wet soil for night crawlers to bait his fishing hook.

Eventually the tissue damage led to tissue death. That was followed by the amputation of the tip of his right index finger by a local surgeon.

When he finally saw The Cleveland Clinic's Nagy Mekhail, M.D., Ph.D., chairman of the Pain Management Center, the hope was to find a way to boost blood flow to the hands, slow tissue damage and avoid the need for further amputation.

Dr. Mekhail tried several methods to get the blood vessels in Mehocic's fingers to relax and open up. Medications that dilate blood vessels were used. Injections to anesthetize the nerves that lead into his fingers, telling them to relax or contract, also were tried.

Nothing seemed to help.

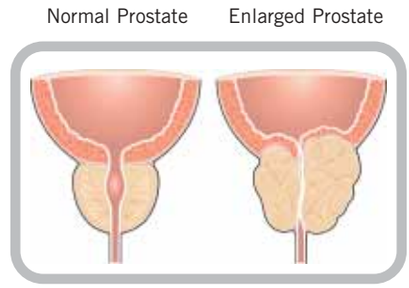
It was time to try a spinal stimulator — a device implanted near the spinal cord, just above the nerve root that leads into the affected area. The idea is to send a low-level pulse of electricity down particular nerves and interfere with the transmission of "bad" signals, such as pain messages or orders to keep the muscles of the vessel walls constricted.

The power for the pulses comes from a box about the size of a deck of cards. It is implanted near the patient's hip and connects to the stimulator by a pair of wires.

"Before they actually implanted it, I test-drove it for a week so they could fine-tune the settings," says Mehocic. "When it's on, I feel a mild tingling, kind of like bumping your funny bone."

To control the signal strength, he moves a hand-held device over the power pack implanted on his right hip. The pack is placed so the bulge causes fewest problems when sitting, sleeping or getting dressed.

"I can turn it off when I go to bed, or adjust it to match my level of pain," says Mehocic, whose fingers now are pink with health. "If I'm out in the garden, digging holes for my irises, and my hands start to hurt, I just turn it up and the pain goes away in about 10 minutes."



Prostate Tissue Tamed by New PVP Laser

For most men with unmanageable symptoms caused by an enlarged prostate, transurethral resection of the prostate, or TURP, is recommended as the "gold standard" for remedying this condition. Now, however, a new procedure is available that uses a laser to reduce the enlarged prostatic tissue while producing TURP-like benefits, such as increased urine flow, improved bladder emptying and decreased night-time urination frequency.

Known as photoselective vaporization of the prostate, or PVP, this approach can be performed as an outpatient procedure and produces few complications, according to James Ulchaker, M.D., a urologist in the Section of Urologic Oncology. Dr. Ulchaker was one of the investigators for the phase II multicenter clinical trial. "The biggest benefit of PVP," says Dr. Ulchaker, "is that it offers significantly less chance for complications that can be challenging to manage both during and after surgery."

PVP differs from TURP because of the unique effect of the laser energy on the prostatic tissue. This effect decreases both blood loss and fluid absorption, thereby decreasing the possibility for additional complications.

Getting on the Vision Bus

Like most cities, Cleveland is home to hundreds of young children who go untreated for ambylopia, or lazy eye, a serious childhood eye disorder that can result in permanent poor vision in one eye. Some children are not treated for other serious eye problems, such as cataracts, while many others simply require glasses to correct a refractive error.

Frustrated by the preventable loss of vision in the very young, Hilel Lewis, M.D., chairman of the Ophthalmology Division and director of the Cole Eye Institute, conceived a program that would detect problems in preschool and elementary school children most at risk – those living in the inner city. Thus was born the idea of the Vision First program. The program was generously funded by local private foundations and corporations, government agencies and individual donors.

"Early detection of childhood eye problems is important," says Elias Traboulsi, M.D., a pediatric eye specialist at the Cole Eye Institute who directs the Vision First program. "If a child cannot use his or her eyes normally, vision may not develop properly."

Beginning in Fall 2002, the fully-equipped Vision Bus, staffed by a Cole Eye Institute optometrist and a full-time technician/coordinator under the supervision of a pediatric ophthalmologist, began making visits to schools in the Cleveland Municipal School District, screening about 50-to-70 students each day. More than 5,000 children have been examined since the screenings began. Of those children, approximately 500 were discovered to have eye problems that necessitated glasses or a referral to a pediatric ophthalmologist. Seventy-two had amblyopia, or reduced vision, and 131 had strabismus, commonly referred to as "crossed eyes."

The Vision Bus couldn't have arrived at a better time for 6 1/2-year-old Derrick Sage, a kindergarten student at Tremont School.

Derrick's mother, Joann Sage, knew her son had a vision problem. "He had to sit really close to the television," she says. "He was right up on it." Mrs. Sage had tried in vain to get her son evaluated at a local hospital. As if in answer to her concerns, a note from the Tremont school nurse arrived in Derrick's lunch box near the end of the school year. "It asked for permission to have Derrick's vision tested," says Mrs. Sage.

Within no time after testing, Mrs. Sage received a voucher that enabled Derrick to get a free pair of glasses. With palpable relief and gratitude in her voice, Mrs. Sage says Derrick is doing "really well" now with his new glasses.

Nipple-Sparing Option

for Mastectomy

It didn't matter that the procedure was difficult; that it would take twice as long; that it would require more staff. What mattered was that it would give women hope. It would make them feel whole again. That is what motivated Joseph Crowe, M.D., director of the Breast Center, to develop a new mastectomy procedure for breast cancer that leaves the nipple intact.

Various approaches to preserving the nipple have been evaluated over the years, but the concern has always been the risk of cancer recurrence due to the concentration of milk ducts beneath the nipple, a site where many breast cancers develop.

Dr. Crowe overcomes this concern by meticulously removing all of the breast tissue under the nipple and areola, leaving only a thin envelope of skin. During surgery, samples are sent to the laboratory for evaluation. If there is any hint of disease in the area under the nipple, the nipple is removed. If the samples are negative, the nipple and areola are left intact for reconstruction.

If reconstruction is a go, Dr. Crowe and his colleague Julian Kim, M.D., are joined in the operating room by plastic surgeons Jillian Banbury, M.D., and Randall Yetman, M.D. By the time reconstruction is completed and the breast has healed, several tiny surgical scars will be the only indication that the patient has had a mastectomy.

With so many choices for surgery, how do women decide that nipple-sparing is their best treatment alternative? "If the patient is a candidate for this procedure, it becomes a personal decision," says Dr. Crowe. "We explain all the options, and ultimately it is the woman's choice."

For Molly Fischer, nipple-sparing turned out to be the perfect alternative.

When Fischer learned she had breast cancer, her doctor recommended a lumpectomy and radiation because the tumor was small. Fischer's father, a retired surgeon, insisted she get a second opinion.

Fischer was fine with that, but she had already decided she didn't want a lumpectomy. "I always said if I was ever diagnosed with breast cancer, I wanted to have both breasts removed." When she met with Dr. Crowe and learned about the nipple-sparing surgery, "It was a bonus," she says.

Fischer underwent surgery and says the cosmetic results are nothing less than remarkable. "I wish I could tell and show every woman what it's like," she says. "I looked in the mirror after surgery and I couldn't believe what I saw. I look normal."

Fertility Preservation for

Cancer Patients

Now that long-term cancer survival is increasing and more women are delaying childbearing, preserving fertility is becoming more of an issue.

So notes Tommaso Falcone, M.D., chairman of the Cleveland Clinic Department of Obstetrics and Gynecology. "With adequate planning, we can initiate a strategy to protect a woman's ability to conceive prior to chemotherapy and radiotherapy," he says.

The most common fertility preservation technique is hormonal treatment to stop the ovaries from releasing eggs during a woman's normal menstrual cycle. To achieve this, a woman must take a hormonal medication several weeks prior to starting chemotherapy to suppress the pituitary gland, which signals the brain to release eggs from the ovaries. By shutting down the menstrual cycle, the eggs can be protected from damage by the chemotherapy.

Another technique, called transposition, involves moving the ovaries away from the field of radiation. The ovaries are detached from the uterus and moved, for example, upwards toward the kidney if the radiation is to be delivered to the pelvis area.

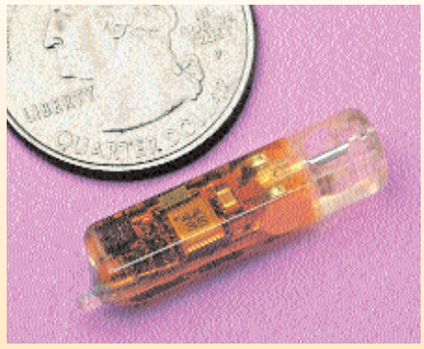
One of the newest approaches to preserving a woman's fertility involves embryo cryopreservation. The preparation for embryo preservation involves *in vitro* fertilization (IVF) and embryo transfer procedure, which was first successfully used in the United States more than 20 years ago.

A woman must take a hormonal medication to stimulate the ovaries to produce many eggs. The eggs are harvested for IVF during a minimally invasive (laparoscopic) procedure under local anesthesia. Following successful fertilization, the embryos are frozen until the woman is ready for them to be placed in her uterus. Success rates range between 20 and 30 percent.

A new option currently under evaluation is ovarian tissue freezing and transplantation, which would be useful when women do not have time for an IVF cycle prior to chemotherapy. In this technique, ovarian tissue (along with its immature eggs) is removed laparoscopically. The ovarian tissue is frozen until the woman desires to attempt pregnancy. At that time, the tissue then would be transplanted into a different, easily accessible location of the body. Following transplantation, the ovarian tissue is stimulated with hormones to produce mature eggs that are harvested during IVF. To date, the reports on ovarian tissue freezing are limited, and no successful pregnancies have been recorded.

Heart burn

An Easier Way to Measure



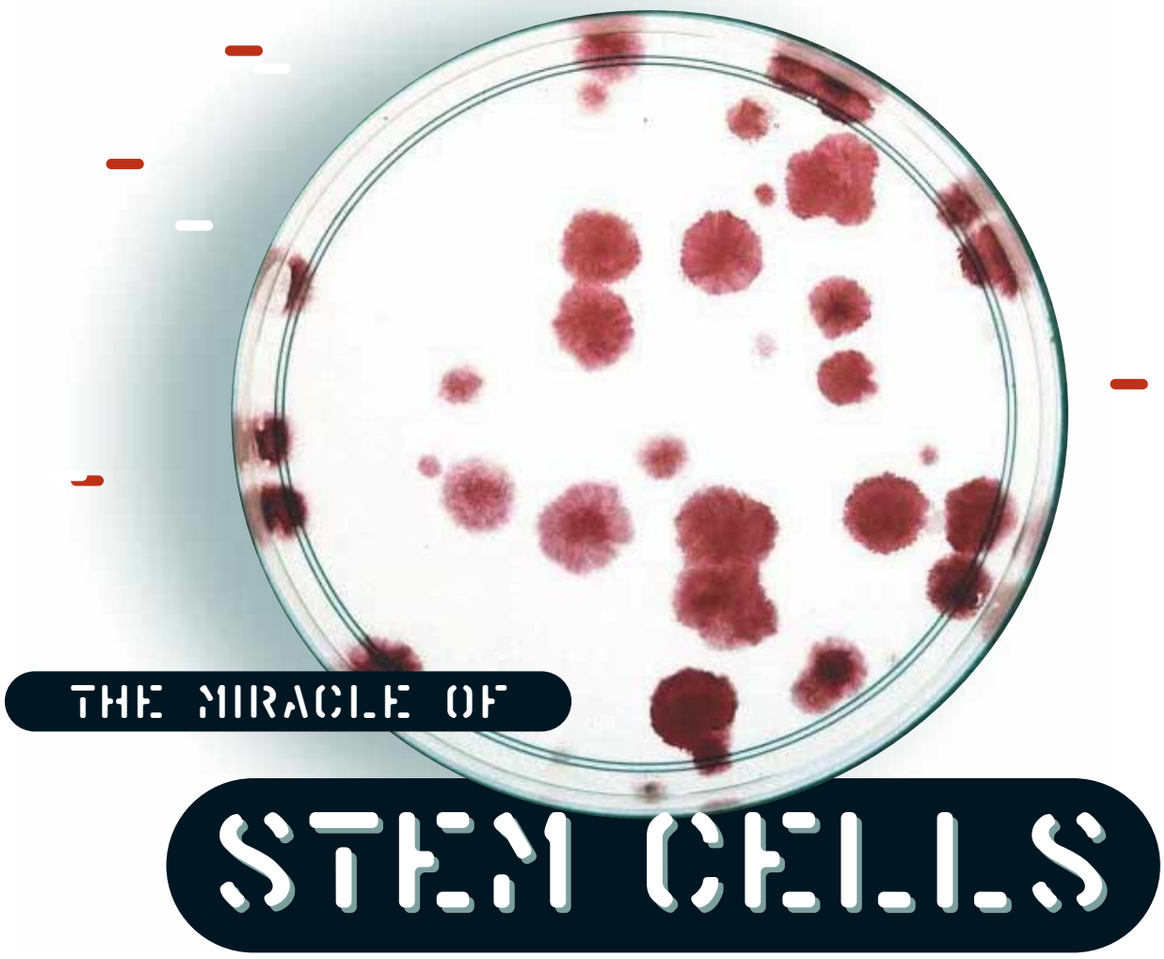
An estimated 21 million Americans suffer from acid reflux disease, affecting men and women equally. Sometimes called gastro esophageal reflux disease (GERD), this painful burning and irritation is caused by stomach acid seeping into the esophagus.

In the past, to help manage their acid reflux, patients were required to wear a nasal catheter for 24 hours while it measured the pH levels in their esophagus. But oftentimes, patients were either too uncomfortable or felt too constrained physically by the catheter to resume normal activity while wearing it. Doctors, therefore, couldn't get an accurate pH level reading.

Now some physicians have begun using radio telemetry to measure pH levels in the esophagus, making that uncomfortable tube through the nose unnecessary. The Bravo™ pH Monitoring System consists of a capsule about the size of a gelcap that is temporarily attached to the esophageal wall with a scope. It transmits pH data through radio telemetry to a pager-sized receiver worn by the patient. Doctors can monitor pH levels for 48 hours with little or no patient discomfort and without inhibiting movement or eating habits. Within 14 days, the capsule passes safely through the digestive tract.

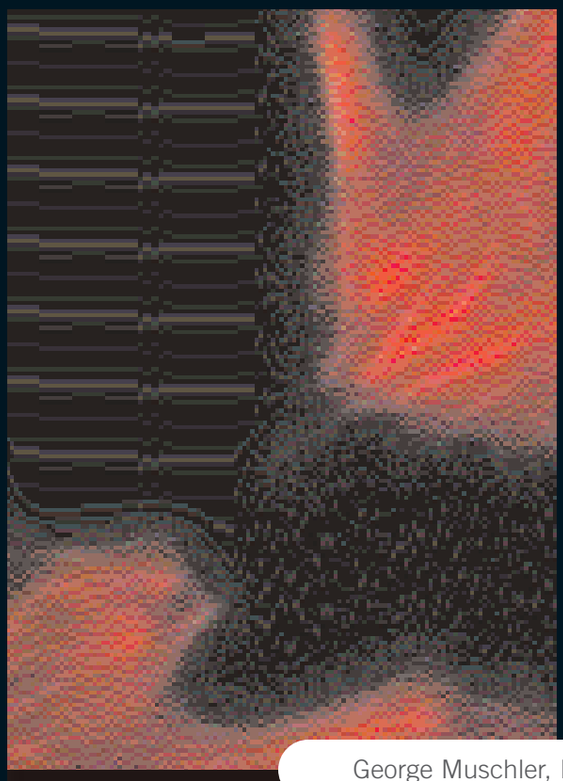
Adult stem cells exist in more tissues than once was originally thought.

The trick is locating and triggering them to do what is needed – heal bone, repair heart muscle, or even cure a devastating disease.

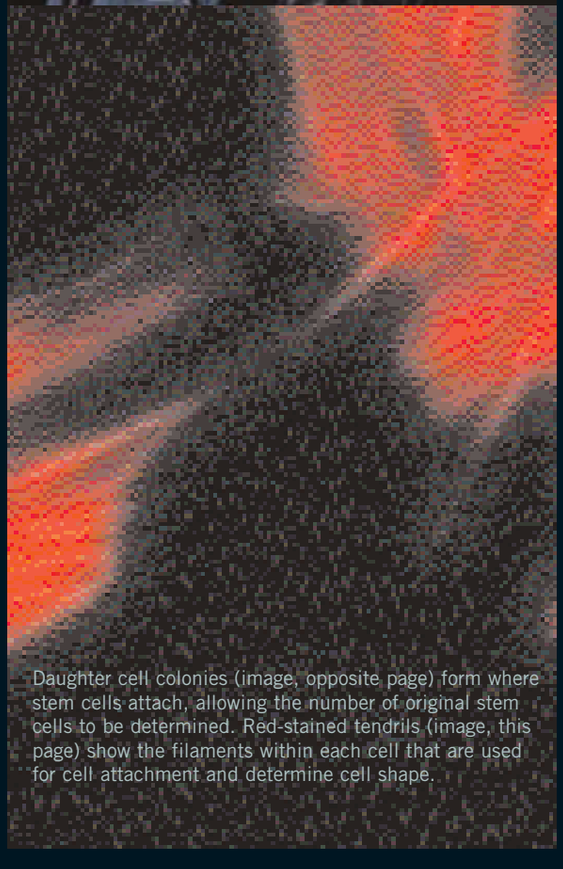


THE MIRACLE OF STEM CELLS

Monique Biggins wanted to win. Her women's softball team was in first place in the tournament. That hot day in August 2001, she stood behind third base, playing short-field, focused on clinching the game, no matter what. She knew that one more out would put her team that much closer to the championship. — The batter pounded a line drive right to Biggins. In an adrenaline rush, **she dove for the ball.** — "I had it in my mitt," she says. But as she hit the ground, her shoulder seemed to get stuck while her body propelled forward. Two years later, she still doesn't know if she got the batter out or dropped the ball. — All she knows is that moment changed her life forever. — "People on the bench said they heard it break," she says. —When she got to the hospital, she overheard the X-ray technician take one look at her films and say, **"Oooh…crunch."**



George Muschler, M.D.



Daughter cell colonies (image, opposite page) form where stem cells attach, allowing the number of original stem cells to be determined. Red-stained tendrils (image, this page) show the filaments within each cell that are used for cell attachment and determine cell shape.

Biggins had shattered her left collarbone so severely that doctors weren't sure what to do with her. Within two days they decided to operate and put a plate into her shoulder, but the pain persisted.

Within months, the plate loosened and Biggins could hear the metal clicking inside of her. Five months later, her doctor operated again to remove the plate. The pain worsened. The doctor operated a third time, using a bone graft from a cadaver. By this time, her shattered collarbone had, in many ways, shattered her life.

Softball – a love since childhood – was out of the question. Perhaps most damaging, she almost gave up playing piano because her left hand wasn't functioning properly. Piano was not just a passion for her, it was to be her next career. She was just starting the second year of a four-year college program as a piano performance major with the goal of becoming a music therapist.

But after that third surgery – and still more pain – her athlete's adrenaline took over and she focused on finding someone who could cure her shoulder.

That's when she called The Cleveland Clinic and found George Muschler, M.D., an orthopaedic surgeon. Dr. Muschler isn't your ordinary surgeon. He also is director of the Bone Biology Laboratory in the Department of Biomedical Engineering in the Lerner Research Institute. When he isn't in surgery fixing bones, he's in his research laboratory engineering solutions to repair bones that won't heal through traditional surgical techniques.

Dr. Muschler followed Biggins for a few months until an X-ray determined that the cadaver bone graft didn't work. She still had a one-inch gap between the bones. Dr. Muschler suggested fixing it in a way that was so new that her other doctor wouldn't have even known about it – with stem cells.

"I knew about the controversy of stem cells," Biggins says. "But he told me right away that he'd take them from my own bone marrow."

NOT ALL STEM CELLS ARE CONTROVERSIAL By definition, a stem cell is an unspecialized cell that has the ability to divide and renew itself. Under certain conditions, it can generate large numbers of daughter cells and these go on to mature into cells with special functions, such as beating heart muscle or new bone to heal a fracture.

Stem cells exist naturally in the body. They're in bone marrow and, although rare, in the blood stream. Stem cells also exist in other tissues and organs, such as the liver, pancreas, brain and maybe even the heart.

Currently, stem cells come from three sources: blastocysts, which are cells isolated from the inner cell mass of a three-to-five-day-old embryo grown in a petri dish in a lab, also called embryonic stem cells; cord blood cells, which are isolated from blood taken from an umbilical cord saved immediately after birth; and adult stem cells, which are collected from a person's own tissues. Of these, only the embryonic stem cells are controversial.

So the goal now for researchers is to find the stem cells, put them where they are needed and then to get them to do what they want them to do – heal a bone after a break, repair heart muscle after a heart attack, or cure a devastating disease like multiple sclerosis.

THE LERNER RESEARCH INSTITUTE Travel west along Cleveland's Carnegie Avenue and on your left, just past 100th Street, you'll see a modern glass and rose stone building that sits back from the road behind a courtyard. The see-through walkways and curved glass structure give visitors a welcoming glimpse into a realm foreign to most: the world of biomedical research.

Inside, amidst walls painted deep shades of purple and turquoise, 130 senior researchers and their staffs are finding solutions to numerous important medical mysteries. And, of those, four are heading programs to learn more about stem cells in the areas of orthopaedics, cardiology and neuroscience. Their departments are expected to grow rapidly – and additional departments will be added – since The Cleveland Clinic was awarded $9.5 million in grant money to launch a Stem Cell and Regenerative Medicine Center in collaboration with Case Western Reserve University, University Hospitals and the biomedical company, Athersys, Inc. (see sidebar, page 13).

The Cleveland Clinic's ongoing stem cell research focuses only on adult and cord blood stem cells, eliminating the controversy that surrounds work with embryonic stem cells. Adult stem cells aren't really anything new. Research on adult stem cells actually began 40 years ago, and they've been used for bone marrow transplants in cancer patients for more than 30 years.

But in the last five years, researchers have discovered that stem cells live in other areas of the body, including circulating blood, blood vessels, skeletal muscle, eyes, skin and the liver. And therein lies the biggest difference between embryonic and adult stem cells. In theory, an embryonic stem cell is the ultimate stem cell because it has the potential to become any type of cell in the body. An adult stem cell, however, seems to be limited in the type of cells it can form.

Another issue is that adult stem cells are rare. Tracking them down effectively is one of the biggest focuses of research. Figuring out how to get them to fix missing or diseased tissue once they're found is the next battle.

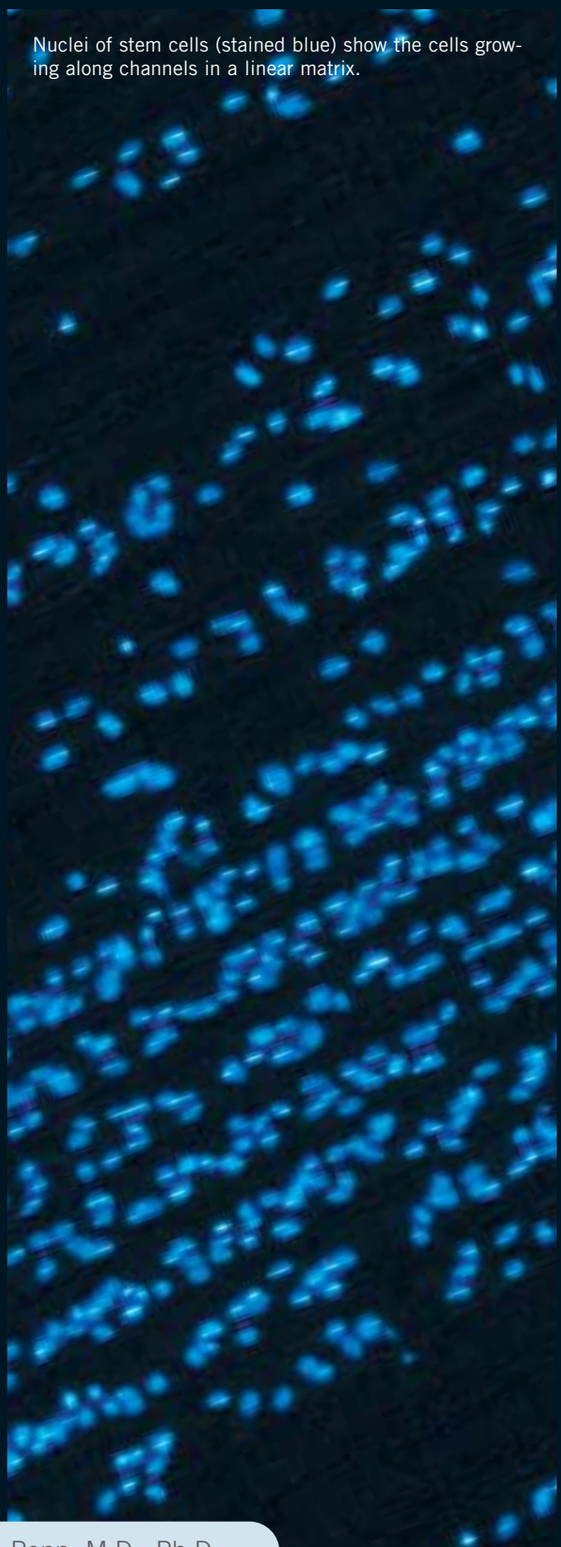
And that's exactly what Cleveland Clinic researchers Dr. Muschler; Marc Penn, M.D., Ph. D.; and Bruce Trapp, Ph.D., are determined to do.

A GREAT BREAK IN ORTHOPAEDIC STEM CELL RESEARCH Dr. Muschler has been using stem cell transplants in patients for more than two years. He is the first physician in the country to selectively harvest stem cells from a patient's own bone marrow, put them into a "matrix" – a material, such as fibers from cadaver bone chips or porous calcium phosphate ceramics – and transplant them into a patient to heal a broken bone. The entire procedure – harvesting and then selectively concentrating the cells for transplantation – takes just 10 to 15 minutes.

The transplanted cells go on to form the new bone that is needed. The method is significantly less painful and risky than traditional methods for bone grafting, which involve cutting into a patient and removing actual bone pieces.

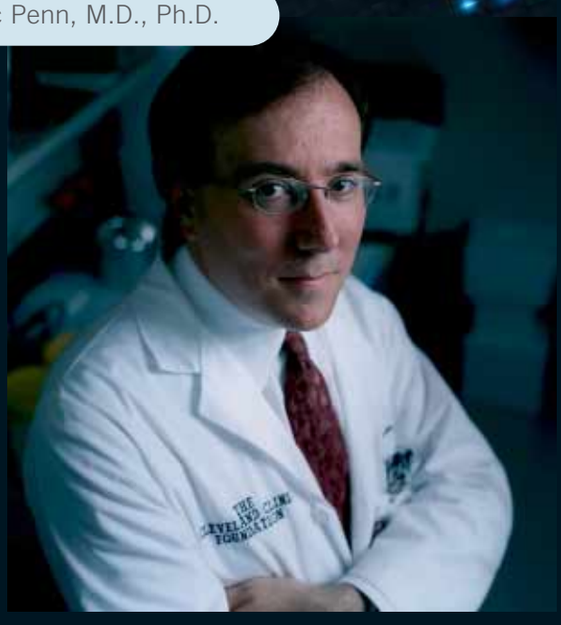
To get the stem cells, Dr. Muschler simply inserts a needle into two spots of the patient's pelvis and draws out bone marrow. Then he uses special technology he designed, called Cellect™, to sort out the stem cells from other cells in the marrow. He adds a clotting material to enhance performance just before transplanting the matrix into the patient.

"The stem cells that form new bone and tissues are stickier than other cells on certain surfaces," he explains. "These small, rare stem cells will selectively accumulate on the matrices of the surface."



Nuclei of stem cells (stained blue) show the cells growing along channels in a linear matrix.

Marc Penn, M.D., Ph.D.



Once the matrix is transplanted into a patient, the cells multiply, growing new bone, healing fractures and restoring missing bone.

For Biggins, her stem cell transplant was a life-saver. Dr. Muschler performed the surgery in May 2002, nine months and three surgeries after her heroic dive for that line-drive ball.

"It felt more solid right away," Biggins says. The shoulder pain lessened, too. And, she says, she had no pain at the two points where Dr. Muschler drew out the bone marrow. Within four months, an X-ray showed the gap in her collarbone had healed enough that she could get back to normal life.

GETTING TO THE HEART OF STEM CELL RESEARCH You're having chest pain. You go to the emergency room and the doctor gives you a shot. But it's not medicine in the syringe – it's stem cells. Soon, your heart repairs itself, and you're better than ever.

It sounds like science fiction, but that day may be less than a decade away.

It's believed – though still controversial – that stem cells do not exist naturally in the heart. They must find their way there from somewhere else, such as from bone marrow or the bloodstream. Then, once they're there, the question becomes how does a stem cell know if it should mature into a muscle cell that helps the heart beat or one that helps create new blood vessels?

Marc Penn, M.D., Ph.D., a cardiologist and researcher in the departments of Cardiovascular Medicine and Cell Biology, is studying the effects of stem cells on the heart. Specifically, he's researching stem cell "homing factors" – in other words, how stem cells find their way to the heart – and then, once they're there, how they mature into cells that repair the heart.

In a study published this year in *The Lancet*, Dr. Penn and his colleagues identified the first stem cell homing factor expressed by the heart. The study showed that the factor, called SDF-1, is only expressed for less than seven days after a heart attack.

"There are six million people who have heart failure. We'd like to treat all those folks. But we'd also like to prevent the next six million people who have heart attacks from ever developing heart failure," Dr. Penn says.

If researchers find a way for stem cells to heal hearts, not only would fewer people die following heart attacks, but also theoretically, Dr. Penn says, heart transplants could become a thing of the past if stem cells can be manipulated to regenerate heart muscle. What is known right now is that if there are stem cells in a patient's bloodstream at the time of a heart attack, then they will find their way to the heart. But after a few days, the stem cells in the bloodstream stop arriving. Simply not enough of them get to the heart to help to repair the damage.

Dr. Penn and other researchers at The Cleveland Clinic are on the leading edge of cardiac stem cell research. Given what is known, they are the first in the country to study the effects of giving a cancer drug called GCSF – granulocyte colony stimulating factor – at the time of a heart attack in select patients. GCSF releases stem cells into the bloodstream.

"The goal is to put a lot of stem cells in the bloodstream at a time when we know there's a homing signal and see if people's hearts get better by doing that," says Dr. Penn. Initial results should be released early next year.

LOOKING AHEAD WITH STEM CELLS FROM THE EYE

A new stem cell therapy that takes cells from the limbus area, the rim around the cornea of the eye, is being used to help restore sight to some patients with limbal stem cell deficiency. These patients usually have corneal damage from chemical scarring, autoimmune disorders, some hereditary disorders or chronic dry eyes that has resulted in decreased vision or loss of vision.

In these cases, the retina is healthy, but patients can't see because the cornea is hazy.

"The procedure works best if you can use stem cells from the patient's own healthy, undamaged eye, if there is one," explains Victor L. Perez, M.D., staff physician at the Cole Eye Institute. Called "autografting," the process takes stem cells from the limbus of the healthy eye and grafts them onto the damaged eye. Once grafted, the stem cells then move in to fix the damage. Dr. Perez continues, "Usually you know within a couple of weeks if it's working. If the rest of the cornea is healthy, patient discomfort goes away and their vision begins to get better. If the cornea is also damaged, a corneal transplant may also be necessary to restore vision."

When corneal abrasion occurs in healthy eyes, the surface layer, or epithelium, is scratched away. New cells move in to cover the surface again. "The limbal stem cells are the source of these cells," says Dr. Perez. "We are born with a given number of these stem cells that live in the limbus. But patients who lose these stem cells are not able to repopulate their cells. Their vision can be greatly affected and in some instances they can become blind."

For patients who have damage to both eyes, donor cells from family members or eye banks also work. The downside is that these cells must be tissue-matched and the patient must take immunosuppressant drugs, just as in solid organ transplantation.

Other advances in eye stem cell research include taking stem cells from a healthy donor and culturing them in the lab. They grow and expand in a petri dish with a biological membrane, and subsequently the patient gains more stem cells that can be used to heal the eye. Unlike stem cells from bone marrow, which still have the potential to become a variety of cells, limbal stem cells are already committed to becoming part of the eye. So in all probability, they remain a stable phenotype and won't differentiate over time into an undesired type of cell.

"There are many people walking around with limbal stem cell deficiency that no one has diagnosed," says Dr. Perez. "So those patients who have had a corneal or epithelial disease, or have been diagnosed in the past with dried surface damage, they just give up. This might be a real possibility for them to restore their vision."

Clinic researchers also are studying the effects of injecting stem cells from a patient's muscle – called skeletal myoblasts – directly into the heart during bypass. Doctors take stem cells from a patient's muscle, grow them in a lab for a few weeks, then transplant them into the patient's heart during bypass surgery.

That means that cardiologists might have two choices in the future: stem cell transplantation or recruiting stem cells already in the bloodstream to get them to the heart.

The latter could have far-reaching implications in medicine.

"If we define homing factors that bring stem cells to the heart then, fundamentally, very similar strategies could be used to call cells to the brain, to the liver, or other organs," Dr. Penn says. "Once they get there, the trick becomes triggering them to become the specific cell that is needed. And, that's the other part we're trying to figure out."

MINDING MATTERS OF STEM CELLS AND THE BRAIN "This isn't a sprint, it's a marathon," says Bruce Trapp, Ph.D., chairman of the Neurosciences Department at the Clinic.

Ultimately, Dr. Trapp wants to find a cure for multiple sclerosis (MS), a chronic autoimmune inflammatory disease that causes lesions in the brain. At the very least, he hopes to find a way to stop the progression of the disease that can rob its victims of muscle usage.

But he's looking way down the road. Perhaps less is known about brain stem cells than any other type.

Right now, Dr. Trapp is just trying to identify where the stem cells that generate brain cells originate.

Research shows that early in the disease, the brain of an MS patient replaces cells in areas damaged by the disease. But not enough cells are being replaced or the ones that are there aren't doing their jobs. It's also not known why, after time, that process breaks down and fewer and fewer natural "repairs" are made, causing irreversible damage.

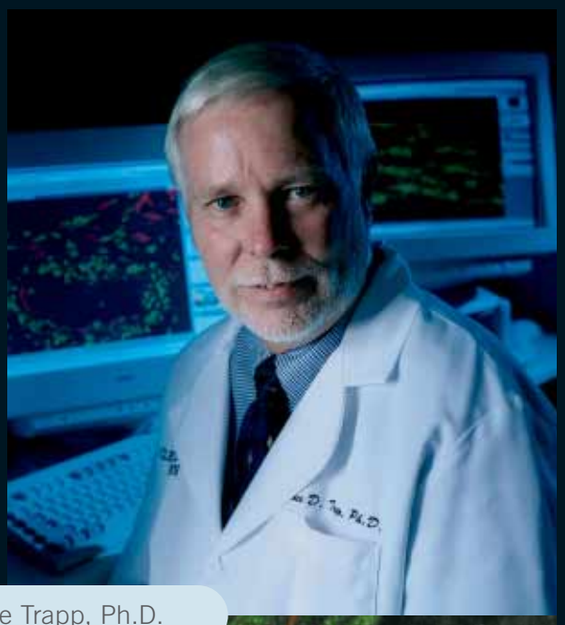
Dr. Trapp's mission is to track down the stem cell that will eventually mature into other cells, in an effort to learn more about the breakdown that occurs in the brain of an MS patient.

So far, Dr. Trapp's research has shown that a cell called an NG2 leads to the development of a cell called an oligodendrocyte. It is the oligodendrocytes that are destroyed in MS. Dr. Trapp is in search of the stem cell that transforms into the NG2 cell that leads to the oligodendrocyte.

To help MS patients, Dr. Trapp's theory is that there may be a way to manipulate the stem cell in the adult brain to produce enough new oligodendrocytes to repair the MS lesions.

While much of the research seems miles down the road of the marathon, Dr. Trapp says he knows he'll reach at least one goal during his lifetime: to slow the progress of the disease enough that MS patients will never need to use a wheelchair.

"Will we ever stop the disease?" he asks, reflectively. "Hopefully."



Bruce Trapp, Ph.D.

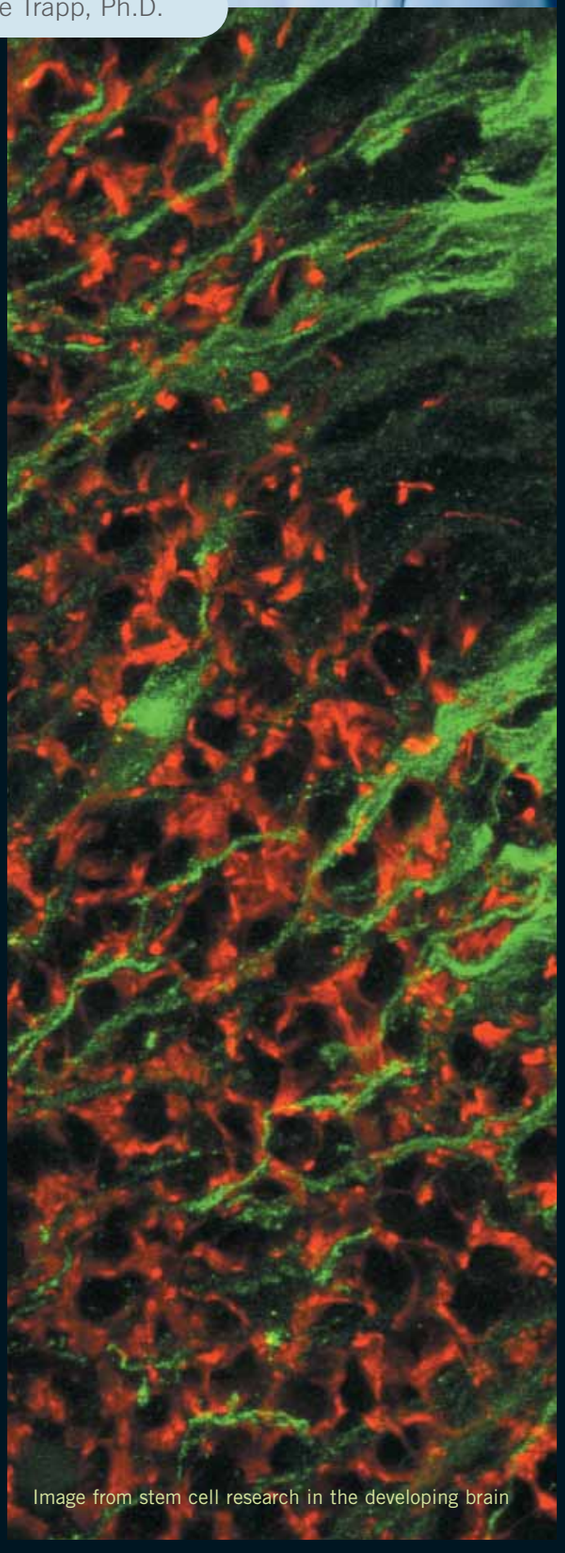


Image from stem cell research in the developing brain

TECHNOLOGY REVOLUTIONIZES THE SEARCH FOR STEM CELLS

Stem cells are an elusive bunch. So where would you go looking for one if you wanted to find it?

Researchers know that they're most commonly found in bone marrow. If you have never actually seen bone marrow, picture a thick wet mass of cells and blood. Which ones are stem cells? Which ones are harmful cancer cells?

While the physicians in offices surrounding him at the Cleveland Clinic's Lerner Research Institute try to figure out how to treat patients with stem cell therapies, Maciej Zborowski, Ph.D., in the Department of Biomedical Engineering creates devices that can track down stem cells and separate them from other cells.

But stem cells are extremely rare in bone marrow and even rarer in blood. If you could quickly and efficiently find enough tiny stem cells among millions of cells, potentially you could save a lot of lives.

That's the theory behind Dr. Zborowski's invention – the quadrupole magnetic flow sorter, or flow sorter, for short – which can process up to 12 million cells per second. The stem cells end up in one area of the device and all the other cells end up on the other side.

Cell separation has enormous diagnostic and therapeutic implications, says Dr. Zborowski.

Not only could you sort for stem cells, but, "We could isolate rare cancer cells from the blood to see if metastasis is occurring," he explains.

But for now, finding stem cells has two major uses. The first is for cancer patients. Since bone marrow matches have to be exact and are rare, it will be possible to take bone marrow from a patient's own body and, after giving chemotherapy or radiation, transplant the healthy stem cells back into the patient, instead of risking that the marrow has cancer cells in it.

Also, isolating stem cells helps other researchers at the Lerner Research Institute to work on developing treatments.

For example, one of the projects of orthopaedist George Muschler, M.D., is to grow cultures of stem cells in petri dishes to try to understand the inner workings of the stem cell. Some cells colonize and divide rapidly, while others develop more slowly. So, how does that contribute to the disease process or to therapies targeted at curing disease?

As his colleagues continue to find stem cell therapies, Dr. Zborowski will continue to create the machines that someday will be commercialized and used all over the world to track down the elusive stem cell.

Maciej Zborowski, Ph.D.

BREAKING GROUND FOR NEW STEM CELL AND REGENERATIVE MEDICINE CENTER

In late October 2003, construction began on the building that will house the Clinic's new Center for Stem Cell and Regenerative Medicine. The Center will be developed in conjunction with Case Western Reserve University, University Hospitals and the biotechnology company, Athersys, Inc., based in Cleveland.

Plans call for a six-story building on East 96th Street, between Carnegie and Cedar avenues, with 14 labs on each floor. The building will be attached to the Lerner Research Institute and at least one floor will be dedicated to the Clinic's new Department of Stem Cell Biology and Regenerative Medicine. The building also will house the Clinic's Institute for Genomic Medicine.

In June 2003, The Cleveland Clinic received two major grants totaling $9.5 million to launch the new center. "We have a strong combination of outstanding laboratory researchers and outstanding clinicians," says Paul DiCorleto, Ph.D., chairman of the Lerner Research Institute. "We have the capability of very rapidly bringing laboratory discoveries to the bedside."

The Center for Stem Cell and Regenerative Medicine will not be located in just one area, however. Research for the center will take place throughout the city of Cleveland. It's expected to create as many as 140 new jobs in the area, many of those at the Clinic.

In the 1980s, the use of stents with angioplasty revolutionized the catheter treatment of coronary artery disease. Now, stenting itself is undergoing a transformation – new metals, filters and drug-coatings are lowering the chance of re-blockage and allowing stents to go where they've never gone before.

SUPER-POWERED STENTS

Thomas Rosler knows the power of the tiny metal stents strategically positioned throughout his body. With five stents in his heart, one in his subclavian artery and two more placed in different sections of his carotid arteries, the 70-year-old Venezuelan knows his participation in medical history in the making has yielded him a monumental payoff.

Fresh from his second carotid artery stenting – a promising experimental procedure gaining popularity and medical nods as an alternative to surgery for opening clogged carotid arteries in the neck – Rosler seems to be sitting still only because he is attached to an intravenous line.

"Look, I feel so happy, you will never understand... I feel like having champagne," he says.

Celebrating aside, things weren't always rosy for Rosler, who flew to The Cleveland Clinic in March to receive stent number five in his heart. Once at the hospital, doctors picked up on a more severe problem in his carotid arteries, which were both almost completely blocked, putting him at a high risk for a stroke.

Thomas Rosler, heart patient

"I knew I had a problem, but not that severe," he says. "I'm experienced with this problem of artery disease because I have been stented in other parts of my body over the last six years. But for the carotid I was always told the solution was surgery; this was the common solution. Obviously, nobody wants to have surgery and you always try to postpone that decision. Stenting was a good choice for me."

It's no surprise to Rosler that his doctors are at the leading edge of stenting advances. The process of inserting a small stainless steel coil into a blocked artery during an angioplasty to prop open and strengthen the diseased area and promote maximum blood flow has been around for about 20 years. Now, recent innovations are bringing super-powered stents to patients with carotid and coronary artery disease.

OPENING UP BLOOD FLOW TO THE BRAIN

Because the brain is more delicate than the heart, special protections had to be created before carotid stenting could be safely performed. The first protected carotid stenting procedure in the United States was performed at the Clinic in February 2000. Carotid stenting involves threading a specially designed filter on a guidewire through a small incision made in the patient's upper hip area and guiding it to the area of narrowing in the carotid artery. Once beyond the blockage, the filter opens up like an umbrella and prevents particles of plaque from going to the brain. A small balloon then is inflated to dilate the carotid artery at the site of the disease. A self-expanding nitinol stent mounted on the guidewire is put in place and expanded to hold the carotid artery open, sending oxygen-rich blood to the brain *(see images at right).*

Unlike stainless steel stents, which are used in the heart and the brain where the areas are protected by the chest and the skull, the carotid stent is designed with nickel titanium, a pliable metal with memory that bounces back to its original shape and size if constricted.

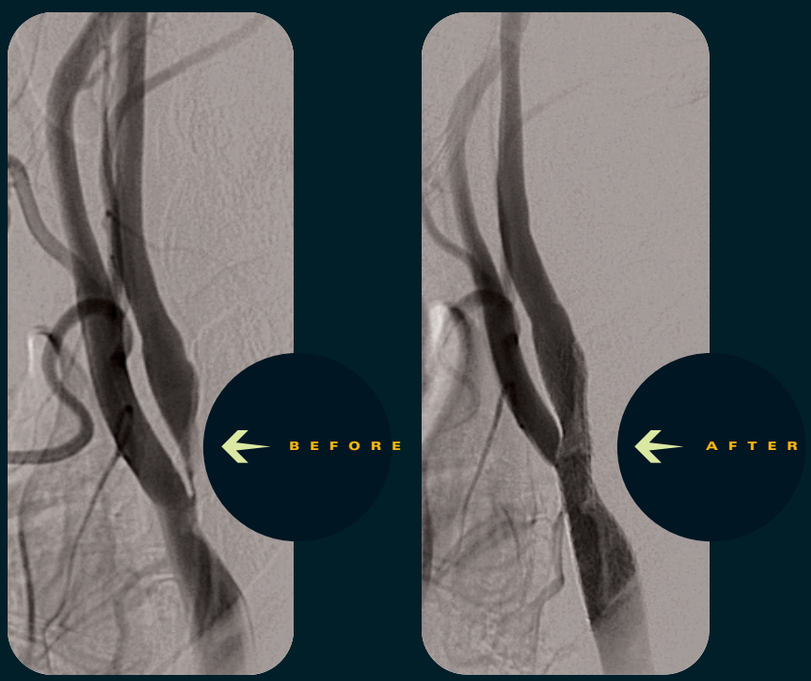
If a stainless steel stent was placed in a carotid artery, it could easily be compressed by pressing on the neck and it would not regain its original shape. This would not only make it ineffective in keeping the artery open, but would also re-block blood flow to the brain.

The innovative nickel titanium carotid stent, "Opens like an accordion, and once it's in place, that's how it wants to stay," says Lynn Oster, R.N., research coordinator of the carotid stent trials in the Department of Cardiology at the Clinic.

The criteria for needing any type of carotid artery intervention revolve around the severity of the blockage and symptoms. If no symptoms are present, treatment is not necessary until there is at least an 80 percent blockage. If there are symptoms, like a transient ischemic attack or a stroke, then the patient should have treatment with even a 50 percent blockage.

Once the stenting is complete, patients are sent home with strict guidelines for monitoring their blood pressure. Patients are followed at specific intervals: 30 days, six months and then annually for between three-to-five years.

CAROTID ARTERIES



The self-expanding stent holds the carotid artery open, sending oxygen-rich blood to the brain.

Jay Yadav, M.D.

SAPPHIRE shines

Although carotid stenting is not yet approved by the Food and Drug Administration (FDA), this promising procedure has had spectacular results from a clinical trial.

Jay Yadav, M.D., director of Vascular Intervention for the Department of Cardiovascular Medicine at the Clinic was the principal investigator in the large multicenter randomized SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) trial. In this trial, data clearly showed that when randomly assigning high-risk candidates to undergo either carotid endarterectomy, in which the artery is surgically opened so that the blockage can be removed from the artery wall, or carotid stenting, the winner was stenting.

"What we found was a resounding decrease in the complication rate in the 30-day results," Dr. Yadav says. "We found in that study that there was a more than 50 percent reduction in strokes, heart attacks and deaths in the stenting group compared to the surgical group."

The complication rate for the stented group was only 5.8 percent, compared to the surgical group where it was 12.6 percent.

"It caused quite a stir," Dr. Yadav says. "Rarely do you have a treatment that is twice as good as the previous treatment."

The data was so compelling that it made the American Heart Association's list of top 10 research advancements for 2002.

The department is performing carotid stenting on seven to 10 patients a week in any one of its current five clinical trials, which are mostly targeted at high-risk individuals. "It is a very routine procedure now; we generally do four or five in one day," Dr. Yadav says.

Patients who are considered high risk have one of several qualifications, including restenosis after carotid surgery, congestive heart failure, prior neck surgery or radiation treatment to the neck for cancer. High risk patients also include those who need bypass surgery or who have severe breathing problems like Chronic Obstructive Pulmonary Disease (COPD).

Why the Leg?

Whether doctors are stenting a carotid or coronary artery, the point of origin for the guidewire with the balloon and stent is always in the leg. "Everything is easier from the leg," Dr. Yadav says. "The femoral artery is bigger and there is less risk of damage to the artery itself." Originally in stenting procedures, the guidewire was put through the arm and this option is still used in cases that warrant it. But Dr. Yadav adds, "Going through the leg works well and is safer for the patient overall."

Angioguard™: The umbrella protection

Unlike the heart, the brain is much more sensitive to particles of plaque that are released during an angioplasty and stenting procedure. What physicians needed was a new technology to keep the particles from getting to the brain, where there was a danger that large enough particles could induce a stroke or death.

So Dr. Yadav, a pioneer in carotid stenting, created the Angioguard distal protection device. The Angioguard, which was used in the SAPPHIRE trial, is a tiny filter that captures plaque particles that break loose during the stenting procedure, preventing them from traveling upward to the brain.

"It's like a very small umbrella with tiny holes in it," Dr. Yadav says. "You put it through the blocked area and on the other side you open the umbrella up. The blood flow continues to the brain through the tiny holes. You can perform the angioplasty and stenting with the filter in place and it captures any particles. At the end of the procedure you collapse the filter with the particles inside of it and remove the filter from the artery."

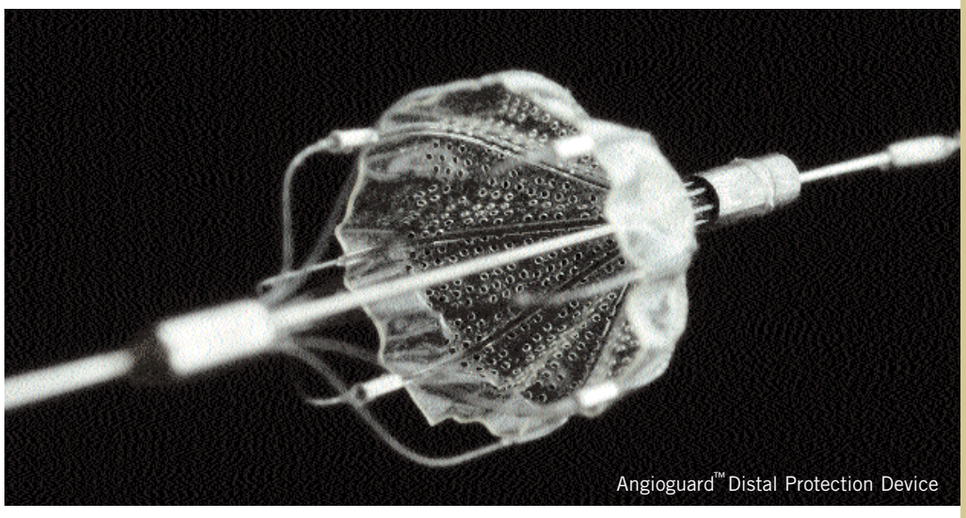
Many patients are now requesting the carotid stent procedure with the Angioguard over carotid surgery. Aside from being safer, it is less traumatic for the patient. There is no scar on the patient's neck and general anesthesia is unnecessary. Patients also go home the next day.

For patient Thomas Rosler, going home the next day was a definite plus, but he admits it was the nifty umbrella protection that won him over.

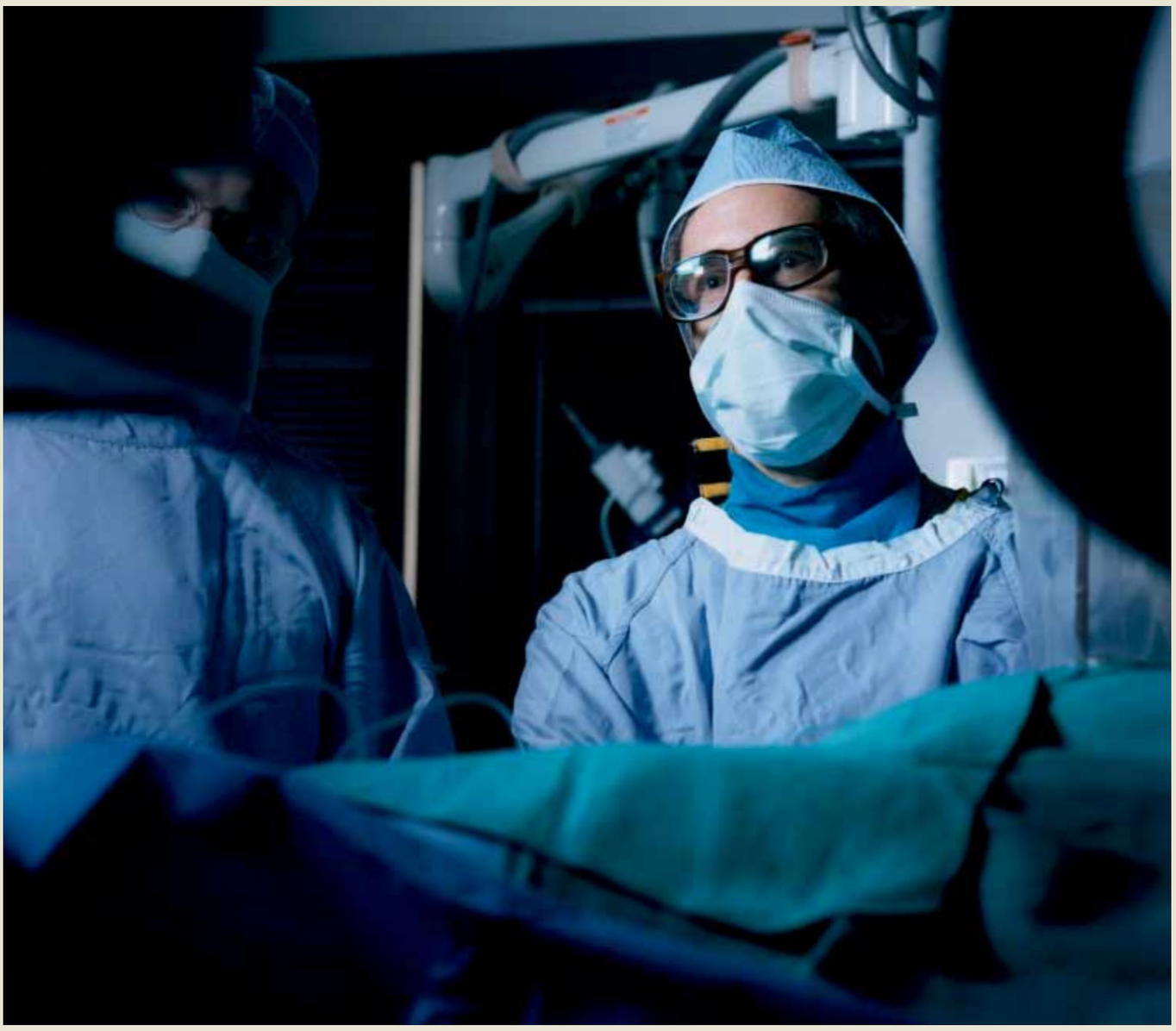
"The umbrella, this is something amazing – to really guarantee that almost none of that dirt will flow into the brain. That is something that really helped me to make the decision to go for it," he says.

"It's like a very small umbrella with tiny holes in it."

Jay Yadav, M.D.



Angioguard™ Distal Protection Device



DRUG-COATED STENTS: A MAJOR ADVANCE

Bare metal stents are a major breakthrough in fighting restenosis – a re-narrowing or blockage of an artery and a common problem in the smaller arteries of the heart and brain. However, procedures using bare metal stents still need to be repeated in about 13-to-25 percent of all cases.

So when the FDA approved the Cypher™ stent – a much-anticipated, drug-coated stent designed to inhibit restenosis – earlier this year, eager patients across the country started making appointments with their cardiologists to have the procedures they had postponed until the new stent officially came to market. Within three weeks of its approval, Clinic cardiologists had performed more than 200 procedures using the new stent.

"Drug-coated stents are a major advance in the treatment of coronary artery disease," says Stephen Ellis, M.D., section head of Invasive Cardiology and director of the Cleveland Clinic Heart Center's Sones Cardiac Catheterization Laboratories. "On average, 13.5 percent of our patients need to come back within the first nine months after their procedure for further treatment, and that is usually due to restenosis."

Cutting restenosis rates in half

Drug-coated stents, also called drug-eluting stents, expand on existing stent technology by delivering a drug into arteries from a coating that is just 10 microns wide, about the width of a hair. The Cypher drug-coated stent, which uses Sirolimus or Rapamycin, slashes restenosis rates to about nine percent, or about half the national average, according to the one-year results of the multicenter Sirolimus-eluting Coronary stent trial (SIRIUS), of which the Clinic was a significant participant. The bare metal stents in the SIRIUS trial had a restenosis rate of about 36 percent.

"The process of restenosis or reblockage within a stent is due virtually 100 percent to the formation of scar tissue, not to a buildup of cholesterol," Dr. Ellis says. "So it's different from the original blockage that necessitated stenting in the first place."

Sirolimus interferes with a variety of biological processes that lead to scar tissue. This means that patients with drug-coated stents should require less repeat revascularizations due to restenosis.

Once placed in the diseased area of the artery, the drug-coated stent immediately starts releasing Sirolimus. The drug quiets cells that have been battered by angioplasty and stent placement. Over

30 days the stent sheds 80 percent of its drug, preventing the formation of scar tissue that can promote new blockages of the blood vessel and blood clots. The artery heals around the stent making it a permanent part of a patient's cardiovascular makeup.

Just as people come in different sizes, so do blood vessels. While the Cypher stent is not available in every size yet, "If the sizes available are the right fit for the blockages and the arteries that need repair, physicians certainly prefer to put them in because of expected better performance," Dr. Ellis says.

Several companies have drug-coated stents under development and the new Taxus™ stent, which is already sold in Europe, is expected to be the first of those available in the United States in 2004.

Questions abound

Not surprisingly, the demand for drug-coated stents is strong. "The coated stent era has started with the usual 'genie out of the bottle' and it really isn't a genie after all," says Eric Topol, M.D., chairman of Cardiovascular Medicine at the Clinic.

The primary problem is that drug-coated stents have not been tested for all the same uses as a bare metal stent and there have been some reports of a possible increase in the risk of stent-related clotting.

The clinical trials of the Cypher stent were limited to people with shorter blockages that filled most of the artery's diameter and who had not been treated previously.

It is still unknown if these stents will help if implanted during a heart attack – a frequent practice with bare metal stents. Other questions also persist: Can they keep open bypass grafts that have re-clogged? What about other stents that have re-clogged? Can they open up blockages on branched arteries, in small arteries and in vessels that are completely blocked? Should they be used in people who have multiple clogged vessels?

The ideal candidates for drug-coated stents include patients who have diabetes, patients with short blockages and those who have a history of restenosis. They must be able to take aspirin and clopidogrel as blood thinners for a protracted period of time. However, the bare metal stent has been highly effective for most patients overall.

"The thing that's crazy is that a non-coated, what we call a 'bare' stent, has worked pretty darn well," Dr. Topol says. "They're great and we have a variety of them. We have a decade of experience with them, so we know their limitations."

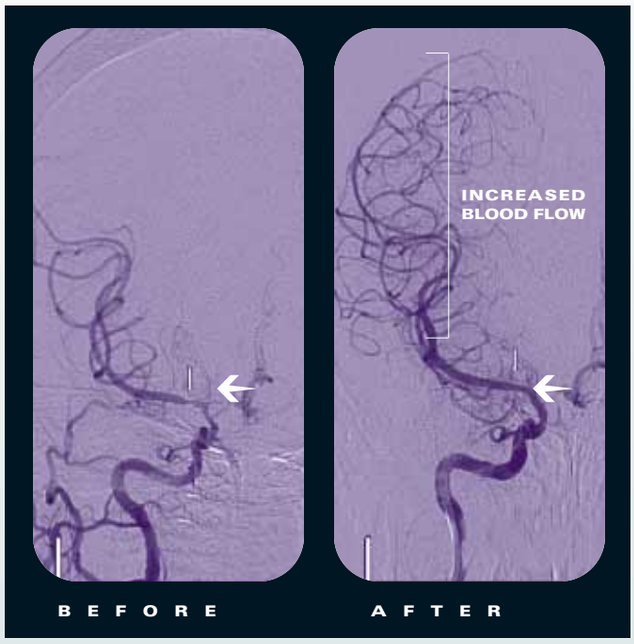
Dr. Ellis agrees. "I think [drug-coated stents] are a major advance, but it's not like this over-enthusiasm has never happened before. I remember a decade ago when stents were first coming out and people would not want to have a regular balloon angioplasty. They wanted to wait for a stent. Even though angioplasty is a highly effective procedure, it's a somewhat analogous situation, although we've obviously made progress."

Although more trials and studies will eventually answer these questions, patients can find some confidence in the statistics.

"If you look at our own data for instance, bare metal stents are effective in 87 percent of our patients," Dr. Ellis says. "The other reassuring point is that restenosis, although unfortunate, is seldom life-threatening."

That being said, he is not surprised by the eagerness of patients who are refusing to have anything else.

"I think in the United States there is a substantial proportion of patients who are quite well-informed, and the data is so compelling that these people are going to demand, or at least request, this sort of stent."



Brain Stenting

First it was the heart. Then came the neck. Now, people with blocked arteries in the brain can benefit from a new application of stenting called intracranial stenting. Though plaque build-up in cranial arteries is not as common as coronary or carotid disease, it's more challenging in terms of treatment.

"The brain vessels are very difficult to access directly and only very limited surgery can be performed," says Jay Yadav, M.D., director of Vascular Intervention for the Department of Cardiovascular Medicine at the Clinic. "The patients we consider for intracranial stenting are at a severe stage of the disease, with TIAs [Transient Ischemic Attacks] and strokes. Careful consideration is given to the risks and benefits. At this stage, there is really no other good alternative." Former alternatives for blockage in the brain involved using blood-thinning drugs, which were not very effective, or angioplasty.

It's only been in the past couple of years that stents are good enough – smaller and more flexible – for the intracranial procedure. Arteries in the brain are quite delicate and easy to tear, which can lead to bleeding and death, so they require stents specifically designed for the brain.

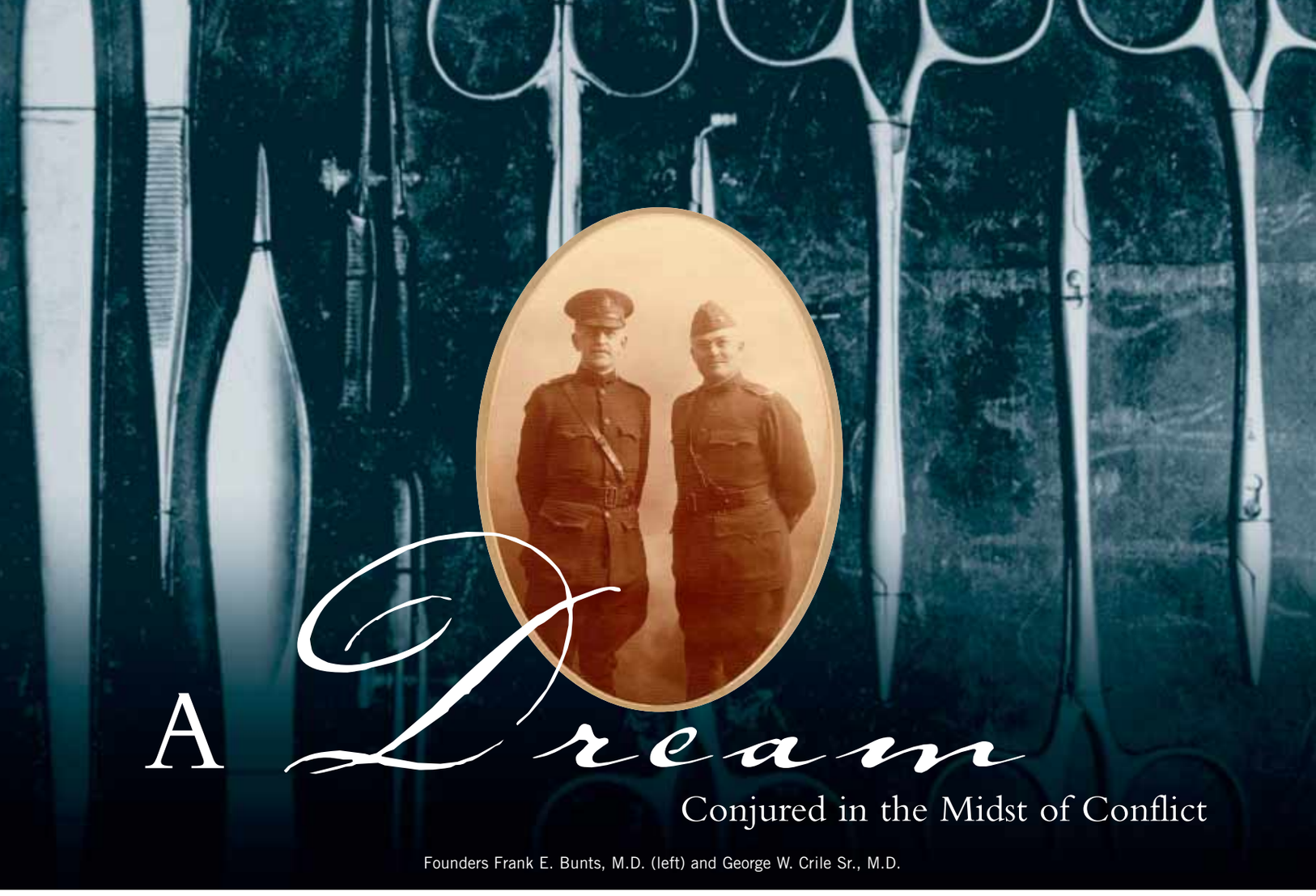
Just as in coronary and carotid stenting, in intracranial stenting doctors slide a guidewire up through the artery to the blockage, inflate a tiny balloon to restore free blood flow and set a bare metal stent in position to keep the area open.

And the procedure is still undergoing refinement.

"We were the first investigators to do intracranial stenting without general anesthesia – we do it with the patient awake," Dr. Yadav says. "We published a paper this year at the American Heart Association Stroke meeting showing that you can do it safely without general anesthesia, which is a big improvement for the patient."

A patient who is awake and aware of what's happening can give doctors valuable feedback during the procedure. If a patient complains of a headache, that means a vulnerable brain artery is being stretched too far and the doctors need to back off. Without that information, the physicians might inadvertently press too hard on the artery and cause a hemorrhage.

Dr. Yadav began introducing the awake-patient technique about two years ago to doctors who treat stroke victims. The Clinic plans to begin a larger, scientifically designed study in 2004 to continue assessing the procedure.



A Dream

Conjured in the Midst of Conflict

Founders Frank E. Bunts, M.D. (left) and George W. Crile Sr., M.D.

The model of a modern, major medical center, The Cleveland Clinic is based on lessons learned in the battlefield hospitals of World War I.

The early 20th Century was an age of ideals and revolutions. It saw the rise of social reform movements, like the crusades for women's sufferage, temperance and racial equality, and the creation of real and fictional utopias, from Vladimir Lenin's Russia to Frank L. Baum's Oz.

Many idealistic dreams were forged in the First World War. The unprecedented savagery of this conflict frightened many people into believing that sweeping social changes were necessary for the future of humanity. While most of the great notions that came out of the war fizzled and died, some not only survived, they thrived. Among these is The Cleveland Clinic. In the words of one of its founders, the Clinic was created as "an ideal setup for the most altruistic and the most effective way of practicing a great profession." It was a dream conjured amid some of the First World War's grimmest scenes.

The war in Europe had been raging for three years before America formally entered the conflict. When President Woodrow Wilson and Congress finally declared war, the first Americans sent to France were not infantry, airmen or sailors. They were a small contingent of medical people from Cleveland. Their leader was a man sometimes described as a dynamo – George Washington Crile, chief of surgery at Lakeside Hospital. With him were many of the physicians and nurses who were later to become The Cleveland Clinic's nucleus.

Dr. Crile was no newcomer to the war. As early as 1914, he, his trusted nurse associate, Amy Rowland, and 11 other Lakesiders had gone to France to be part of the medical action in what was shaping up to be the most violent war in history. After three months of caring for the wounded, Dr. Crile and Rowland returned to Cleveland, rounded up their colleagues, and formed a base-hospital unit. Thanks to Dr. Crile's organizational energy, the group was ready to go the moment America elected to join the conflict.

The Lakeside Unit was assigned to staff a hospital near Rouen in war-beleaguered France. Among the physicians serving there between May 25, 1917 and January 22, 1919 were Dr. Crile's stateside physician partners, Frank E. Bunts, M.D., and William E. Lower, M.D.

But the restless and inquisitive Dr. Crile couldn't be contained at a single location and got the Army to name him director of the Division of Research. In this capacity, he was "able to move about and visit the stations wherever the action was." Among the innovations he introduced to wartime medicine were blood transfusions and nitrous oxide/oxygen anesthesia as an alternative to ether for surgery.

Well before the war, Dr. Crile had been interested in shock and the effect of trauma on physiological function. Combat inspired him to broaden his studies to include the "effects of fear and exhaustion on the human body."

Quotations in this article were taken from *George Crile, Volume I,* edited by Grace Crile and published in 1947 by J.B. Lippincott Company, New York.

And examples of fear and exhaustion abounded. In his diary, Dr. Crile, describes marching soldiers who were so tired that they slept while they walked. He arrived at an old schoolhouse to find more than 500 wounded, some "dying, some dead, but everyone was in deep sleep. Bleeding – yet asleep; limbs shattered – yet asleep…!"

Though the horrors of war oppressed him, Dr. Crile took full advantage of the opportunities it offered for observation and study. He called the war, "research on a colossal scale. The methods of years can be overthrown in a night. We have no fixed ideas."

In addition to medical observation, Dr. Crile also observed the organization of care in the military. In his official position, he went up and down the front lines, "observing, recommending, [paying special attention to] a group where there seems to be an unnecessarily high mortality rate, changing this or that method of handling, until they get better results." Consciously or not, he was acquiring data that could eventually be used to help him organize a more effective and efficient civilian medical operation, when the time came.

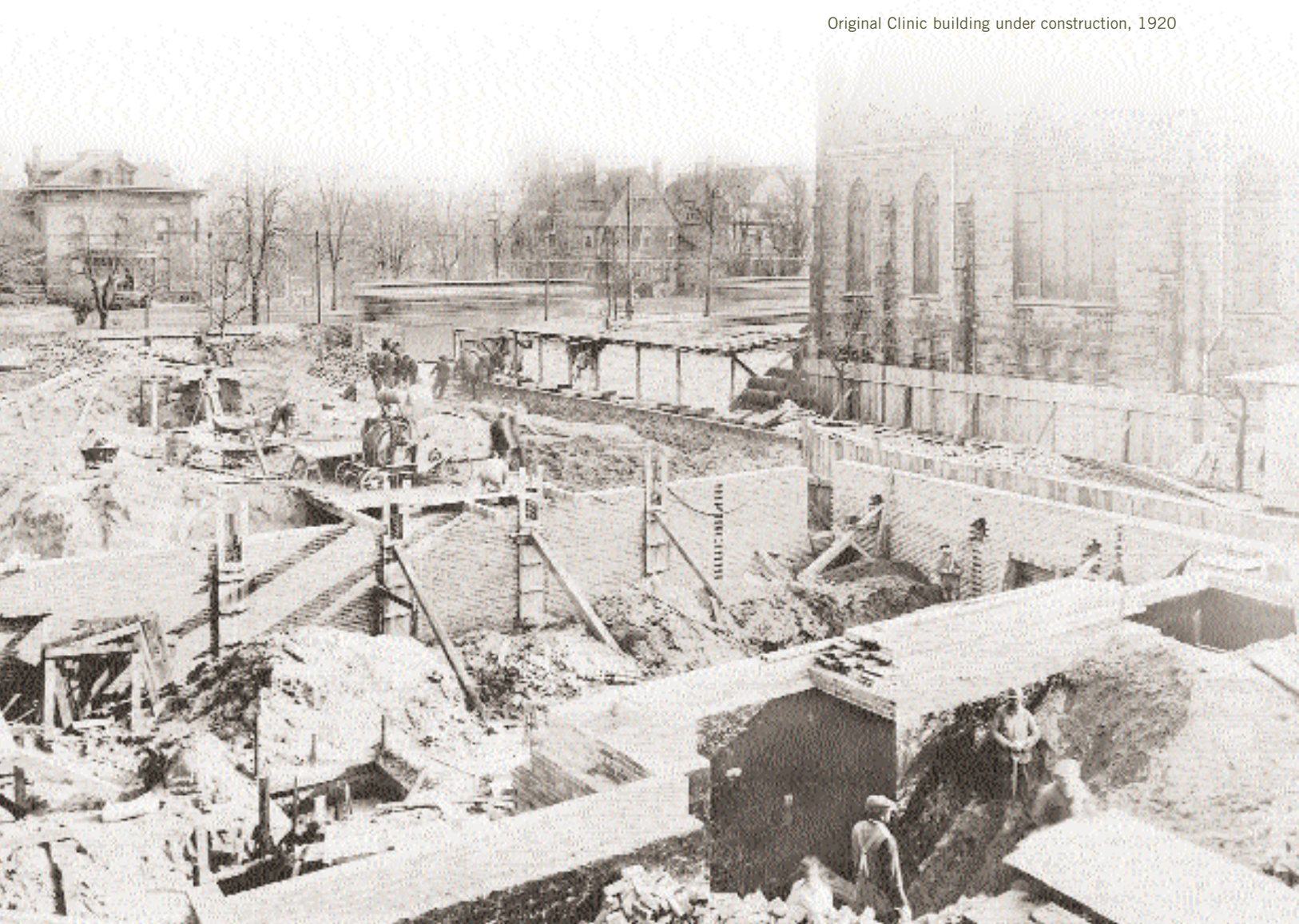
In 1917, he returned temporarily to the United States to report to the Army authorities in Washington and to be presented to President Wilson. Dr. Crile had prepared "A Suggested Plan of Clinical Organization of the Medical Service of the U.S. Army" that he had written on the boat over. His friend William Mayo, M.D., one of the founders of the Mayo Clinic, read the report and enthusiastically endorsed it. Before returning to France, Dr. Crile saw the Army adopt many of his suggestions as it reconstructed its medical department.

Back at the Lakeside Unit in Rouen, Dr. Crile's colleague Dr. Lower performed a primitive form of heart surgery. His patient had a "bullet lying at the apex of the heart and embedded in its outer covering" and moving "in a rotary manner with each heart beat." In an operation that Dr. Crile believed was the first of its kind, Dr. Lower removed the bullet under nitrous-oxide oxygen and novocaine. An assisting physician later spoke of the thrill he experienced holding the patient's beating heart in his hand – a rare opportunity in the days before open-heart surgery.

Though they were cousins and had shared a medical office for more than a decade back in Cleveland, Dr. Crile and Dr. Lower couldn't have been more different in temperament and personality. Where Dr. Crile was energetic, instinctive and partial to sweeping generalizations, Dr. Lower was a master of the particular – careful, methodical and frugal to a fault. The third man in the Cleveland practice, Dr. Bunts, stood somewhere between these two poles. Reflecting on their personal differences in his war diary, Dr. Crile marveled that despite all they had been through as partners and rivals, the three nonetheless had always been able to "act as a unit."

As the war wore on, Dr. Crile's diary records him working in field hospitals where "night shifts were working in a three-table operating room. Groups of wounded are lying on stretchers in the dimly lit anteroom… They are moaning. Guns are booming."

Original Clinic building under construction, 1920



Completed Clinic building at the corner of East 93rd Street and Euclid Avenue, which opened February 1921

The war finally ended on November 11, 1918 – Dr. Crile's birthday. The flood of incoming wounded stopped. At the end of a day's work, Dr. Crile and Dr. Bunts (now heading the Lakeside Unit) warmed themselves by the stove and enjoyed long, wide-ranging conversations. Earlier in the war, Dr. Crile and Dr. Lower had shared similar talks during long walks in the forest beyond the hospital gates.

Dr. Crile wrote that these "discussions of ideals, stimulated by the roar of cannon, the uncertainty as the outcome of war and of life itself, formed the background for the organization of the Cleveland Clinic."

Military life had given the three men "a rare opportunity to study organization." They were struck by the efficiency of Army medicine. This included, "the advantage which accrues to the patient who is in a hospital in which he commands the services of the internist, the surgeon, the specialist, the X-ray department, the pathologist and the bacteriologist, and a continually active ensemble of doctor, nurse and scientists." They wanted their ideal clinic to have similar collaboration among specialties.

Once they had returned to America, the three surgeons did not waste any time. They took on a fourth partner, internist and war veteran John Phillips, M.D., and less than a year after the Armistice, formed a corporation and leased land at East 93rd Street and Euclid Avenue for a new outpatient building (a location chosen, in part, because there was plenty of space for parking nearby).

"Our dream of the Cleveland Clinic was already taking shape," wrote Dr. Crile. That dream was unquestionably informed by the founders' military experience. The military had shown them the effectiveness of multispecialty care – where physicians with expertise in different areas acted as a unit to care for complex disorders. It also showed them the value of research carried out alongside patient care – how such research was more rapidly responsive to patient needs and could be sooner applied to their treatment. These elements, along with physician education, became the cornerstones of The Cleveland Clinic's mission: "To care for the sick, investigate their problems, and educate those who serve them."

Founder
William E. Lower, M.D.

Founder John Philips, M.D.

Only two years after the war's end, the new institution was granted a state charter. The terms were simple but unusual for the time. At a time when for-profit medicine was the norm, it would be a not-for-profit practice. And while fee-for-service medicine was the standard of the day – with each physician an "owner" – the Clinic would be a group practice instead, with staff physicians working for a salary like any employee. All earnings not used for salaries and expenses would be ploughed back into the institution to pay for education and research. This is the model The Cleveland Clinic follows to this day.

At the time of its founding, the only roughly similar institution was the Mayo Clinic in Rochester, Minnesota, founded in 1889 by the Mayo brothers, William and Charles (who was Dr. Crile's hunting buddy). In fact, it was William Mayo who delivered the keynote address at the official dedication of The Cleveland Clinic, February 26, 1921. The following Monday, the Clinic opened its doors to the people of the community. Forty-two patients showed up that first day.

Today, The Cleveland Clinic sees more than two million patient visits a year. As greater Cleveland's largest employer, and a tremendous engine of prosperity for the region, it is leading the way into a future of science and technology unimaginable to the turn-of-the-century physicians who brought it into being. It is – in the words of current chairman and CEO Floyd D. Loop, M.D. – a "commonwealth of intellect, the republic of the mind, and the best example of physician-managed health care."

"...TO ACT AS A UNIT"

"...To Act as a Unit" is the official history of The Cleveland Clinic, whose fourth edition is currently being prepared by editor John D. Clough, M.D. Fascinating in all its editions, "To Act as a Unit…" *(available online at www.clevelandclinic.org/act) highlights the development of specialty medicine, research and education at The Cleveland Clinic, and the strong and dedicated personalities who helped make world class care a reality. In the excerpt below, the book explains how The Cleveland Clinic made the first step in expanding its physical plant.*

The public accepted the Clinic so enthusiastically that it soon became apparent to the founders that they needed an adjacent hospital, even though the staff continued to have hospital privileges at Lakeside, Charity, and Mt. Sinai hospitals. Considering the prevailing attitude toward group practice and the corporate practice of medicine, there was ample cause for concern about whether the hospitals would continue to make available a sufficient number of beds to the staff of the new clinic.

With the prospect of being frozen out of hospital beds a real possibility, the Clinic purchased two old houses on East 93rd Street just north of Carnegie Avenue and converted them into a 53-bed hospital, the Oxley Homes, named for the competent English nurse who was put in charge. In 1928, Lower wrote, "Dr. Crile suggested one day if we could get two houses near together on 93rd Street, not too far from the Clinic, we could fix them up and use them for a temporary hospital. The suggestion was made at noon. At 2 P.M. a patient of Lower's – a real estate agent – came in to see him professionally. After dispensing with the professional visit, Lower incidentally asked if she knew of any property on 93rd Street which might be bought or leased – preferably the latter as we had no money. She said she would find out. She returned in an hour reporting that two maiden ladies down the street had two houses they would be glad to lease as they wanted to go to California to live. Lower gave the agent $100 to go and close the deal. About 5 P.M. of the same day, Dr. Lower asked Dr. Crile about the property he thought he should have. He replied 'Two houses near together on E. 93rd Street.' Lower said, 'I have them!' Crile said, 'The hell you have!' Thus closed the second land deal on 93rd Street and the first step in the formation of a hospital."

JOHN SHERWIN:
Leading the Clinic Forward

After surviving a disastrous fire, the Great Depression and another world war, the Clinic was growing rapidly. The institution's stability depended on steady direction. So, when The Cleveland Clinic's talented president, Edward C. Daoust, unexpectedly died in a plane crash in 1947, the institution could have been stalled by administrative chaos. It was longtime Clinic supporter, trustee and Executive Committee member John Sherwin who stepped in to provide balanced leadership.

A Yale University graduate who served as a successful banker before venturing into iron ore supply, Sherwin (and other Executive Committee members) sacrificed evenings over the course of eight years, determining the best way to run the Clinic.

Under the Executive Committee's direction, administration and policy became the responsibility of the trustees. This group of successful business executives from various industries maintained public accountability for the Clinic. The entire physician operation was designated the responsibility of the physicians. In 1948, with acceptance of this plan, Sherwin was elected president.

Later in Sherwin's presidency, after much debate and effort, an additional group was created to avoid unethical third-party interference with the doctor-patient relationship, as mandated by the American Medical Association. Called the Board of Governors, it consisted of staff-elected physicians who took on certain leadership duties formerly handled by the Board of Trustees. This new group would gain increasing responsibility in the coming years.

Sherwin's son, John (Jack) Sherwin Jr., describes the basis for his father's enthusiastic support of the Clinic, "He was always interested in health care and liked the way the Clinic provided a balance of research, education and care for the sick, as well as the methodology and the management structure based on salaried professionals. He thought this was a good thing." Sharing a similar belief in the Clinic's core goals, Jack Sherwin today serves as a Clinic trustee.

The result of Sherwin and the other leaders' intense effort and time during this period, all sacrificed without compensation, was a plan for the basic system of Clinic governance that is still in effect today. They created a division of power, enabling more democratic and effective leadership across the Clinic.

Serving a total of 60 years as a trustee, including terms as president and also as chairman of the board, Sherwin perpetuated the Clinic's mission of patient care, research and education in several key ways. In 1946, he helped establish the Clinic's Research Division by recruiting Irvine H. Page, M.D., who became a leader in research as well as a favorite weekend tennis partner. Sherwin enhanced the Clinic's research efforts by establishing the very first endowed chair in the Clinic's history, presented in Dr. Page's honor. Sherwin also was instrumental in incorporating the Frank E. Bunts Education Institute to further the mission of education.

Sherwin's contributions and dedication were truly revolutionary, and his family joined him in fostering the Clinic's mission. Sherwin's late wife, Frances, was the niece of Frank E. Bunts, a Clinic founder. She felt strongly that the hospital should have a chapel, which the Sherwin family provided for in honor of all four Clinic founders.

Above: John Sherwin Sr., President, The Cleveland Clinic, 1948-1957

Dangerous rise: Colon Polyps in Children and Teens

Rhiannon Bailey with her mother, Rita Wojtkowski

Every parent has heard these four simple words at some point in time. Normally, the phrase would not elicit too much concern. A missed homework assignment. Money needed for a school activity. Permission to go to a party or sleepover.

But when Rita Wojtkowski's then 13-year-old daughter, Rhiannon Bailey, casually remarked, "Oh, by the way, Mom…," she proceeded to tell her mother that after going to the bathroom, she noticed blood on the toilet tissue.

Wojtkowski recalls checking the next day: "It wasn't just a little blood. Both pieces of toilet tissue were covered with blood and there was more in the toilet. I knew this wasn't just a hemorrhoid."

She immediately took Rhiannon to see her Buffalo, New York pediatrician. The pediatrician didn't find an obvious source of the bleeding, so she ordered a barium X-ray of Rhiannon's colon.

The X-ray results gave Wojtkowski a shock. According to the radiologist, the problem looked like one or more polyps in the colon. "I was amazed," says Wojtkowksi. "Polyps in a 13-year-old? I thought that was something 60-year-olds get, not children." The radiologist went on to say that he didn't think the polyps had turned to cancer, but they could if they were not removed.

Colon polyps are mushroom-like overgrowths of intestinal tissue that project into the colon. They have a rich supply of blood, so stool passing by can cause irritation and bleeding. About 50 percent of people over the age of 60 will have at least one polyp. The incidence in children, while rarer, is becoming more common.

"Polyps in children are usually different than polyps in adults," explains Robert Wyllie, M.D., chairman, Department of Pediatric Gastroenterology. "Polyps in adults are typically adenomas – growths that already contain abnormal tissue. But polyps in teens and young children are commonly juvenile polyps, which are an overgrowth of the normal tissue making up the bowel wall. There isn't really any change in the mucosa, the lining of the intestine, that indicates you have abnormal cells."

After hearing her child might have colon polyps, Rita Wojtkowski placed another call to her trusted pediatrician. Rhiannon was referred to a Buffalo-area gastroenterologist who recommended she see another

CONTINUED ON PAGE 26

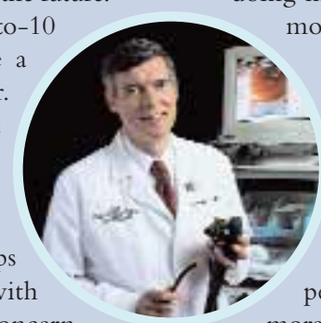
Multiple polyps: *a trend for concern*

Until recently, finding multiple polyps in a young child was an uncommon occurrence.

But today, "Finding multiple polyps in children is not unusual," says Robert Wyllie, M.D., Cleveland Clinic Pediatric Gastroenterology Department chairman.

The problem with the increasing numbers of polyps in young children and teens is not that they bleed and have to be removed, but what they portend for the future.

"In children with more than six-to-10 polyps, it appears that the polyps have a tendency to change over time," says Dr. Wyllie. "There seems to be an increased risk of the polyps developing abnormal cells and these cells have the potential to become malignant."



Cases with less than six-to-10 polyps are usually simple juvenile polyps and, with some exceptions, there is only a minor concern about the polyps being or becoming malignant. Cases where the patient has more than six-to-10 polyps confined to the colon are classified as juvenile polyposis coli. Some children can have many polyps – even hundreds – occurring throughout their gastrointestinal tract, including the stomach, small bowel and even pancreas. This disease is called generalized juvenile polyposis. Patients with juvenile polyposis coli or generalized juvenile polyposis have a higher risk of developing polyps that become dysplastic or cancerous in the future.

Unfortunately, data is scarce about multiple colon polyps in young children. But Dr. Wyllie is concerned about the trend. "We have been doing colonoscopies on children routinely since about 1980. We aren't doing more colonoscopies. I think we are seeing more polyps.

"If we are seeing increased numbers of polyps in young children, what are the implications for them as they become adults?" questions Dr. Wyllie. "Today, it is estimated that five-to-six percent of all adults will develop colorectal cancer. That is an astounding number. What will that percentage be 30, 40, 50 years from now if more cases of multiple polyps are occurring in young children now?"

Dr. Wyllie recommends that parents be pro-active if they notice their child experiencing rectal bleeding. "When rectal bleeding occurs in a child or teenager they should be checked by their primary care physician. If they have persistent painless rectal bleeding and the child's physician can't find a cause, then further evaluation is needed by a pediatric gastroenterologist."

gastroenterologist, one who specializes in treating children, at The Children's Hospital at The Cleveland Clinic.

At the Clinic, they saw pediatric gastroenterologist Marsha Kay, M.D. "Dr. Kay was very reassuring, although you can't help but worry," says Wojtkowski, a part-time occupational therapy assistant. "She told us that juvenile colon polyps are quite common. And chances are that's what Rhiannon had."

"About one-to-two percent of children develop polyps," explains Dr. Kay. "And about a third of children with polyps become significantly anemic as a result of the bleeding." Dr. Kay scheduled a colonoscopy and also an endoscopy for Rhiannon's stomach.

When a polyp is found during a colonoscopy or endoscopy, a tiny instrument can be passed through the scope and the polyp is painlessly removed. Occasionally, surgery is required to remove polyps in the small intestine that are out of reach of endoscopy.

The day after her arrival at the Clinic, Rhiannon headed to the pediatric outpatient surgery center accompanied by her mother and grandmother. With the help of a sedative, she was able to sleep through her colonoscopy and endoscopy.

During the colonoscopy Dr. Kay discovered a large, two-to-three centimeter polyp,

about the size of a penny, in Rhiannon's colon. The polyp was immediately removed and sent to the Clinic's pathology laboratory. During the endoscopy, Dr. Kay saw no polyps in Rhiannon's stomach.

When the pathology lab report came back, the results were unusual.

"It turned out that the polyp was a tubular adenoma, the type of growth that occurs in people in their 50s or 60s. The type that is abnormal and could progress to colon cancer if left alone," Dr. Kay says. "This was not what we were expecting."

She adds that when she saw the polyp through the scope, it didn't look like a typical juvenile polyp. A tubular adenoma takes a couple of years to develop, so it had probably been there for some time. Dr. Kay cautioned, "Although the majority of polyps in teens and younger kids are benign, some are not."

Rhiannon has long since returned home and now, three years later, she eagerly pursues the activities and tumultuous life of a high school senior. While a number of other ailments afflict her – kidney stones and gallstones among them – none has stopped her. Active on her school's Leadership Team, Rhiannon also plays on the tennis team and remains a good student. After school, she works as a cashier and has saved enough money to achieve every teen's dream – buying her own car. She continues to work hard, still banking the money, but this time putting it aside for college.

Because Rhiannon's case was not just a simple juvenile polyp, she requires regular screening. She has a colonoscopy every year, so that if more polyps develop, they are promptly removed. Says Rhiannon, "I know this is something I'll have to watch out for the rest of my life, but I can do that. I'm just glad we found out what was wrong. I'm glad I can do something about it."

Colon polyps: what to look for

- *Painless rectal bleeding*
- *Abdominal cramping*
- *Diarrhea*
- *Anemia*

Help for Those with Inherited Colorectal Cancer

Approximately 130,000 cases of colorectal cancer are diagnosed in American men and women each year. In about five percent of people with colorectal cancer, a critical mutation to some of the genes that control colon cell growth and death is passed from a parent to a child – it is inherited.

The David G. Jagelman Inherited Colorectal Cancer Registries at The Cleveland Clinic provide education and support to families affected by colon cancer syndromes. These syndromes include Hereditary Non-Polyposis Colorectal Cancer (HNPCC), Familial Adenomatous Polyposis (FAP), Juvenile Polyposis and Peutz-Jegher's Syndrome. Of the 31 registries in the United States dedicated to inherited colorectal cancer, the Jagelman Registry is the largest.

"Inherited colorectal cancer is suspected when colorectal cancers occur at an unusually young age or in multiple generations of a family," explains James M. Church, M.D., director of the David G. Jagelman Inherited Colon Cancer Registries and staff surgeon in the Department of Colorectal Surgery. "The Jagelman Registry helps save lives by promoting prevention and early detection of hereditary colon cancers."

Families with hereditary colorectal cancer syndromes who join the registry receive specialized services and continued monitoring of their condition. The registry provides patients with educational resources about the disease, tests, surgical options and lifelong surveillance protocols. The registry staff encourages patient participation in study protocols; discusses the appropriateness of genetic testing; provides support to ease fear of tests and surgeries; and provides counseling on insurance issues, loss of employment or death of a loved one.

For information about the Jagelman Inherited Colorectal Cancer Registries, call 800/223-2273 ext. 46470 or go online to www.clevelandclinic.org/registries.

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THE CLEVELAND CLINIC
Every Life Deserves World Class Care

Eric Topol, M.D.,

Chairman of Cardiovascular Medicine at The Cleveland Clinic,

answers questions about

C-Reactive Protein

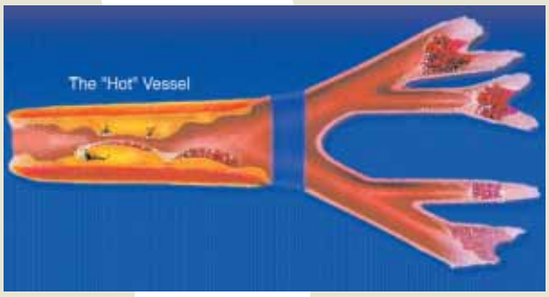
The first heart disease indicator to be recommended by the American Heart Association in twenty years entails only a surprisingly simple, inexpensive blood test. This high sensitivity C-reactive protein (hs-CRP) test takes the traditional cardiac check-up a step further, pinpointing those people who are at a much higher risk than others for heart disease, America's leading cause of death. From hs-CRP results, doctors gain crucial insight into inflammation of the blood vessels around the heart, a factor not considered until now for patients at risk.

Q: What is C-reactive protein? How does it relate to heart disease?
A: The body produces C-reactive protein (CRP) during the general process of inflammation. When a disease called atherosclerosis damages arteries around the heart, they become inflamed, which triggers CRP production. For years we thought that diseased arteries around the heart slowly narrow, then clog or collapse and cause a heart attack. While this does occur, it is much more rare than had been anticipated. And that theory didn't explain the patients who were fine one day, but had a heart attack the next week. We have since found that in some people inflamed, softened artery walls develop weak areas that can rupture suddenly, causing a heart attack. Also, plaque can build up quickly in inflamed arteries, increasing the risk of blood clots.

Q: How do doctors test for CRP?
A: Physicians measure CRP with a simple, convenient blood test that does not require fasting. General CRP blood testing has been around for years, but only one kind, the high-sensitivity C-reactive protein (hs-CRP) test, helps determine heart disease risk. Patients should ask their doctors about hs-CRP specifically. With hs-CRP test results, a level above three raises major concern because it means a person's risk for heart attack is at least doubled. One to three merits some concern, but is not serious. Below one is where we want all patients. Readings of 50 and above are possible, but we generally attribute a level higher than 10 to an infection somewhere in the body, not arterial inflammation.

Q: How does the hs-CRP test compare to other indicators, such as cholesterol and stress tests?
A: The exercise stress test tells us when narrowed arteries cause a shortage of blood going to the heart. It is still a vital risk indicator. LDL cholesterol is important to watch because it can narrow and clog arteries. There are two types of LDL cholesterol, the bad kind and the really bad kind, which we call oxidized LDL cholesterol. The available cholesterol test does not differentiate between these two types; it only tells a person's total LDL level. However, this bad, oxidized type, which hurts the arteries and speeds up plaque formation, has a direct correlation to CRP levels. Arteries can produce CRP directly at sites where there is cholesterol buildup. So, hs-CRP testing offers a window into how much of the especially bad cholesterol a person has in his or her blood.

Q: How do people know if they need an hs-CRP test?
A: People who have suffered a heart attack or stroke and those with at least one risk factor, such as family history, high blood pressure, high cholesterol, smoking or diabetes, should be tested. While the American Heart Association and Centers for Disease Control just recently recommended hs-CRP testing as an option for those already at risk, The Cleveland Clinic has used the hs-CRP test routinely for at-risk patients for over three years. Hs-CRP is a great test for people with one or two risk factors who wonder if they are really in jeopardy of a heart attack or a stroke. It's probably not useful for people without any risk factors.



THE INFLAMED VESSEL

In the blood vessel to the left, cholesterol buildup is present (yellow); but that's not the only heart disease risk factor pictured. Doctors are also turning their attention to the diseased area of the vessel marked by inflammation (dark red and white).

Q: How often should CRP levels be tested?
A: There's no cookbook solution. If someone comes in high and then works on lowering their CRP levels, I might re-check it in a month or two. But, if the initial level is low, I may not check it again for two-to-five years. It really depends on the patient and adoption of lifestyle changes or other treatments.

Q: Is arterial inflammation the only cause of high CRP?
A: Inflammation in the body due, for instance, to infection or a serious arthritic flare, can raise CRP. Before getting an hs-CRP test, patients should tell their doctors if they are experiencing health problems that can cause general inflammation, for example, joint problems or a respiratory infection. If tested while ill or injured, it's important to get re-tested once healthy. But, pinpointing an alternative reason for a high hs-CRP reading doesn't eliminate the increased risk for heart disease or the value of the hs-CRP test. Inflammation anywhere in the body makes the arteries vulnerable because the cells and substances in the body that drive inflammation are thrown into high gear. Inflammation itself fuels further inflammation.

Q: What treatments are available to reduce CRP levels?
A: A proper balance of weight and diet is the number one treatment. The second is exercise, which together with diet is quite potent. Many people will drop their CRP level, indicating reduced inflammation, by losing a significant amount of weight. Fat cells don't just lie around. They actually produce CRP. Getting rid of fat directly lowers total inflammation. Also, if necessary, medications, including aspirin, statins (also used to reduce cholesterol) and clopidogrel (lowers blood clotting ability) can be used.

Q: Not all doctors use the newly recommended hs-CRP test. How should patients address this?
A: People should at least be aware of this simple test for inflammation. We're in an era of patient empowerment, thanks to tools such as the Internet. Hopefully, these patients will mention hs-CRP testing to their doctors if the physicians don't bring it up first.

MENTOR TO YOUNG SKATERS LEAVES $5 MILLION LEGACY

Helen Meyers McLoraine's

gift supports cancer patient education and outreach.

Less than a year before a teenage Scott Hamilton won his first national figure skating title, he almost called it quits. His family's financial resources were exhausted, and the amateur arena of the late seventies left the future world champion with few options. But Denver coach Carlo Fassi recognized his talent, and before Mr. Hamilton could hang up his blades, Mr. Fassi put the Hamilton family in touch with Helen and Frank McLoraine, investors in a Colorado ice rink. Inspired by Helen Meyers McLoraine's love of skating, the couple offered to sponsor the young athlete on his path to Olympic gold.

Before she passed away in January of this year, Mrs. McLoraine aided the careers of more than 50 young skaters, including up-and-coming Cleveland skater, Tim Goebel. But for all the support this perpetually upbeat woman offered young athletes, sponsoring skaters made up only a small sliver of her overall philanthropic contributions.

Her giving priorities included education, medical research and youth social welfare, and her generosity extended to major philanthropies such as the University of Chicago (her alma mater), the Salk Institute for Biological Studies and The Cleveland Clinic. In her estate plan, Mrs. McLoraine generously bequeathed $5 million to the Cleveland Clinic Taussig Cancer Center's Scott Hamilton CARES Initiative, the Cancer Alliance for Research, Education and Survivorship at the Clinic, to extend patient education and outreach. Recognizing her tremendous generosity, the Cancer Center's Patient Resource and Education Center will be named in her honor.

Helen McLoraine and Scott Hamilton

Mrs. McLoraine's interest in the Cancer Center stemmed largely from her friendship with Mr. Hamilton, who was treated for cancer at the Clinic. In her life, she was instrumental in the success of the Scott Hamilton CARES Initiative, which Mr. Hamilton launched in partnership with The Cleveland Clinic. In addition to her bequest, Mrs. McLoraine gave more than $1 million to the Cancer Center during her lifetime.

Mrs. McLoraine, who listened first and talked second, felt directly responsible for how her philanthropic contributions were put to work. She approached giving in the same manner as investment decisions, by meeting an organization's leaders, researching the cause and asking direct, pointed questions. Her clear-eyed perspective not only led to a successful career as an oil and gas investor, but leaders in the skating sport phoned her for advice as the international skating scene evolved.

The McLoraines' gifts to various organizations and skaters never came with strings or expectations for a relationship, Mr. Hamilton says. But, when needed, the couple's emotional support was readily available to young people. About a year after he had moved far from his family in Bowling Green, Ohio to train in Denver, Mr. Hamilton's mother passed away. During this rough period, Mr. McLoraine's charm and Mrs. McLoraine's maternal nature comforted Mr. Hamilton. From there, a close relationship developed. In particular, Mr. Hamilton and Mrs. McLoraine maneuvered many of life's challenges together, from Mr. McLoraine's passing to Mr. Hamilton's later battle with cancer.

MILLERS INSTRUMENTAL IN EMERGENCY CARE

Active Clinic supporters'

gift names the emergency services they helped found.

Sam and Maria Miller

In 1989, when Floyd D. Loop, M.D., first took the helm as CEO and chairman of The Cleveland Clinic, many community members offered congratulations. Not Sam Miller. He walked up to the new CEO and said, "You've got a problem."

After listening to a brief rundown of how the Clinic could improve its operating strategy, Dr. Loop knew that Mr. Miller would be vital to the hospital's future. Dr. Loop was so intrigued by Mr. Miller's dead-on insight, that he agreed to a 6:00 a.m. meeting that Saturday. That weekend appointment began a tradition of early morning meetings in which Mr. Miller, a Cleveland Clinic trustee since 1991, holder of seven honorary degrees and co-chairman of Forest City Enterprises, Inc., imparted his wisdom and business sense to the newly named Clinic leader.

Dr. Loop recently hailed Mr. Miller as one of the Clinic's greatest trustees. While the Millers have offered great philanthropic support, Mr. Miller also has given valuable time, energy and wisdom, Dr. Loop says. His wife, Maria, also plays a leadership role, serving as chairperson of "An Evening with Scott Hamilton and Friends on Ice" annual gala, benefiting the Cleveland Clinic Taussig Cancer Center and the Scott Hamilton CARES Initiative.

Together, the Millers passionately pursued their vision of a Cleveland Clinic serving the immediate neighborhoods with emergency care. Dr. Loop credits Mr. Miller as a major influence in the Clinic's move to offer emergency services in 1994.

"There's no question that the Clinic provides a true community service with emergency care. It wasn't always that way, but it is now because of Sam and Maria," says Charles Emerman, M.D., chairman, Emergency Medicine.

When the couple made a recent $8 million commitment to the Clinic, the Emergency Medicine Building on Carnegie Avenue was re-named in their honor. The Millers offered their major gift in gratitude to the doctors, nurses and all other employees at the Clinic. Further extending their appreciation, they recently committed an endowment to provide annual cash awards to Clinic employees who demonstrate excellence in their fields. Mr. Miller was recently named a Distinguished Fellow of The Cleveland Clinic, honoring his many exemplary contributions.

GLICKMANS TAKE ACTION

Carl and Babs Glickman

Through personal experience,

Carl and Babs Glickman learned about specialized urological treatment needs – and took pro-active steps to meet them.

When Carl D. Glickman attended dialysis sessions while awaiting a kidney transplant, he could have spent the many hours tethered to a machine feeling sorry for himself. Instead, he chose to brighten the long stretches of time for the children intermingled with adults in The Cleveland Clinic's dialysis unit.

Frequently, Mr. Glickman brought toys and books to entertain the kids and help make the experience less intimidating. The children appreciated the small gifts, but the larger picture – a daunting room packed with older adults and medical equipment – stuck with Mr. Glickman.

After returning to an active lifestyle, Mr. Glickman did not forget the people he met during his health ordeal. To show thanks for the expert diagnosis, treatment and supportive care he received, Mr. Glickman and his wife, Babs, donated $8 million to the Clinic's Urological Institute. In honor of their generosity, the facility was renamed the Cleveland Clinic Glickman Urological Institute. *U.S. News & World Report* has ranked the institute second in the United States for the past four years and the best in Ohio every year since 1990, a tradition of excellence the Glickmans hope to extend with their support.

But, this enormous gesture was not enough for the Glickmans. Recalling the frightened children Mr. Glickman had encountered during his days in dialysis, the couple proposed and helped fund a separate, pediatric dialysis facility named in honor of Mr. Glickman's kidney donor. The Judith M. Power Dialysis Unit at The Cleveland Clinic Children's Hospital for Rehabilitation opened in March 2003.

In addition to a comprehensive, multidisciplinary pediatric dialysis team, the young patients at the Power Dialysis Unit enjoy a child-friendly environment complete with recreational therapists, schoolteachers, video games, movies, educational murals and a locomotive train.

It's this action-minded approach to philanthropy that has earned Mr. Glickman the title Distinguished Fellow of The Cleveland Clinic, the highest honor bestowed upon those who have gone above and beyond in service and contributions to the Clinic.

Mr. Glickman has served as an advisor and leader in many capacities. He was instrumental on the Leadership Committee for the successful Digestive Disease Center campaign. He currently co-chairs the Cleveland Clinic Glickman Urological Institute's Leadership Board.

GRATEFUL LONG-DISTANCE PATIENTS MAKE MAJOR PLEDGE

South African couple

supports the quality care that draws them far from home.

As soon as the leading man in South Africa's steel trade learned he needed a heart bypass, his local cardiologist referred him to the Cleveland Clinic Heart Center on the other side of the world.

Many people would not consider a hospital more than 7,000 miles away, but surgery in Cleveland was a mere pit stop for Eric Samson, who leads The Macsteel Group, an international steel distribution service headquartered in South Africa. He scheduled his procedure and recovery time to coincide with New York and London business meetings.

Inspired by the quality of care at The Cleveland Clinic, Mr. Samson and his wife, Sheila, recently pledged a large, multimillion-dollar gift to the Cleveland Clinic Heart Center, honoring Mr. Samson's surgeon, Delos Cosgrove, M.D., chairman, Thoracic and Cardiovascular Surgery.

Mrs. Samson, who for 41 years has always traveled alongside her husband, has undergone surgery for breast cancer at the Clinic, and Mr. Samson was additionally treated for a colon polyp. The native South Africans come to the Clinic for major medical procedures, but also drop in for regular check-ups. The Samsons, who could go anywhere in the world for health care, have their reasons for returning to the Clinic.

"We found that The Cleveland Clinic is considerate with patients, something that's really exceptional," says Mr. Samson. During his first meeting with Dr. Cosgrove, he was impressed not only by the surgeon's care and dedication, but with his attitude, which immediately set Mr. Samson at ease. "Dr. Cosgrove just radiates confidence. He can't help it. As a surgeon, he's confident in the skill of his hands," Mr. Samson says.

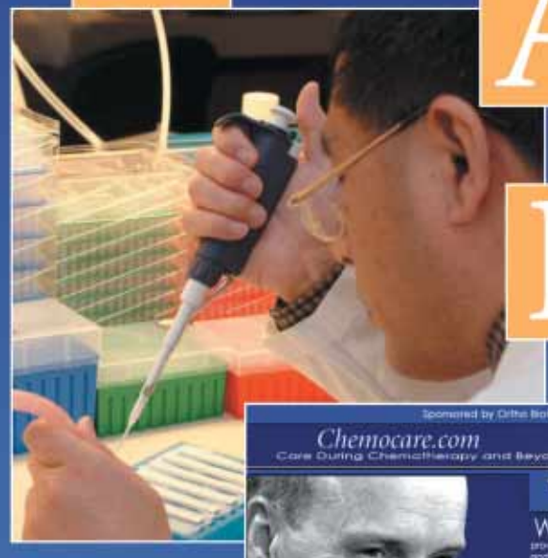
Mr. Samson has reason to be confident in his own choice of profession as well. Worldwide, The Macsteel Group, headquartered in Johannesburg, South Africa, moves about 20 million tons of steel and iron ore in a year. Mr. Samson's role with the company was forged in 1958 when he joined his father's South African wire and steel agency. A few years later he moved the business into steel merchandising. In the 1970s, Macsteel burst onto the international scene opening offices in the United States and United Kingdom. Today, it is one of the largest private companies in South Africa and oversees more than 100 locations across the globe.

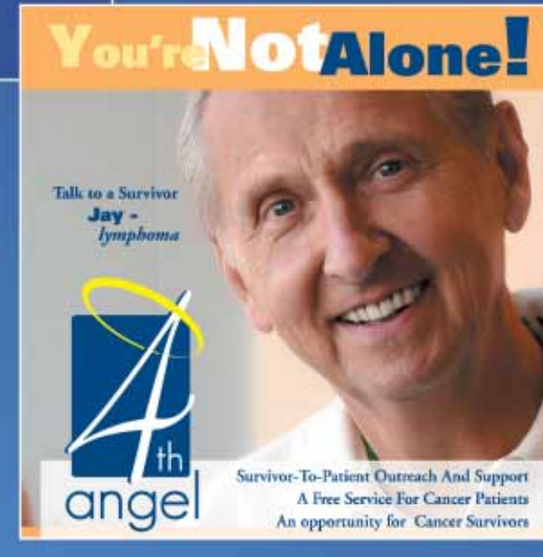
Eric and Sheila Samson

Scott Hamilton CARES Initiative

Inspired at The Cleveland Clinic. Touching lives everywhere.

Cancer **A**lliance for **R**esearch **E**ducation and **S**urvivorship





The Scott Hamilton CARES Initiative - the Cancer Alliance for Research, Education and Survivorship - continues to grow. Now in its fourth year, CARES is funding research and enhancing patient care with innovative patient programs. CARES' cutting-edge approach drives the 4th Angel Mentoring Program - a one-on-one peer support mechanism for cancer survivors, and Chemocare.com, a website dedicated to helping patients and family members better understand their chemotherapy experience. To learn more about the Scott Hamilton CARES Initiative call 216-445-2573 or visit www.scottcares.org

For information about the annual benefit ice show and dinner, please call the gala Hotline at 1-800-445-0804.

The Cleveland Clinic
Taussig Cancer Center

Opening Doors

Helping cancer patients understand and care for their disease is the life work of Ruth Fritskey, M.S.N., R.N.

"No admittance." For a little girl staring at that sign in the hospital where her grandfather lay dying, it was the beginning of a journey to unravel the mystery of what goes on behind those forbidden doors.

"I grew up in an era where kids had to be 13 in order to visit patients in a hospital," says Ruth Fritskey, M.S.N., R.N., program director of the Patient and Public Cancer Education Program at the Cleveland Clinic Taussig Cancer Center. "My grandpa was dying in a hospital bed and I wasn't allowed to visit him. I didn't understand what was happening, and that began my fascination with hospitals. I guess going into nursing was an answer to my curiosity."

Ruth Fritskey, M.S.N., R.N.

Fritskey likes to get to the bottom of mysteries – and wants her patients to understand those mysteries as well. In her role in the Cancer Center, she helps cancer patients piece together information to puzzle out what is happening to their bodies.

Using her knowledge and desire to educate as many patients as possible, she helped establish the Clinic's Cancer Answer Line in 1992. An information service available to the public, the Cancer Answer Line is a toll-free hotline staffed by registered nurses Monday through Friday, 8:30 a.m. to 4:30 p.m. EST.

"Patients call to get information on cancer, and we help them navigate the process of trying to deal with this scary diagnosis," Fritskey says. "Sometimes patients don't want to bother physicians by asking 'what does this mean?' Or maybe at the time, they're just too shocked to ask questions.

"We are here once the realization comes to them, and they start seeking knowledge."

With a self-described gift of gab and the ability to bring daunting medical jargon down to "kooky analogies" so they are comprehensible, Fritskey's goal is two-fold: guide patients into making educated decisions about their care, and increase their understanding of the disease, its progression and treatment.

"A patient hears from the doctors that he has an unknown primary tumor, but the doctors don't know where it started. What the patient doesn't get is what does this mean? How can you not know?" Fritskey compares it to going to a house that has burned down to cinders. "Sometimes there is enough left of the house to tell what kind of house it was. Sometimes there isn't."

When Fritskey saw the Cancer Answer Line fulfilling a huge need in the patient population, she turned to the Internet as another tool. Scott Hamilton, an Olympic figure skating champion and cancer survivor, came to her wanting to raise awareness of common chemotherapy side effects and to empower and inspire fellow cancer patients. A partnership was created, and chemocare.com was born.

The Web site is a very comprehensive resource, detailing drugs, side effects, and everything else that a person might need to know when going through the chemotherapy experience.

"I feel proud to be bringing this service to the public, and I am representing The Cleveland Clinic. Any positive attention I receive helps patients, and that's what I'm here for."

Patients really *are* her specialty. "I have spent my entire career focused on cancer nursing, and the last 10 years on cancer education, specifically. Although I am no longer at the bedside doing physical care, I still consider myself in patient care – just on a much larger scale. I get to touch so many more patients' lives than if I were still in clinical nursing. It is a good fit for me."

Cancer Resources

www.chemocare.com

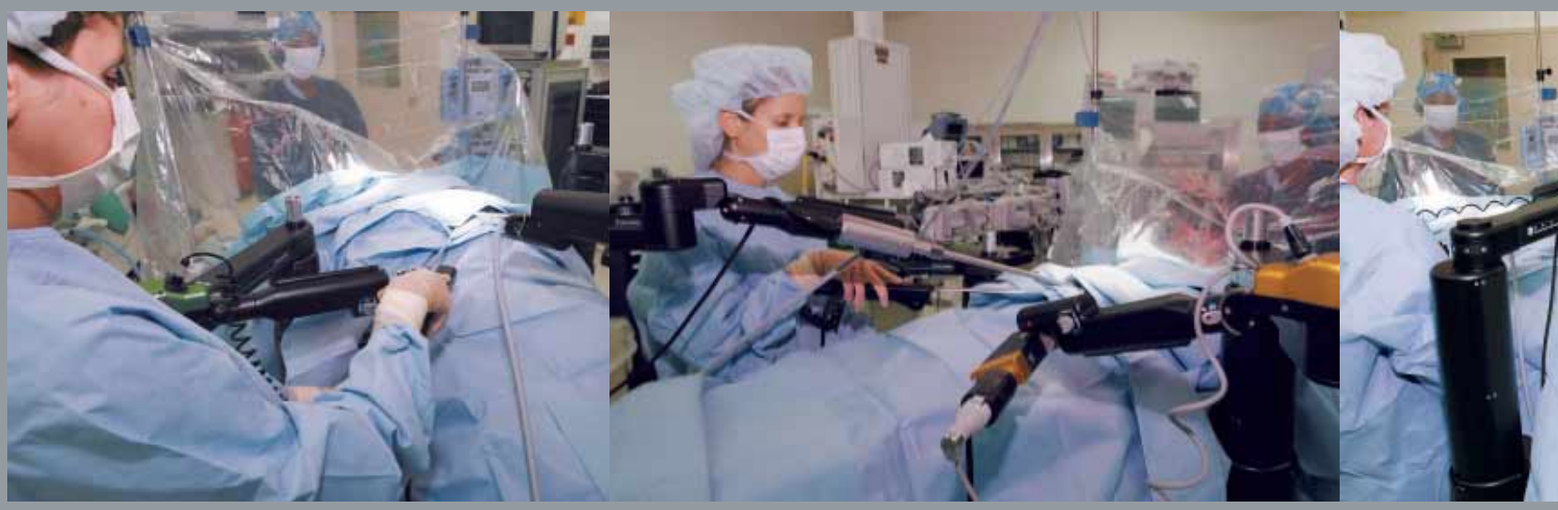
Chemocare.com, a collaboration between Olympic figure skating champion Scott Hamilton and The Cleveland Clinic, provides the latest information about chemotherapy and serves as an inspiration to cancer patients and their families, caregivers and friends.

The Cancer Answer Line

Sometimes cancer-related questions or requests for clarification can be answered by someone other than a physician. A nurse specialist is available Monday through Friday, 8:30 a.m. to 4:30 p.m. EST, to assist you. Call 216/444-7923 or toll-free 800/862-7798.

Move Over R2D2:

Robot-Assisted Surgery Offers a Different Option



Meredith Waugh, R.N., head nurse of Cardiothoracic Surgery at Cleveland Clinic Florida Weston, and Dr. Douglas Boyd with the robotic surgery system.

If you came across the term "robot-assisted" in a book, you might think of those two hapless droids in the movie "Star Wars" who helped Luke Skywalker, Han Solo and Princess Lea fight the evil empire. Or it might conjure up the image of an automobile factory assembly line, with its row upon row of mechanical arms piecing together car parts.

But add the word "surgery" to the term and you have a different definition to consider: a new innovation in heart bypass surgery.

Using robotics, heart surgeons maneuver four thin robotic arms through small incisions in the chest that are no larger than the size of a pencil. Tiny instruments and a camera the size of a dime are attached to the robotic arms, which are manipulated by the surgeon from a computer console ten feet away from the patient. The entire operation is performed via an image projected on a computer console.

"Contrast this technique with conventional open heart surgery, where surgeons must cut open the chest and perform the operation by manually manipulating larger instruments and it's a whole new ballgame," says Douglas Boyd, M.D., chief of Cardiothoracic Surgery at Cleveland Clinic Florida Weston.

In fact, it was the option of having this new type of surgery that sent Philip Carr, a former FBI agent, to see Dr. Boyd.

One day last May, when his routine of exercise and speed walking was interrupted by burning in his chest and tingling in his arms, Carr headed straight to his physician at the Clinic. He consulted with several doctors before it was determined that he needed open-heart bypass surgery. At first, he balked, remembering the stories his friends had shared about their open heart surgeries. "For one thing, they experienced intense pain every time they moved or coughed," he says. "And the recovery was a long one."

Carr, mentally tough and meticulous – holdover traits from his crime-fighting career and investigations – decided to look for other options.

What he found was a relatively new procedure that in some cases can be performed instead of traditional open heart surgery. The procedure, called robotic-assisted heart surgery, is a rapidly growing phenomenon in minimally invasive heart surgery.

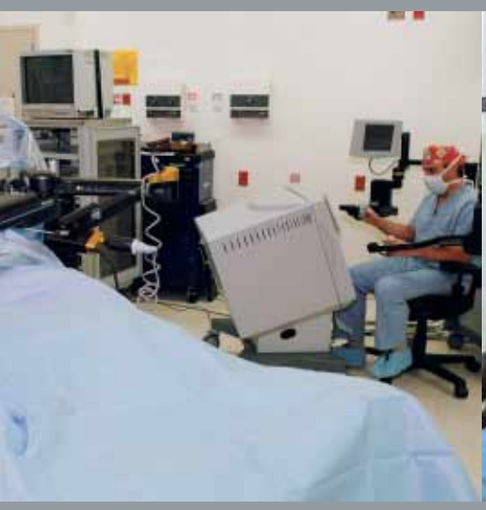
Traditional open-heart bypass surgery involves placing the patient on a heart-lung bypass machine to circulate oxygenated blood during surgery. The surgery is performed through a six-to-eight inch incision on a stopped heart. With minimally invasive bypass surgery, the surgery is done through an incision about three-to-four inches long. Depending on the technique, the surgeon may or may not stop the heart and use the heart-lung bypass machine. Because no bones are broken with minimally invasive surgery, there's less pain and suffering, minimal scarring and a lower rate of complications. There's also a faster recuperation period: after conventional heart surgery, it typically takes patients about three months to return to 80 percent normal. With minimally invasive surgery, they're feeling better within days.

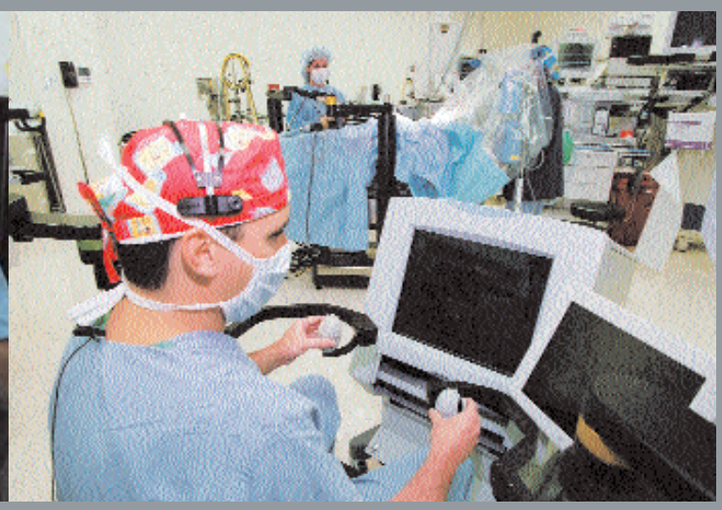
Using robots in minimally invasive surgical procedures allows surgeons to have better control over the surgical instruments and a better view of what they are doing.

"Robotic surgery makes it easier for surgeons to maneuver instruments," explains Dr. Boyd, the heart surgeon to whom

"...it's a whole new ballgame."

Douglas Boyd, M.D., chief of Cardiothoracic Surgery at Cleveland Clinic Florida Weston





Carr was ultimately referred. "Using conventional, larger instruments through such tiny holes would be like trying to sign your name accurately while holding a foot-long pencil by the eraser," he says. "The system also filters out human tremors and allows for more accurate surgery."

Dr. Boyd, one of the world's leading experts in robotic-assisted surgery, has performed more than 300 of the procedures – more than anyone in the country. Formerly the director of the National Center for Advanced Surgery and Robotics at the London Health Sciences Center in Ontario, Canada, Dr. Boyd completed the world's first closed-chest, beating-heart coronary artery bypass surgery in 1999.

Carr had his robotic-assisted bypass on a Tuesday, had two stents implanted on a Wednesday, and on Friday morning was released from the hospital. "The day after I got out I was walking 20 minutes twice a day," he says.

Dr. Boyd says Carr's recovery time is typical. "It's less invasive so it's less traumatic."

Dr. Boyd, who trained in labs for four years to get familiar with the techniques, says that while some robot manufacturers offer crash courses, there still are no standard training programs. It's something he and a circle of peers are working on developing. "You can't just buy a robot and do the surgery," he says.

> "The day after I got out I was walking 20 minutes twice a day."
>
> Philip Carr, robotic surgery patient

Because Carr was not obese and the targeted artery was on the surface of his heart, he was a good candidate for the procedure. Still, he didn't immediately agree to it. "I gave it a lot of thought," he says. "When he [Dr. Boyd] told me that he was a pioneer of the procedure, both my daughter and my son-in-law, who is a research scientist, helped confirm this through Internet research. They also went along with me for a consultation."

Dr. Boyd reassured Carr that if he started the procedure and was unable to complete it with robotics, then he would opt for the usual open-heart bypass surgery. Trying the robotic surgery first would not prevent a successful traditional surgery if that became necessary.

Dr. Boyd advises patients considering robotic-assisted surgery to ask their prospective surgeons how long they've been performing the procedure, as well as how many cases they've worked on. "Like anything else, the more experienced you are, the better you are," he says.

According to Dr. Boyd, the future of robotic-assisted surgery looks promising. "Because of today's technology and their active participation in video games, medical students have better video hand and eye coordination than we ever had. There will be a whole future of robotic surgeons better than my peers and me because they're being brought up with this kind of visual-motor processing. The new age of telesurgery is upon us."

New Medical College Addresses Need

Will train the next generation of leaders of clinical and translational research

Eric Topol, M.D.

Eric Topol, M.D., sees a crisis ahead in the field of medical research. Dr. Topol, chairman of the Department of Cardiology and The Cleveland Clinic's provost and chief academic officer, says that discoveries for the prevention and treatment of disease could stall in the coming years as fewer and fewer students pursue careers in medical research. And this is why The Cleveland Clinic and Case Western Reserve University have become partners in creating a new medical school program that will train physician investigators.

The Cleveland Clinic Lerner College of Medicine of Case Western Reserve University is set to enroll its first group of 32 students for classes beginning in July 2004. It will be the only medical school program in the United States that is solely dedicated to turning out physician investigators.

"Less than two percent of the nearly 700,000 physicians in the United States are prepared to perform clinical research. This is a group or species of physicians who are currently at risk of extinction," says Dr. Topol. "We need to train the next generation of leaders of clinical and translational research now."

The close collaboration between the Clinic and Case was critical in creating this unique college. "The Cleveland Clinic is an excellent academic medical center and it just so happens that we have a great university only two blocks away," says Dr. Topol. The pact has the potential for spurring collaborative research and drawing young research talent from all over the country.

"We will train a select group of students who have curiosity and passion and who want to go beyond patient care," Dr. Topol continues. "These are students who feel that there is nothing more gratifying than research aimed at curing or preventing disease."

Andrew Fishleder, M.D.

Developing this innovative program has been a major undertaking. **Andrew Fishleder, M.D.,** executive dean of the college, says students will gain clinical experience in the very first year. The basic science curriculum will be organ-system based and blended with the clinical curriculum. The research curriculum will be integrated throughout the program beginning in year one. Students will gain hands-on experience in both translational and clinical research in the summers before the first and second years of medical school. Cutting edge research topics also will be addressed throughout the clinical curriculum.

To provide students with time for a substantive research experience, the course of study for the M.D. degree will extend over five years. "Each student's curriculum for the last three years will be unique, based on their research project and individualized learning objectives," Dr. Fishleder continues. "An M.D. adviser and a research adviser will help students achieve their professional goals."

The college program will be delivered primarily at The Cleveland Clinic in the education facilities of the Lerner Research Institute. Students also will have opportunities for clinical and research rotations at the Case School of Medicine and its other hospital affiliates in Cleveland. Teaching methods will focus on active, hands-on learning principles, with the core basic science curriculum centered on problem-based learning.

Lindsey Henson, M.D., Ph.D.

"This is a unique approach to educating medical students that integrates research training throughout the program," says **Lindsey Henson, M.D., Ph.D.,** vice dean for Education and Academic Affairs. "The curriculum and evaluation methods are designed to foster skills in problem-solving, teamwork, life-long learning, self-reflection and other attributes of successful physician researchers from the very first day of medical school. No other M.D. program is designed this way. We also expect students to develop close relationships with faculty and with one another, given the small class size and the extensive faculty resources at The Cleveland Clinic and Case."

TRANS FATS

Eat, Drink and Avoid

Health conscious consumers will soon get the number on one of the most insidious elements in today's processed foods. They'll get the number, that is, of grams of trans fatty acids, or trans fats, in every serving of packaged foods.

In July, the Food and Drug Administration (FDA) announced that manufacturers of food and dietary supplements will be required to list the amount of trans fats contained in each food product. This is the first major change to the nutrition facts label since its adoption in 1993.

Trans fats behave like saturated fatty acids in our bodies. They raise the bad (LDL) cholesterol and lower the good (HDL) cholesterol. These mostly man-made, artery-clogging fats are found in some of America's favorite foods: donuts, chips, crackers, cookies, margarine, fried foods, candy bars and many other frozen and convenience foods.

The new legislation dictates that manufacturers must comply by January 2006, but because the issue has many consumers concerned, a large number of manufacturers will add trans fat information to their product labels in the next few months.

"We have been hearing about some of the dangers of trans fats in our diet but consumers haven't had a way to really clearly identify what contains trans fats and what doesn't," says Cindy Moore, director of nutrition therapy for The Cleveland Clinic and a spokesperson for the American Dietetic Association. "Now that we will have a listing on the nutrition facts panel, everything will be in one place. Consumers can get a better picture of what foods are healthier choices and what foods they may want to limit."

Hydrogenation the main culprit

Although small amounts of trans fats occur naturally in animal products such as dairy and meat, the main culprit is a process called hydrogenation, used by food manufacturers to make oil more solid and increase a product's shelf life. The more processed foods and convenience foods you consume, the more trans fats you will probably have in your diet.

"We have to assume, until the manufacturers tell us otherwise, if a product has partially hydrogenated oil or hydrogenated oil, then the product is likely to contain trans fats," says Moore.

No safe level identified

"In their 2002 report, the National Academy of Sciences indicated that the best goal would be to have no trans fats at all in our diet, but for consumers in our country, that is not practical, and the report could not identify a safe level," Moore says. Currently the FDA estimates that Americans consume about 5.8 grams of trans fats each day.

And there's another twist to take into account.

"In order for the FDA to be consistent with other food label regulations, they have indicated that if a product contains less than 0.5 grams of trans fatty acids per serving, the manufacturer can indicate on the food label that it contains zero trans fats," Moore says. The thing to watch then is the serving amount, something easy to double and triple without even realizing it.

No one is immune to the effects of trans fatty acids on the body. There is no safe amount of trans fats allowed in the diet according to weight and height. But for children and more sedentary adults, the amount of trans fats in the diet should be proportionally less than for someone who is an active adult, Moore says.

Common Gene Variation Could Double Prostate Cancer Risk

Groundbreaking research led by two Cleveland Clinic scientists is closing in on prostate cancer, the second leading cause of cancer death among men. Robert H. Silverman, Ph.D., discovered a gene that is linked to hereditary prostate cancer, and research by Graham Casey, Ph.D., revealed that a common variation in this gene may double the risk of prostate cancer in some men. Their findings may lead to a genetic test that could prompt earlier treatment and save lives.

Dr. Silverman was the first scientist to isolate and clone the gene RNaseL (pronounced r-n-ACE-el) in a Cleveland Clinic laboratory 10 years ago. In 2001, he began to work closely with the International Consortium of Prostate Cancer Genetics group which, in the February 2002 edition of *Nature Genetics,* published a key finding, capturing national and world headlines.

"We believe that RNaseL causes or contributes to the death of prostate cancer cells," explains Dr. Silverman. "But when RNaseL mutates, it ceases to function and prostate cancer occurs."

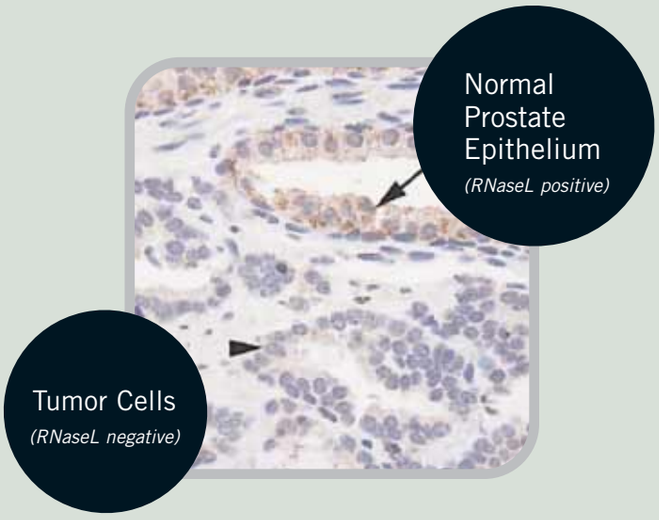
Dr. Silverman's news allowed Dr. Casey, a research geneticist at the Lerner Research Institute who was conducting a study on hereditary prostate cancer, to focus on that gene and search for variations in RNaseL that might predispose the person to prostate cancer. Over a five-year period, Dr. Casey and his collaborator, John Witte, Ph.D., at Case Western Reserve University, recruited 877 men for a research study on risk factors for prostate cancer.

"We were looking for genes like RNaseL but we weren't focused on that region of the genome. When Bob [Dr. Silverman] confided the results about RNaseL, we looked – when we were allowed to – in that region for genetic variations," Dr. Casey says. "It worked out just as we were hoping it would."

Adds Dr. Silverman, "Neither one of us could have done the entire study ourselves. One of the strengths of the Lerner Research Institute is that you have a critical mass of people working in the right areas that collaborate, and it fosters good communication."

Dr. Casey recalls his excitement when the analysis of his study was finally completed last year.

"I was walking around, shaking with excitement. It was a lot of work that was finally paying off. It was thrilling," he says. His findings were published in the December 2002 edition of *Nature Genetics.*



The image above shows a section of the prostate with normal and cancer cells. RNaseL, stained with an antibody, shows brown here. Image used with permission of Nature Publishing Group.

Dr. Casey's research revealed that up to 13 percent of prostate cancer cases might be triggered by a common variation of the RNaseL gene, called R462Q. "The exciting thing about the R462Q variant in RNaseL is that it is the most common risk variant in cancer that has ever been identified," Dr. Casey explains. In comparison, the mutation of the widely known BRCA1 gene accounts for less than five percent of breast and ovarian cancers.

Through the biochemical work performed in his laboratory by Ying Xiang, M.D., Ph.D., Dr. Silverman found that the R462Q variant cripples the normal function of RNaseL, which kills prostate cancer cells, but does not stop it from working completely. This means that RNaseL's effectiveness in preventing uncontrolled cell growth is weakened, and increases the chances of cancer developing.

Dr. Casey's research also determined that nearly 60 percent of the 877 men in the study possessed at least one copy of the R462Q variant. What's more, men who inherited a copy of the variant from one parent had a 50 percent increased risk of prostate cancer, compared to men who carried only the normal RNaseL gene. But men who inherited two copies of the mutation, one from each parent, had more than double the increase in risk of developing prostate cancer, compared to men who didn't carry the variant.

If additional studies now in the development stage confirm these original findings, it may lead to the production of a simple screening test that will give doctors a clearer picture of a man's risk, which could prompt earlier treatment and prevent deaths. Dr. Casey says a simple genetic test could be available for doctors to use within three-to-five years.

Synthetic HDL May Reverse Buildup of Arterial Plaques

A new study that appeared in the November 5, 2003 edition of the *Journal of the American Medical Association* provides strong evidence that five weekly infusions of a synthetic form of "good cholesterol," or HDL, can remove significant amounts of plaque from these arteries.

"This is an extraordinary and unprecedented finding," says Cleveland Clinic cardiologist Steven E. Nissen, M.D., who directed the 10-center nationwide study. "This is the first convincing demonstration that targeting HDL, good cholesterol, can benefit patients with heart disease, the leading cause of death in the United States." Traditional therapies for atherosclerosis have focused on lowering levels of "bad," or LDL, cholesterol.

The development of this investigational drug is an unusual story. About 30 years ago, researchers discovered 40 individuals in Limone Sul Garda in Northern Italy who appeared perfectly healthy, despite having very low levels of good cholesterol. Subsequent investigation revealed a variant in a protein known as Apolipoprotein A-I, which is a component of HDL. This variant was named ApoA-I Milano after the city of Milan, where the initial laboratory work was done.

Pre-clinical studies conducted by researchers at Esperion Therapeutics, Inc., showed rapid removal of plaques from diseased arteries. The Esperion scientists then approached Dr. Nissen to help them design a study to determine whether infusions of the ApoA-I Milano/phospholipid complex could reverse coronary plaque buildup in patients with heart disease.

In The Cleveland Clinic-directed study, patients who were given the synthetic protein showed a dramatic decrease in arterial plaques, whereas a comparison group given saline showed no change in plaques.

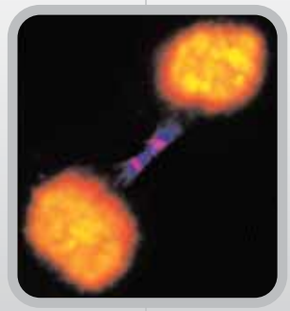
Although encouraged by the strong, positive outcome of the study, Dr. Nissen emphasizes that the current trial was only a small "proof of concept" study. "Much more testing needs to be performed to determine whether this unique form of HDL can be used routinely to treat patients with atherosclerosis," he says. Dr. Nissen continued, "Nonetheless, this study represents a paradigm shift, offering new hope for a devastating and common disease."

Critical Step in Cell Division Discovered

Cleveland Clinic senior researcher Seng Hui Low, Ph.D., looked at the cell sample under a microscope. She had added an antibody to a cell line grown in the lab to see if anything would happen.

At first glance, it appeared to be a waste of time. She jotted down her observations in her notebook: "Nothing to see. Only dirt."

But before discarding the sample, she decided to look again. This time, she realized the "dirt" appeared on the cell in an exact pattern. Her boss in the Department of Cell Biology, Thomas Weimbs, Ph.D., took a look too, and realized that by accident his lab had just made a huge discovery in the world of cell division.



When a cell divides, the nucleus in the middle splits in two and the cell, wanting to give each nucleus its own home, starts to squeeze itself in the middle. That gives you two ovals connected by a bridge called the midbody. The cells disconnect at the bridge and what's left are two separate cells, each with its own nucleus.

But, scientists have never known exactly how those cells sever themselves from the midbody.

The discovery in Dr. Weimbs' lab determined that two proteins, syntaxin 2 and its partner, endobrevin, are critical to cell division.

Current anti-tumor drugs on the market stop cell division altogether in both cancerous and non-cancerous cells. But those drugs act on other functions besides cell division in all body cells. They cause some devastating side effects on, for example, the nervous system, an area where cells don't divide.

"Theoretically, if we could find drug targets that work at a step that is more specific to cell division, such as this midbody cleavage, we might be able to identify drugs that only inhibit this step and not others in normal cells," Dr. Weimbs says. "We might be able to block cell division very specifically in cells that promote cancer growth, but leave other cells alone."

Image: A dividing cell that shows nuclei in yellow, the midbody in blue and syntaxin 2 in pink.

New Ways to Detect Heart Trouble Sooner

Myeloperoxidase. Nitrotyrosine. You probably haven't heard these words yet, but there may come a day when you get tested for them as commonly as you get your cholesterol level checked. Ongoing studies from The Cleveland Clinic's departments of Cell Biology and Cardiovascular Medicine have found that measuring the levels of myeloperoxidase (MPO) or nitrotyrosine in a patient's blood can serve as strong indicators that a patient has underlying coronary artery disease, the leading cause of heart attacks.

THE IMPORTANCE OF MPO

MPO is an enzyme found in white blood cells. "It's the only enzyme in humans that can make chlorinating oxidants. Basically, it makes bleach," explains lead researcher Stanley Hazen, M.D., Ph.D. "It's part of how our white blood cells kill pathogens."

Atherosclerotic lesions are loaded with MPO, which means there's chemical warfare going on within the heart arteries, causing inflammation and oxidative tissue damage. But MPO doesn't generate finely targeted smart bombs as part of the body's defenses. It also hurts healthy tissue surrounding the site of activation.

Among Dr. Hazen's early studies was one that showed that patients with an elevated MPO level in their blood had a 20-fold risk of developing heart disease. In contrast, patients with a high C-reactive protein level showed a three-fold risk for developing heart disease, while patients with a high cholesterol level only had a 1.3-fold risk of developing heart disease.

In a clinical study recently appearing in *The New England Journal of Medicine,* Dr. Hazen and his colleagues demonstrated the benefit of using an MPO level in evaluating patients presenting to the emergency room with chest pain. When added to existing diagnostic tests, MPO testing increased the ability to predict future adverse cardiac events, such as heart attack, stroke, bypass surgery or coronary angioplasty, or death from 50 percent to more than 90 percent of the time.

THE SIGNIFICANCE OF NITROTYROSINE

Oxidation, as well as inflammation, contributes to atherosclerosis. "Oxidation is like rust," explains Dr. Hazen. The problem is, until recently, it was not known what forms of oxidation occur within a diseased artery – information critical to learning how to block disease progression and to maintaining a healthy heart.

Dr. Hazen and researchers in his lab reasoned that there must be a way to measure oxidation within a person and see if it predicts coronary artery disease.

Nitrotyrosine is a modified protein generated by nitric oxide-derived oxidants. Dr. Hazen's research shows that patients who have elevated levels of nitrotyrosine in their blood have a 25-fold risk for heart disease.

What's more, the predictive value of elevated MPO and nitrotyrosine levels for heart disease is additive. While patients having an elevated level of either MPO or nitrotyrosine have marked increase in risk for having atherosclerosis, patients who have elevated levels of both markers have an even greater risk of having extensive artery disease.

The next step is to develop simple blood tests that can be used as routinely as cholesterol or pregnancy tests to screen for MPO and nitrotyrosine levels.

Stopping Transplant Rejection

Imagine a day when you could walk out of the hospital, a new heart pumping in your chest, and you never have to worry about your body rejecting the organ.

While that day is years away, new research is heading in that direction.

Robert Fairchild, Ph.D., co-director of the Transplant Research Program at the Cleveland Clinic Glickman Urological Institute, says he imagines his work leading to a "cocktail" of drugs, given briefly at the time of transplant, that will allow a recipient's body to become naturally tolerant to the new organ and to not reject it.

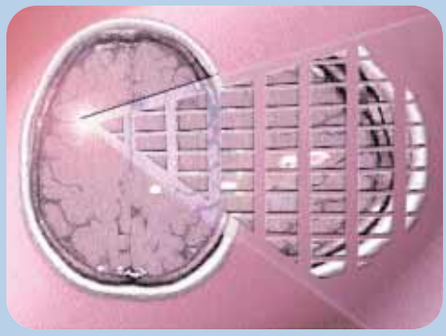
"Transplantation is such a daunting process because graft rejection is the strongest immune response in the body. That's why we have to use such potent immunosuppressant drugs – so those grafts aren't rejected," Dr. Fairchild explains. "The biggest challenge in transplantation is to find a way to convince T-cells, which are reactive to antigens in the graft, to be quiet and behave."

Dr. Fairchild wanted to identify the factors directing the T-cells into the graft. Molecules produced in grafts, called chemokines and adhesion molecules, help the T-cells stop and enter the graft tissue, where they perform immune functions that destroy the vessels and the graft tissue.

But, there are 55 different chemokines and about 20 different adhesion molecules. That makes for numerous potential partnerships.

"The strategy is to ask what is the synergy between specific pairs of chemokines and adhesion molecules," Dr. Fairchild says. "If we can quiet the inflammation in the graft by inhibiting this chemokine-directed traffic into the graft, then that might provide a window to induce the body's acceptance of the graft without the ongoing use of immunosuppressant drugs."

Early Detection of Brain Tumors and Other Neurological Diseases



Researchers, led by Damir Janigro, Ph.D., director of the Clinic's Cerebrovascular Center, have discovered two markers in blood serum that can help detect blood-brain barrier disruption. Since brain tumors are among the toughest cancers to treat, this research may lead to new blood tests that can detect blood-brain barrier disruption and tumors in the brain quicker than methods currently used.

The blood-brain barrier is a lining of cells, fused together, that works as the body's natural protection against allowing foreign substances to get into the brain. That barrier can break when there's a problem within the brain, such as lesions from multiple sclerosis or a brain tumor, both primary or metastasized from cancer elsewhere in the body.

Currently, disruption of the blood-brain barrier must be detected through an invasive spinal tap or expensive magnetic resonance imaging (MRI). Neither tests are routine or cheap.

To look for markers, the researchers used patients undergoing a procedure called intra-arterial chemotherapy. For this procedure, physicians surgically disrupt the barrier to get the chemotherapy drugs directly into the brain.

Researchers took blood samples prior to disruption and immediately following disruption, searching for substances in the blood that weren't there prior to disruption, but then appeared when the blood-brain barrier was opened.

What they found after disruption was something called S100B, a protein found in brain cells. In related work, the researchers found another marker, called transthyretin monomer (TTR), that showed up when the blood-to-cerebrospinal fluid barrier was breached.

"Neither of these markers gives you any information other than to say that something is wrong. It doesn't tell you exactly what's wrong, but both tests are important," says Dr. Janigro. "Once it's known that a patient's blood-brain or blood-to-cerebrospinal fluid barrier is broken, a physician can order further tests to discover the exact cause of the disruption."

Despite their diagnostic limits, such tests may be critical to early detection of neurological diseases. A physician is much more likely to order a finger-prick blood test for S100B and TTR than a spinal tap or an MRI.

Dr. Janigro says he foresees the day when there is a panel of blood tests that can indicate the presence of neurological diseases – from brain tumors to Alzheimer's.

An Independent View

By Natalie Manco as told to *Cleveland Clinic Magazine*

I've never been able to tolerate bright light. I always wear sunglasses outside because I'd just be a wreck without them. When I was a baby, only a few months old, my mother took me to the doctor because I kept squinting and closing my eyes outdoors.

He knew right away what was wrong: I have congenital glaucoma, which causes too much pressure in the eyes because the normal fluids don't drain properly. If the pressure gets too high, it permanently damages your vision and can lead to blindness. They told me that glaucoma is common among older people, but rare in children.

I had a lot of surgeries, 10 of them, when I was little. We traveled to a children's hospital nearby in Missouri for most of the surgeries. The procedures, called bilateral trabeculectomies and trabeculotomies, were supposed to relieve the pressure in my eyes. They worked fine until I was about 16, then my doctor performed a filtering procedure.

When I was around 18, the pressure in my eyes went up again and my doctor referred me to Dr. Edward Rockwood at The Cleveland Clinic for a further assessment. Dr. Rockwood performed a mitomycin C trabeculectomy in both eyes. A year later, he implanted a special tube-shunt, called a Baerveldt Glaucoma implant, in my left eye to drain the fluid. This has worked well to control the pressure.

> "... I started noticing a cloudy film over my eyes in the mornings, then clearing later in the day. It was like looking through a dirty window."

Unfortunately, a lot of damage was already done – and damage caused by glaucoma is irreversible.

After high school, I started noticing a cloudy film over my eyes in the mornings, then clearing later in the day. It was like looking through a dirty window, and it gradually got worse.

I've always had to hold things close to my eyes when I was reading, but it eventually got to the point where I couldn't read at all. I couldn't even see to balance my checkbook. It was really hard to do all the reading for the college psychology course I was taking and after I finished I decided not to begin any new courses. The reading was just too hard on my eyes.

Dr. Rockwood sent me to Dr. Roger Langston at the Clinic, who explained that the glaucoma had severely damaged my corneas, the membranes covering the eyes. He was concerned that I'd go blind without corneal transplants in both eyes. So in 1999, he did both surgeries within a few months of each other. I turned 22 years old in-between the surgeries.

I had the surgery videotaped so I could see what the doctors did. It was fascinating! Dr. Langston removed the cornea really fast, in just a few minutes. Stitching in the new cornea took a lot longer.

After each surgery, I couldn't work for two weeks and lifting heavy things was out of the question. No strenuous activity at all. I became restless and ready to become really active again, although I was also afraid I would accidentally damage the new cornea. Every day I asked Dr. Langston when I could do this or that. The day he said I could go rollerblading, I was so excited! I fell down and was scared I had damaged my cornea. But, the stitches stayed in.

I'm used to not being able to see well and I try not to let it affect me. I walk to work because I don't want to ride the bus alone or depend on someone else to drive me. Sometimes I wish I could drive myself wherever I need to go, but overall I'm pretty independent.

Before the transplants I felt like I was always looking through a thick fog. When I walked to work I couldn't clearly make out the "Walk/Don't Walk" signs and so I used to watch the traffic flow to help me judge when it was safe to cross. Now I can see the "Walk/Don't Walk" signs. I'm so happy that I can see better! My sister recently had a baby and I was thrilled to be in the room when she gave birth. I'm so grateful I was able to watch the whole thing.

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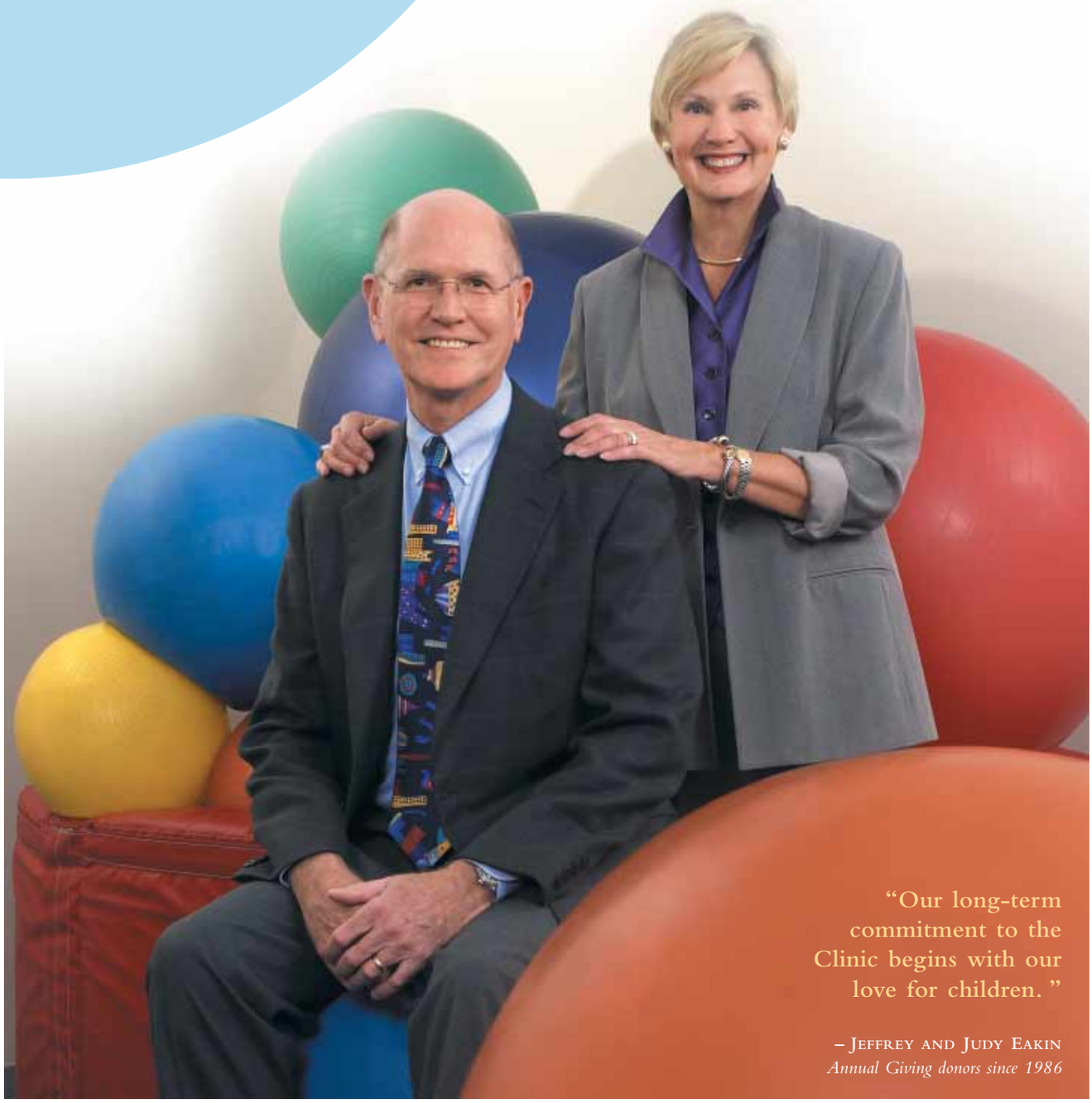

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