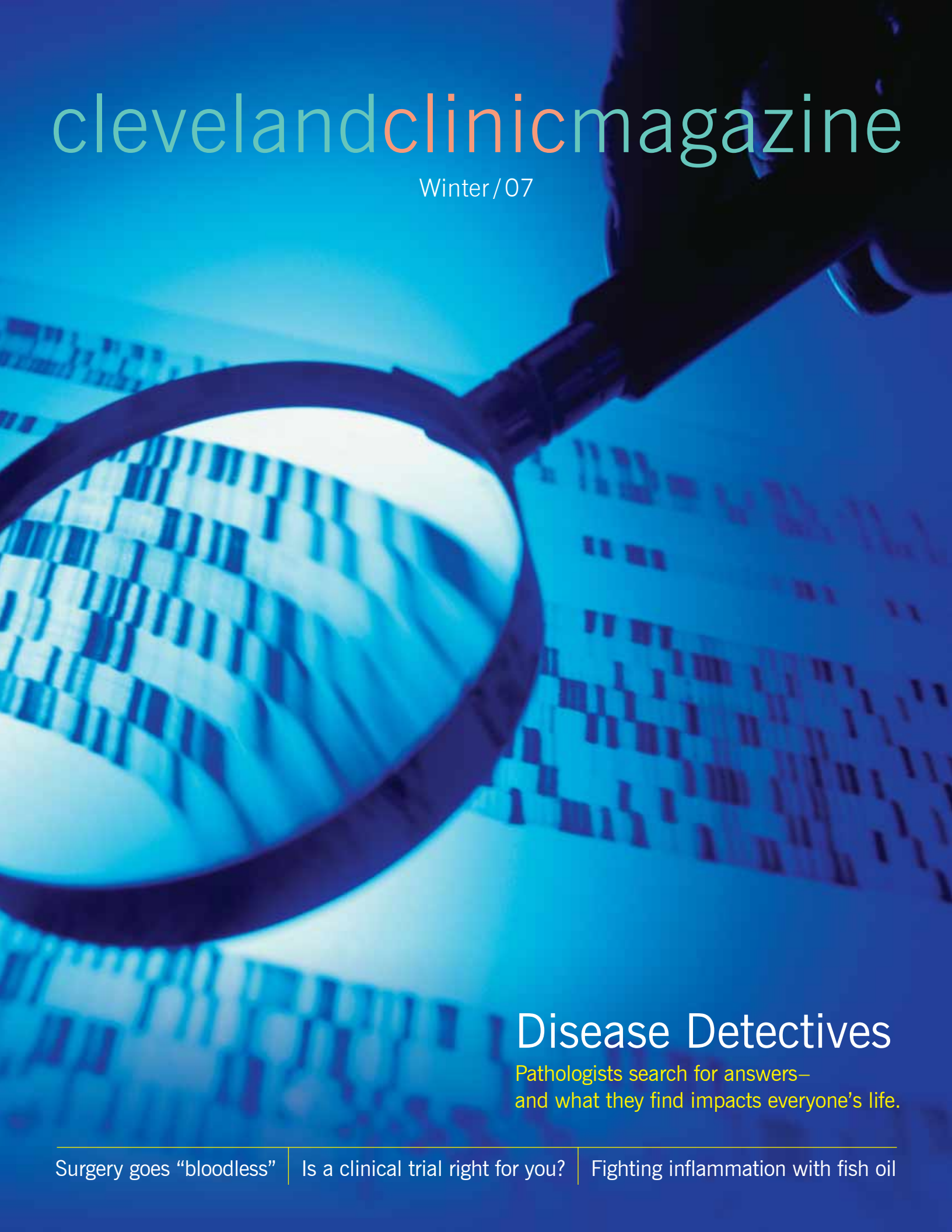

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Winter/07

Disease Detectives

Pathologists search for answers–
and what they find impacts everyone's life.

Surgery goes "bloodless" | Is a clinical trial right for you? | Fighting inflammation with fish oil

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Departments

Questions, comments or requests for more information:

E-MAIL
clevelandclinicmagazine@ccf.org

MAIL
Managing Editor
Cleveland Clinic Magazine
Cleveland Clinic/W14
9500 Euclid Avenue
Cleveland, OH 44195

WEB
clevelandclinic.org/ccm

Innovation Management and Trust

Cleveland Clinic is proud to be an innovative and entrepreneurial institution. We have pioneered new ideas and inventions for more than 85 years. As pioneers, we are often among the first to face new challenges and changing conditions. Such has been the case with conflict of interest. Cleveland Clinic has been a leader in the national discussion of conflict of interest as it relates to medical discovery. We are setting standards that will maintain the highest level of integrity, without affecting the pace of innovation that is so critical to the future of patient care.

In September 2006, Cleveland Clinic hosted the first National Dialogue on Conflict of Interest and Innovation Management Summit. The dialogue included recognized leaders in academic biomedical research, industry, government, medical research publishing, bioethics and professional medical organizations. Participants came away with a new appreciation for the hazards and complexity of these many-sided issues.

Conflict of interest arises most often around innovation and entrepreneurial activity. In many cases, innovation has become synonymous with entrepreneurial activity. Just last year, the Council on Competitiveness, in its call for action titled *Innovate or Abdicate*, said, "America's challenge is to unleash its innovation capacity to drive productivity, standard of living and leadership of global markets. For the past 25 years, we have optimized our organizations for efficiency and quality. Over the next quarter of a century, we must optimize our entire society for innovation."

Several factors have increasingly driven conflict of interest discussions. New knowledge is one such factor. The total amount of new knowledge doubles every two-and-a-half years. This intellectual capital increases the potential for innovation. The enhanced potential for the development of new products and services has attracted increased corporate interest. The fact that healthcare is 16 percent of the GDP and 25 percent of all federal expenditures also has captured corporate attention.

The 1980 Bayh-Dole Act is often seen as a major conflict of interest accelerator. It was passed to encourage universities to commercialize their intellectual capital. The act has contributed to breakthroughs in computing, nanotechnology, communication, genomics and minimally invasive therapies, stimulating an increasingly entrepreneurial spirit in the academic healthcare community. This entrepreneurial activity has led to the formulation of an increasingly sophisticated set of rules governing conflict of interest.

Increased scrutiny in this rapidly changing environment has led some to conclude that even the appearance of conflict of interest is detrimental and should be avoided at all cost. It has caused others to conclude that any economic incentive is corruptive of parties involved in innovation, and that entrepreneurial activities may result in patient harm.

There is no question that the crossroads of innovation and commerce harbor forces that are complex, conflicting and potentially corrupting. However, there are management tools that can be deployed at these crossroads–simple, complementary and constructive tools–including clearly documented and uniformly enforced standards for incentives, disclosures, transparency and accountability, as well as standard operating procedures for the full, factual and fair adjudication of non-compliance.

At Cleveland Clinic, we are continually reviewing and revising our conflict of interest policies to assure the continuing integrity of our patient care mission. We hope to accelerate the development of constructive policy that will continue to inspire, incentivize and support the work of our most gifted physicians, scientists and others, and maintain the highest standards of scientific ethics and patient care.

We find it useful to frame these issues as innovation management rather than conflict of interest. Managing innovation is an essential, fundamental and comprehensive activity. Managing conflicts is a necessary and important part of the larger innovation management process.

Today, innovation is imperative. We cannot become what we must in patient care and scientific discovery if we fail to innovate. Nor can we achieve what we must without the trust of our patients. I am confident that with successful innovation management, we can retain that trust and continue our role as pioneers of new treatments and explorers of new medical horizons.

Delos M. Cosgrove, M.D.
CEO and President

Reshaping Infant Heads

The "Back To Sleep" campaign–the one that urges parents to put babies to sleep on their backs–clearly has saved lives. It's estimated that deaths from Sudden Infant Death Syndrome (SIDS) have dropped by 50 percent since the campaign's launch in 1992. But the campaign also seems to have had a different type of effect on some babies: flat, odd-shaped heads, known medically as positional plagiocephaly.

When a baby continually lies in the same position, the back of his or her head can flatten. In some cases, the flattening on one side may cause the forehead to protrude on the opposite side, giving the infant a distorted head shape. Without intervention before the baby turns 1 year old, the head could stay flat.

Current medical thought is that positional plagiocephaly may cause some health issues over time because of distortion to the face and jaw area. Parents who suspect positional plagiocephaly should immediately bring it to the attention of their pediatrician.

For babies with severe flattening, special helmets can be used to painlessly reshape the baby's head. Frank Papay, M.D., Pediatric Plastic Surgery, received a patent on a new, unique type of helmet that uses inflated air pillows, referred to as "bladders," inside the helmet. The bladders put light pressure on the unflattened part of the head or on the area of the forehead that protrudes, as well as on the opposing unflattened side of the back of the head to reduce the amount of growth there. A void in the helmet is left in the opposite areas to encourage growth.

The helmet is made from a clear plastic material that allows physicians and certified orthotists to determine how well a baby's head is growing and rounding to be normal. Helmets are cast and modified specifically for each child.

"We recommend that the baby wears the helmet for 15 to 18 hours a day," explains Kirsten Richards, a certified prosthetist at Cleveland Clinic. "We get the best results with younger babies who still have a lot of growing to do."

Helmets have been fitted for infants as young as 2 months, although most babies are between 4 and 6 months old when they first come in. Babies will wear the helmet for about four months–or through 2 centimeters of circumferential growth. In some cases, the baby may need to be fitted with a second helmet until head growth is complete.

Detecting Down Syndrome Early

By measuring the thickness of a fetus's neck using a sophisticated ultrasound, in combination with two blood tests, physicians can screen for certain birth defects much earlier than with traditional ultrasound alone.

"First-trimester combined screening is one of the most accurate, noninvasive methods we have for determining a fetus's risk for Down syndrome," says Elliot Philipson, M.D., Obstetrics and Gynecology.

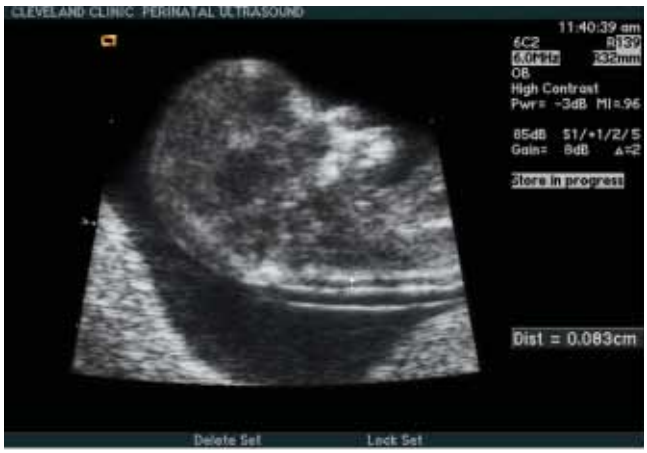
Close to the end of the first trimester, a special ultrasound can be used to determine the nuchal translucency (NT), or thickness measurement, of a fetus's neck. Studies have determined that increased thickness may indicate a higher risk for chromosomal abnormalities and certain birth defects. Because the risk assessment is performed using noninvasive ultrasound, it poses no danger to the fetus. In addition, it offers higher detection rates for Down syndrome than were previously possible using traditional ultrasound testing. NT measurements also can be taken from more than one fetus in the womb, as in the case of twins.

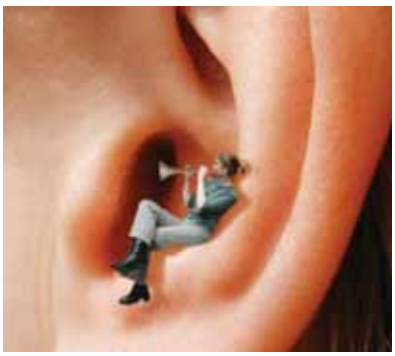
In first-trimester combined screening, two blood tests also are performed in conjunction with NT. One test screens for pregnancy-associated plasma protein A, referred to as PAPP-A, and the other for beta human chorionic gonadotropin (hCG).

"The most accurate results are obtained if testing is done between 11 and 12 weeks gestation," notes Dr. Philipson. At that time, the test will detect approximately 87 percent of fetuses with Down syndrome. Testing results generally are available in about four days.

Ultrasonographers and physicians performing NT measurement need special training and use high quality equipment. They also must be certified by the Fetal Medicine Foundation in London, the organization that sets the international standards and provides software that allows a doctor to evaluate the fetus.

Although there is no risk to mother or child, it may not be possible to obtain an accurate NT measurement on the first attempt because of the position or movement of the fetus. "Fortunately, we can wait for the fetus to shift position and obtain an accurate NT measurement a few hours later," says Dr. Philipson.





New Tinnitus Treatment is Music to Patients' Ears

Whether being able to hear the smoke alarm blare in the dark of night or listening to the latest release from a favorite singer, we appreciate our hearing. But some people wish they could hear just a little bit less. According to estimates by the American Tinnitus Association, more than 12 million Americans experience tinnitus, a constant ringing, buzzing or whooshing sound in the ears. Of the people affected, about 1 million experience it so severely that it becomes difficult to hear, work or even sleep.

"Tinnitus can be caused by hearing loss or loud noise, as well as health problems including allergies, tumors and problems in the heart and blood vessels, jaws and neck," says Craig Newman, Ph.D., Head of Audiology and co-director, with Sharon Sandridge, Ph.D., of Cleveland Clinic's Tinnitus Management Clinic (TMC). There is no cure for tinnitus; however, a number of therapies can help desensitize the patient or mask the tinnitus sound.

The TMC recently became one of just a handful of centers in the U.S. to offer the Neuromonics Tinnitus Treatment (NTT), an innovative form of acoustic therapy. During the three-phase NTT program, patients listen to a musical signal delivered through earphones from a custom-programmed processor that's about the same size and weight as a cell phone. The processor is loaded with specially selected music that contains an embedded acoustic signal. The signal, which sounds like a shower, provides instant relief from tinnitus.

In the initial phase, patients are instructed to listen to their NTT device for at least two to three hours a day at times when their tinnitus is at its worst. "Music therapy causes progressive relaxation and provides patients with a way to escape from their tinnitus, while the shower sound affords a masking effect," Dr. Sandridge explains.

During stage two, the shower sound is removed. "Even though they can hear their tinnitus, because it is coupled with the pleasant music, the brain no longer fixates on the tinnitus or identifies it as a threatening sound," Dr. Sandridge says. After six months, patients enter the final stage, during which they only use the NTT device as needed.

"Patients who have used this device usually achieve an acceptable level of relief after six months, whereas it can take 12 to 18 months to reach maximum benefit using other forms of sound therapy," Dr. Newman comments. "In addition, other programs require listening for about 8 hours each day."

Dr. Sandridge adds, "Patients generally find the music of the NTT program much more pleasant than the white noise presented in other forms of sound therapy."

Prior to enrollment in the TMC, all patients are seen by an otolaryngologist to rule out any tinnitus-causing condition that would require surgical or medical treatment. They also must undergo a complete audiological evaluation.

Crowing About Knee Pain Relief

Most people don't think of a chicken's red spiky head ornamentation when they think about pain relief. But that's exactly what a viscosupplement, an injectable treatment for osteoarthritis pain, is derived from: rooster combs.

Osteoarthritis is a condition in which the cartilage surrounding the bone joint has worn away, causing friction and pain with movement. It is caused by injury to the joint, aging and general wear. Different from rheumatoid arthritis, osteoarthritis is not characterized by inflammation in the joint.

The first viscosupplement became available on the U.S. market almost a decade ago. At the time, it was thought to be a last resort in treating osteoarthritis of the knee. Today, viscosupplements are a first-line treatment, used in conjunction with other traditional therapies.

For patients who aren't candidates for knee surgery due to other health conditions or for those who want to avoid surgery, viscosupplements can be a source of long-term pain relief.

Treatment with a viscosupplement requires a series of injections. Given a week apart, each injection contains about a half teaspoon of a gel-like substance called hyaluronic acid, which is naturally present in normal joint fluid and many other body tissues.

"It provides some lubrication and shock absorbency to the joint," says A. J. Cianflocco, M.D., a physician specializing in non-operative orthopaedic medicine. "In addition, it has an anti-inflammatory effect, an analgesic effect for pain relief, and provides nutrition to the cartilage."

Currently, five types of viscosupplements are available. Dr. Cianflocco says that all work about the same, but he cautions that four of the five are made from rooster combs, making those products strictly off-limits to anyone with a chicken or egg allergy. The fifth product, however, is bioengineered so patients with egg and chicken allergies have an alternative.

Viscosupplements have few side effects. Rarely, there may be injection-site discomfort or joint swelling and inflammation, which can be relieved with an anti-inflammatory agent such as ibuprofen, rest and ice. It also can take up to three months after starting treatment for some patients to feel the effects of viscosupplements. Patients who need more immediate relief can receive cortisone injections prior to starting treatment. Those injections can't be given at the exact same time as the viscosupplement, but they can be given about a month before the viscosupplement to provide temporary relief until the viscosupplement begins to work.

Once the treatment starts working, relief usually lasts six months or longer. The milder the arthritis, says Dr. Cianflocco, the better the viscosupplement works. But, he warns, a viscosupplement isn't a one-stop solution. Patients should continue other prescribed therapies, including physical therapy, ibuprofen, non-steroidal anti-inflammatory agents, and even bracing of the joint, if necessary.

The Patient With Lagging Legs

Joe* is certain he has the perfect job. As a groundskeeper for his town's parks and recreation department, he never misses a little league game and he knows the blooming beds of annuals are thanks to his hard work. He can't imagine spending days confined to a cubicle–the baseball fields, playgrounds and picnic areas are his "office." But lately, Joe stalls when he moves too fast.

By the time he makes his way from the park toolshed to the baseball field 50 yards away, his legs remind him that it will be a long day: His calf muscles ache and burn, and he quickly tires. He has to stop and rest during the long stretch between the baseball diamond and the playground. Ten minutes later, his legs feel new again.

Joe is always on his feet, except for the half hour during lunchtime when he relaxes in his maintenance vehicle. No more smoke breaks since he kicked the habit last year.

"Bad circulation," he told his boss, defending his fatigue and sore legs from co-workers' jabs that his retirement days are nearing. At 63, Joe never planned on sitting on the bench. Now, however, he feels he may have no choice–his legs may not let him stay active.

Joe decides he better see his doctor, who won't be pleased that he hasn't shed the pounds she recommended he lose at last year's appointment. During that visit, she also let Joe know that, because of his family history and high-fat diet, he fell into the high-risk category for diabetes and heart disease. Joe figures he can cut out his fast-food habit to clean up the high cholesterol, but he isn't ready to hang up his coveralls because of aching legs.

THE OFFICE VISIT

Heather Gornik, M.D., listens to Joe describe his daily activities. She conducts a thorough medical evaluation, including measuring blood pressures in both of his arms. She feels the pulses in his neck, arms, abdomen and legs, and listens to the pulses for sounds like little swishes, called bruits, which are a sign of tight blockages.

She inspects his feet and toes for sores. Knowing Joe's pre-diabetic status, she tests his cholesterol and fasting blood sugar levels. She's pleased that Joe has stopped smoking, but notices that he has gained another five pounds in the past year.

Joe explains that his achy legs usually feel better after resting. He says his father always had bad circulation and shows Dr. Gornik a few worm-like varicose veins in both of his legs. She asks him when he began to notice his leg symptoms. Joe replies that, despite years of working in the field, the symptoms flared up for the first time only a few months ago.

Dr. Gornik, a cardiologist and vascular medicine specialist, forms a few theories based on her evaluation and discussion with Joe:

OSTEOARTHRITIS–A degenerative joint disease caused by a breakdown of cartilage in joints, especially in weight-bearing regions like hips, knees and spine. Pain after exercise or use of the joint is one of the disease's symptoms.

NEUROPATHY–Malfunction of the nerves, resulting in tingling, numbness, tightness; or burning, shooting or stabbing pain in the feet, hands and other extremities. Diabetic neuropathy is caused when high blood sugar cells damage nerve cells in the body over time.

PERIPHERAL ARTERIAL DISEASE (PAD)–Cholesterol plaque blocks the arteries that provide blood flow to the legs, causing pain, or claudication, while walking. PAD is most common in patients age 50 and older. Some patients diagnosed with PAD have no aching symptoms.

CHRONIC VENOUS INSUFFICIENCY– Patients with severe varicose veins or a prior blood clot in the legs may develop pain in the legs with exercise. Patients with chronic venous insufficiency often have severe varicose veins, leg swelling and changes in the appearance of the skin of the legs, suggesting prior blood clots.

SPINAL STENOSIS–Narrowing of the spinal canal, which can squeeze and irritate nerve roots that branch out from the spinal cord. With spinal stenosis, pain in the thighs, calves and buttocks is worse with walking or exercise.

Joe's cholesterol levels are moderately high, so Dr. Gornik prescribes medication. She notices his blood pressure is borderline elevated and recalls that he has a family history of stroke. She suggests he take a daily baby aspirin to reduce his risk of a heart attack or stroke.

A family history of diabetes puts Joe at higher risk of developing the disease. High blood sugar cells can trigger symptoms similar to those Joe describes–aching in feet, tingling in the legs.

Heather Gornik, M.D.

Joe's excess weight puts unnecessary pressure on his hips, back and knees, which could contribute to knee pain from osteoarthritis. His varicose veins could indicate chronic venous insufficiency, but they are likely too mild to suggest prior blood clots. Still, Dr. Gornik is concerned about Joe's pain while walking.

During the examination, Dr. Gornik notices that Joe's pulses are diminished in both of his legs. She also hears bruits over the pulses in his groin area. She performs an ankle-brachial index (ABI) test, which measures blood pressures in both arms and from each ankle using a small ultrasound device. The pressures are used to calculate an index number for each leg by dividing the ankle pressure by the arm pressure. The ABI ranges from 0 to 1.4. An ABI greater than 0.91 and less than 1.4 is considered normal.

Joe's ABI measures 0.89 in the right leg and 0.81 in the left leg, both borderline scores.

Finally, Dr. Gornik conducts a detailed musculoskeletal exam to test for neuropathy. She uses a thin wire, known as a monofilament, to test the sensation in Joe's hands and feet. Next, she tests Joe's muscle strength, walking abilities, balance and reflexes to determine potential problems with spinal discs. Joe tells her he has never suffered a fall on the job, and his hands are those of a man who works outdoors–rugged, strong and with a firm grip.

WHAT COULD BE THE CAUSE OF JOE'S CONDITION?

For Dr. Gornik's diagnosis, please visit our Web site at clevelandclinic.org/ccm.

**The patient and history presented in "Diagnosis Challenge" are fictional.*

Disease Detectives

Whether you know it or not–if you've ever had a blood test, a Pap smear or a biopsy–a pathologist has helped you out.

Each block of ice looks like a miniature piece of modern art. Pink and red swirls paint winding trails through the stark white frost. The seemingly abstract image can be almost anything to the untrained eye. But to the person who creates these icy blocks–the pathologist–the images hold answers that can have life-altering consequences.

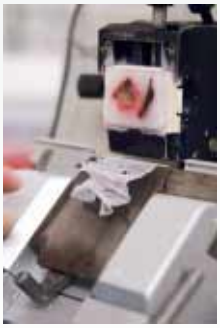
"Pathologists bridge the gap between straight science and patient care," explains William Hart, M.D., Chairman of Pathology and Laboratory Medicine. "We are the ones who make the ultimate diagnosis."

Pathology is a medical specialty rarely understood by the general public. Yet, for all of its anonymity, these dedicated scientists and physicians have an extremely important impact on patients' lives.

"We touch all areas of medicine and, therefore, everyone's life at one time or another," says Dr. Hart. That connection to the patient makes pathology both unique and indispensable.

Take, for example, the anatomical pathologist. This is the person who analyzes surgical tissue cuttings, as well as biopsy and cellular specimens for disease–all while the patient's surgeon and other physicians stand by awaiting the results that will dictate how treatment will proceed.

Speed, and accuracy, are vital.



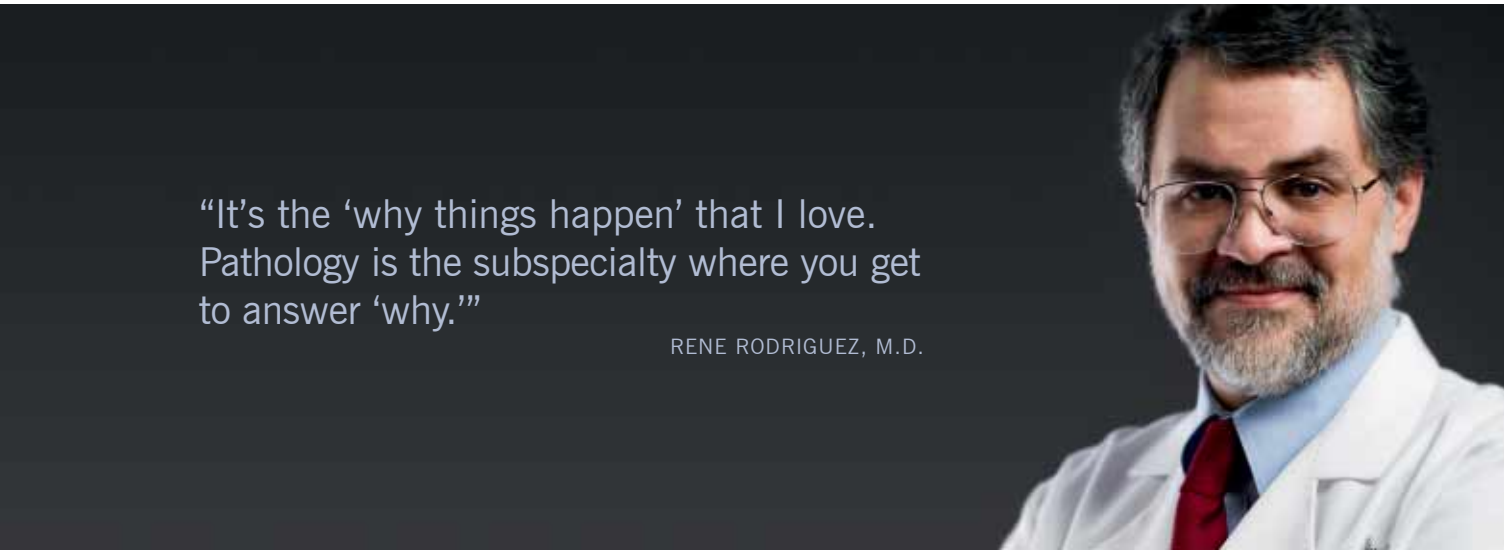
When the surgical specimen arrives at the front window of the Pathology laboratory, it is quickly catalogued and given to the pathologist. A piece of the tissue is cut and placed in a small square mold. White gel and liquid nitrogen freeze the specimen into a block of ice. The blood and tissue within the ice create the pink and red twisting pattern.

Using a razor blade, the pathologist assistant shaves off a fragile layer of the ice and places it on a slide. The sample needs to be, literally, razor thin–thinner than a single hair–without crumbling. Tissue samples that don't need to be examined immediately are chemically preserved, dehydrated and saved indefinitely in wax, allowing the samples to be shaved over and over again as needed for additional testing. Once on the slide, a small amount of dye is applied to the shaved tissue sample. The stain provides contrast and multiple colors, making the tissue easier to view under the microscope. Pathologists use multiple dyes or stains to highlight different aspects of tissue and permit in-depth evaluation. Knowing which additional stains will uncover the correct diagnosis is an important part of a pathologist's work.

To make an accurate diagnosis, the pathologist must know a complete repertoire of cell shapes and formations. Most tissue samples need an extensive analysis that cannot be completed while the patient is in surgery. Examination during surgery can be critical, however, to answer specific questions that determine the next step of the procedure. Sometimes, the pathologist can tell from the sample how far a disease, such as cancer, has advanced. Other features in the tissue may help determine the likelihood of survival for the patient.

Crucial information, gathered from a tiny block of ice.

(Left) Before any patient undergoes surgery, his or her blood is screened by a powerful machine called Galileo. (Above) Surgical specimens are frozen into small ice blocks and cut into thin samples for examination.



Pathology comes from the Greek word "pathos," which means "feeling, pain, suffering" and "logos," meaning "the study of." Therefore, pathology is, literally, the study of disease.

For many people, the term pathology conjures up images from popular television shows such as CSI, where forensic pathologists try to unlock clues to solve murder mysteries. These images link the idea of what pathologists do exclusively with performing autopsies. But in actuality, looking at organs after death to uncover why the patient died is only a small part of a pathologist's work.

Pathologists are physicians who complete four years or more of additional study after medical school. Unlike on television, pathologists spend most of their time diagnosing living patients. They examine bodily fluids–blood, urine, spinal fluid–as well as tissues removed for biopsy. They will look at a child's sweat to determine if he or she has cystic fibrosis, sign off on annual Pap smears and screen blood before transfusions. They research disease processes and help discover ways to cure or prevent diseases, such as developing immunizations or stopping the deadly Asian bird flu from becoming a pandemic.

Yet, for all they do, the pathologist is generally invisible to the patient.

"Pathologists impact patient care by the diagnoses we make," explains Jeffrey Uchin, M.D., a first-year pathology resident at Cleveland Clinic. "It's like the role of an air traffic controller. They don't fly the plane, but you wouldn't want to be in the air without one."

Instead of working from a control tower, Cleveland Clinic pathologists work in a technologically advanced laboratory that occupies four floors in the "L" building on the main campus. Each floor houses a different pathology specialty: Microbiology on the fourth floor, Molecular Pathology on the third, Transfusion Medicine and Anatomic Pathology on the second, and the Automated Core Laboratory–for standard blood tests and urinalysis–on the first floor. The one commonality each floor has is the abundance of microscopes, trays of test tubes, piles of Petri dishes, solutions for staining and other "media" used to encourage culture growth.

"The Pathology lab here performs more than 7 million tests a year," notes Dr. Hart. "We have 40 pathologists and scientists, and a staff of more than 700 employees to handle our pathology needs."

It is those employees–lab technicians, medical technologists, cytotechnologists and the pathologists–who work behind the scenes to ensure that every patient gets an accurate diagnosis.

Rene Rodriguez, M.D., knew the minute he wanted to go into medicine. He was about 10 years old when his science teacher dissected a rabbit and held up the heart. He decided then that he would be a doctor, and probably a cardiologist at that.

Today, he is one of just two cardiovascular pathologists at Cleveland Clinic.

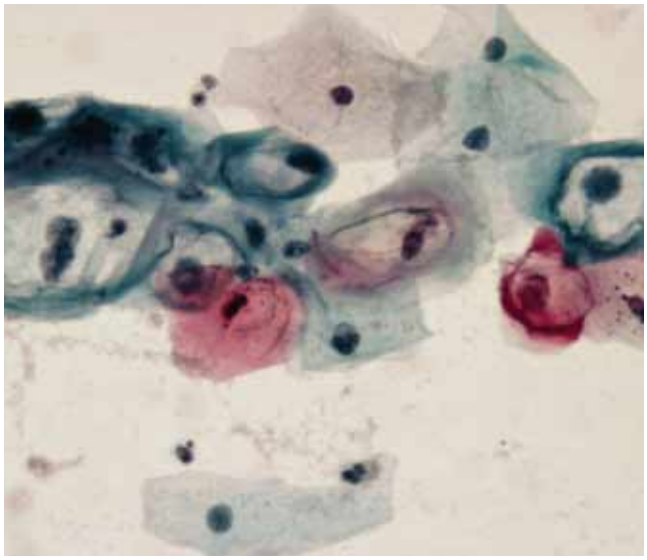
When asked why he chose pathology over being a cardiologist, Dr. Rodriguez gives a quick, assured response. "It's the 'why things happen' that I love," he explains. "Fixing things is interesting. Surgery also is very interesting. But, in the end, answering 'why' was most appealing to me. Pathology is the subspecialty where you get to answer 'why.'"

Cardiovascular pathologists, as the name implies, study diseases of the heart and blood vessels. One of these areas of study is heart transplantation. Here, biopsies are examined to determine if a patient's body is rejecting the newly transplanted heart.

"The minute the transplant is performed, rejection becomes a threat," says Dr. Rodriguez. "That risk never goes away. We take frequent cardiac biopsies and examine them for the presence of antibodies, those harbingers of rejection. We notify the patient's physician about what's going on, so that the physician can adjust the treatment appropriately to keep the transplanted heart working."

An inquisitive nature is what seems to drive these disease detectives. "Every slide is a new mystery," says Dr. Uchin. "There's something going on here and I want to know what it is."

Dr. Uchin says he had no desire to go into pathology when he started medical school in 2001. A former teacher, he was sure that he wanted to continue working with children. Even after doing a fellowship in pathology, he insisted to anyone who asked that he was doing it merely for extra experience–not to build a future career.



Cervical smear showing cells infected with the Human Papilloma Virus (HPV). HPV has been implicated in the development of cervical cancer.

"Pathologists impact patient care by the diagnoses we make," explains Jeffrey Uchin, M.D., a first-year pathology resident at Cleveland Clinic. "It's like the role of an air traffic controller. They don't fly the plane, but you wouldn't want to be in the air without one."

But several weeks into his pediatric rotation, he wasn't happy.

"I was managing patients and their care, but I didn't feel like I was using my mind the way I wanted to. I didn't feel like I was problem-solving. At that instant, I realized I missed pathology."

Every day Dr. Uchin previews hundreds of slides, sometimes starting as early as 4 a.m. Because he is still a resident, an experienced pathologist always reviews each slide with Dr. Uchin and makes the final diagnosis. That's because getting something wrong in this field can be a matter of life or death.

"I can't stress how important it is in pathology not to miss anything," says Jennifer Brainard, M.D., Head of Cytopathology. "You have to always ask yourself the questions, 'Am I missing something here? Is there something else going on that I'm not thinking about?'"

Part of Dr. Brainard's work is reviewing Pap smears–her lab processes 67,000 Paps every year–and they have multiple measures in place to ensure accuracy.

Cleveland Clinic was the first lab in the world to use a Thin Prep imager–a machine that prescreens Pap tests. The advantage of the Thin Prep system is that it uniformly distributes cells across the slide in a single layer, significantly increasing the accuracy of diagnosing cervical cancer.

"With conventional Pap tests, it's common to have cells on top of each other," says Dr. Brainard. "This can result in false negatives as abnormal cells can be hidden under normal cells."

Every Pap is screened by a cytotechnologist, a person who is trained in the details of normal and abnormal cells. Dr. Brainard says that even with the more accurate Thin Prep system in place, approximately 15 to 20 percent of all negative Pap smears are manually checked to ensure that they are, in fact, negative. All abnormal Paps then are assessed by a cytopathologist, who scrutinizes the sample's deviations to determine the diagnosis.

Finally, that same Pap smear sample can be used to run a test for the Human Papilloma Virus (HPV), the virus that causes cervical cancer. The combined information from the HPV test and the Thin Prep Pap can identify patients who may have or may be at risk for developing cervical cancer.

The Thin Prep imager is just one example of the technology Cleveland Clinic uses throughout its four floors of pathology laboratories. Physicians from all over the country send samples here for diagnoses or second opinions.

For standard blood tests, racks of test tubes flow through the analyzing machine. The machine reads a bar code stuck to the tube to know the patient's name, its assigned unique identifier and what tests the doctor has ordered. Inside the machine, a robotic arm takes a drop of blood from the tube and puts it into a cup where chemicals are added for testing purposes.

FISH technology can be used to diagnose diseases as different as brain tumors or bladder cancer. It does this by allowing pathologists to visualize a patient's chromosomes to discern abnormalities or genetic mutations.

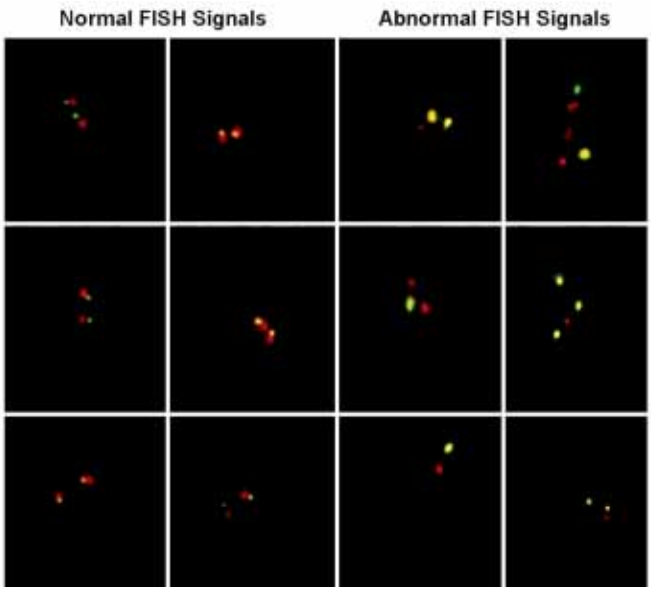
The results pop up almost immediately on a computer screen–and go into a system for doctors to easily access. Any result that could lead to a critical life or death diagnosis is automatically retested.

The machines can test 800 to 1,000 blood samples per hour, says Barbara Zingale, MT (ASCP), Education Coordinator for the Division of Pathology and Laboratory Medicine.

The second floor boasts technology that is literally Cleveland Clinic's lifeblood. Here, shipments of donated blood–hundreds of pints–arrive from the Red Cross several times each day.

Before undergoing any surgery at Cleveland Clinic, every patient has his or her blood screened by a powerful machine called the Galileo. The Galileo tests blood for its type and to determine what antibodies are present. All of this testing used to be labor-intensive work: Technicians would manually mix blood in clear glass test tubes, shake them, then visually check the sample for clumping, which would indicate two incompatible types of blood. Now, the Galileo handles the workload.

One of the most advanced areas is on the third floor: Molecular Pathology, which employs the latest techniques in genetic testing, including DNA testing. Also located in the same area is the laboratory devoted to FISH, or "Fluorescent In-Situ Hybridization." For years, Cleveland Clinic was one of only three medical centers nationwide that had this technology available. Now, more centers do, but Cleveland Clinic still reviews slides from all over the country.



FISH technology can be used to diagnose diseases as different as brain tumors or bladder cancer. It does this by allowing pathologists to visualize a patient's chromosomes to discern abnormalities or genetic mutations.

Using special colored markers, or probes, technologists can count chromosome pairs in numerous cells to see whether or not a chromosome is missing in the cell or if there is an extra one that should not be present. Both situations could indicate a serious health problem.

It is eye-straining work in a dark room, but the benefits to patients are well worth the effort. After treatment for bladder cancer, for example, a simple urine test viewed with FISH technology can replace the uncomfortable process of physically reaching into the bladder with a scope to ensure the cancer has not returned.

Earlier this year, the Food and Drug Administration approved a new vaccine to protect against two of the primary Human Papilloma Virus (HPV) strains known to lead to cervical cancer. The story of the vaccine development belongs just as much to the hundreds of research pathologists who worked alongside scientists for 25 years, studying HPV and cervical cancer, establishing the link between the two.

Much of today's pathology research focuses on detecting and isolating genetic markers, referred to as biomarkers, for diseases. By determining the specific biomarker for a disease, patients who carry that biomarker, and therefore have a high risk for developing the disease, can be proactively treated.

Fifteen years ago, Mary Bronner, M.D., Director of Gastrointestinal Pathology and Head of Morphologic Molecular Pathology, started investigating a relatively uncommon disease called ulcerative colitis (UC). This chronic inflammatory disease of the colon is one of two conditions, the other being Crohn's disease, frequently lumped into the category of inflammatory bowel disease (IBD). Dr. Bronner also has a personal connection to her work: She has suffered from Crohn's disease for 33 years.

UC is a risk factor for developing colon cancer. Says Dr. Bronner, "Having UC doesn't mean that, without a doubt, you'll get colon cancer. However, if you develop UC, colon cancer becomes a strong possibility."

The normal management plan for a UC patient is to undergo lifelong periodic colonoscopies, taking a minimum of 33 biopsies from each procedure. "Colonoscopies are expensive and uncomfortable. They're necessary, but nobody likes them," Dr. Bronner says grimly.

Eliminating the patient's discomfort is important. So, too, is eliminating needless tests. "Of the whole universe of patients with chronic gastrointestinal [GI] inflammatory diseases, only about 10 percent will ever develop into cancer," notes Dr. Bronner. "This means we're doing all this uncomfortable and expensive testing on patients, when 90 percent of them don't need it."

Through their research, Dr. Bronner and her colleagues determined that there are genetic tests that may tell physicians whether a specific patient is going to develop GI-related cancers.

"The exciting thing about these genetic cancer-risk markers is that you can find them in a very small sample of tissue, just a tiny biopsy about the size of a grain of rice from the outer edge of the colon, so you don't have to do a full colonoscopy," Dr. Bronner says. "By using these new genetic tests, we would only need one biopsy–not 33." She smiles, "When patients hear that, they get very excited."

Dr. Bronner's initial findings convinced the National Institutes of Health to fund a study to further test these genetic biomarkers. "Originally, we developed the biomarkers from pathology samples taken from patients who had already developed cancer. It's retrospective data," she explains. "Now we're going to test these markers 'prospectively.' In the new study, we'll look at a group of UC patients whose cancer risk is unknown. We'll take pathology samples, test them and track those patients into the future."

Dr. Bronner is optimistic that this study could pave the way for a major breakthrough in GI-related cancers. "It's critical to be able to single out the 10 percent of patients who are at high risk–they're the ones who really need the colonoscopy."

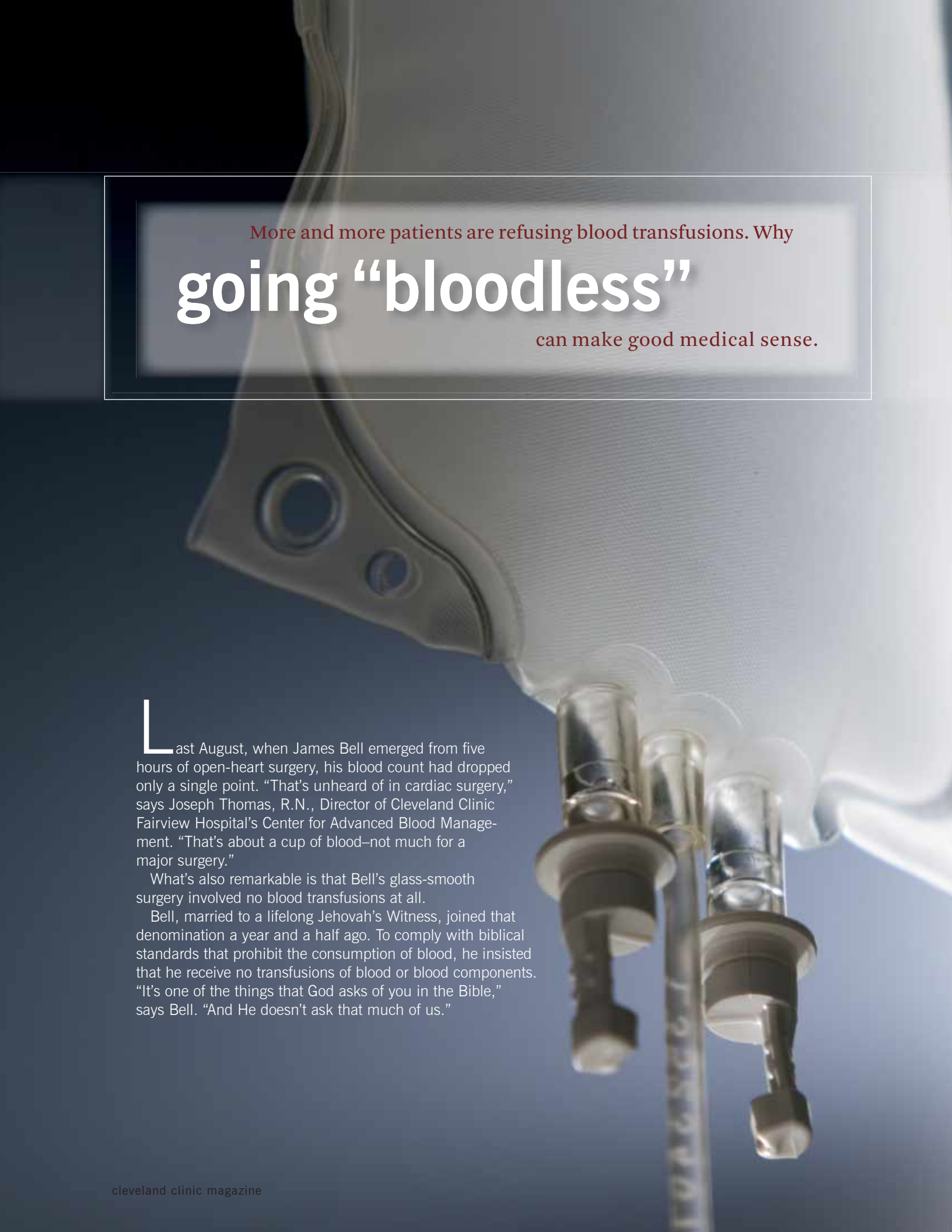
If the trial is successful, new biomarkers to detect high-risk patients could make it into clinical practice within five years. "Which is a dream come true for me," says Dr. Bronner. "Not only because I've been working on it for so long, but also because I'm an IBD patient. I'd like to know: 'Am I in the 10 percent who needs frequent colonoscopies, or the 90 percent who don't need to worry so much?' These biomarkers may make the difference to a lot of people."

Like Dr. Bronner, cardiac pathologist Dr. Rodriguez faces the unknown in his research. Although heart transplants have taken place for more than 25 years, it is the cardiovascular pathologists who are trying to unravel the mystery of why some people suddenly reject a transplanted heart that seemed to be functioning well for years.

"We don't know how to control chronic rejection," Dr. Rodriguez says. "Every transplant patient is going to develop chronic rejection, which affects the vessels of the heart, and we don't have a clue what triggers it and how to stop it. We have to keep looking and asking 'why.'"

To a new, up-and-coming pathologist like Dr. Uchin, the ability to detect the cause of a condition, to impact patients' lives, even from afar, is what drives him to continue in the behind-the-scenes field of pathology. "While I miss interacting with patients, I know I've helped in their care. Even if they never meet me, I'm here for them."

Through their research, Dr. Bronner and her colleagues determined that there are genetic tests that may tell physicians whether a specific patient is going to develop GI-related cancers.



More and more patients are refusing blood transfusions. Why

going "bloodless"

can make good medical sense.

Last August, when James Bell emerged from five hours of open-heart surgery, his blood count had dropped only a single point. "That's unheard of in cardiac surgery," says Joseph Thomas, R.N., Director of Cleveland Clinic Fairview Hospital's Center for Advanced Blood Management. "That's about a cup of blood–not much for a major surgery."

What's also remarkable is that Bell's glass-smooth surgery involved no blood transfusions at all.

Bell, married to a lifelong Jehovah's Witness, joined that denomination a year and a half ago. To comply with biblical standards that prohibit the consumption of blood, he insisted that he receive no transfusions of blood or blood components. "It's one of the things that God asks of you in the Bible," says Bell. "And He doesn't ask that much of us."

Years ago, Bell's insistence on upholding his faith's tenets would likely have been a death sentence. Back then, open-heart surgery without transfusion was unheard of. But new technologies–along with a growing awareness that blood conservation and minimizing or eliminating transfusions benefit patients, hospitals and the world blood supply–are changing the way surgery is performed today.

"Even 10 years ago, we couldn't have done a major surgery with so little blood loss," says Richard Treat, M.D., Fairview Hospital's Chairman of the Department of Surgery and Medical Director of the Center for Advanced Blood Management.

Dr. Treat, who has practiced medicine for 30 years, says that early in his career physicians were not sympathetic to patients who refused blood transfusions. "In the '50s we had a paternalistic philosophy. Attitudes were different: The doctor knew best. Physicians did not accept someone saying, 'I refuse a transfusion.'"

All that changed when the Patient Self-Determination Act became federal law in 1991. Hospitals were required to inform adult patients of their right to make their own medical care decisions. "Simply put, patients have the right to say no," says Dr. Treat. "Patients who refused transfusions had to be accommodated. Even if it meant they might die."

And many did, notes Dr. Treat. "At that time, physicians did not have the training to properly manage blood. We didn't know how. Many patients didn't survive. We needed to create better methods."

James Bell's surgery is a good example of these better methods. Bell didn't require an emergency procedure, but he was suffering from a significant artery blockage that meant surgery "had to be done within days rather than weeks," according to Thomas. The hospital admitted Bell and launched a plan to ready him for transfusion-free heart surgery.

Prior to his transfer to Cleveland Clinic Fairview Hospital, Bell had been receiving a clot-inhibiting agent that needed 24 to 48 hours to work its way out of his system. If physicians had operated while that agent was active, Bell could have bled to death in the operating room. The hospital team used those two days to administer the drug Procrit, a synthetic version of the hormone erythropoietin that is naturally produced in the kidneys to stimulate the bone marrow to produce more red blood cells. They also added intravenous iron, which helps build hemoglobin, and tested his body's ability to properly clot.

Immediately before surgery, a small amount of Bell's blood was mixed with calcium and thrombin, a clot-promoting enzyme. The mixture–called platelet gel–was sprayed on his incisions during surgery. The gel galvanized his platelets, fragments of cells produced in bone marrow, to clump together to promote clotting at the surgical site.

The surgical team also employed a cell saver, a machine that collected Bell's blood from the surgical area, then cleaned and anticoagulated it before returning it to his body. They closely monitored Bell for hypothermia, since loss of body temperature–accelerated during an operation because a sedated patient cannot shiver–slows clotting.

During recovery, bleeding from Bell's chest tube was carefully scrutinized. The number of blood draws taken for lab work, as well as the amount of blood taken, was held to a minimum. More Procrit and iron kept his blood count up. Bell went home just five days after being admitted.

"We've reviewed and refined pretty much every aspect of the surgical process," says Dr. Treat, "all with the patient's needs and using less blood as the goals. Avoiding transfusions and developing better methods of blood management isn't about waiting for a new tool or drug to come along. It's something we're working on now."

Progress in blood management is due in large part to a better understanding of anemia–a condition in which there are not enough red blood cells to carry a sufficient amount of oxygen to the body's tissues. While there are health risks associated with long-term anemia, it's only recently been learned that patients can cope with lower blood counts–especially on a temporary basis–than previously thought.

Normally, the average person's blood count–the level of oxygen-carrying hemoglobin in red blood cells–is about 13 or higher. Traditional practice has been to transfuse a patient if his or her count dropped below 10. Now, a movement is under way, based on established medical evidence, to change that practice so that transfusions are only performed if the blood count drops below seven or if there is a demonstrated need present.

"If a person can survive with a blood count of four, do we really need to give blood to a patient with a blood count of nine?" asks Thomas, who recently saw a patient with aplastic anemia (a condition in which the bone marrow doesn't produce enough red or white blood cells or platelets) *walk* into the hospital with a blood count of 1.9. "This was an unusual case," notes Thomas. "But it highlights the need we have for more research on blood management. We need to have a better understanding of when a patient truly needs to be transfused rather than follow just a laboratory value."

Dr. Treat agrees, saying that blood has long been viewed as "kind of a freebie," used even when it may not have been necessary. "We're not trying to stamp out transfusions by any stretch of the imagination," he says. "But we're trying to establish good blood utilization for the best interests of patients."

Mark Froimson, M.D., an orthopaedic surgeon at Cleveland Clinic, says that patients want to know that they have options. "If they're interested in a blood conservation approach to their surgery, it's available. They need to communicate with their physicians so that we can work with them appropriately."

Earlier this year, the Blood Conservation Committee was created within Cleveland Clinic. The committee's goal is to comprehensively assess and then integrate best blood conservation practices. Dr. Froimson chairs this team, which is made up of multidisciplinary specialists including surgeons and internal medicine physicians who have an impact on blood use in patient care.

"Nationally, there is very little data available on best practices in blood management," says Dr. Froimson. "However, we're such a large institution, with so many patients and surgeons, that we can look at our own data and identify opportunities to adopt new protocols. The center at Fairview has been instrumental at sharing its best practices."

What's being learned is that anemia can be managed both in the pre- and post-operation phases, particularly for non-emergency cases. "Pre-operatively, the goal is to 'buff up' or stimulate the patient to maximize his/her blood potential," says cardiac perfusionist Glenn Koyl.

When there is more time prior to surgery, something as simple as improving nutrition can enhance an anemic patient's blood production. Foods high in vitamin B2, folic acid, iron and protein–meats, poultry, green leafy vegetables, eggs–are all beneficial. They also can help post-operatively if the patient is anemic. "It does work," notes Koyl. "It just doesn't work quickly." Two to four weeks may pass before diet causes a rise in blood count.

Another method is to remove some of the patient's blood just before surgery and replace it with a saline solution that acts as a non-blood volume expander. This process, known as hemodilution, allows any blood lost during surgery to be replaced with the patient's own blood through transfusion. Hemodilution does temporarily cause anemia, but at a level tolerable to most patients.

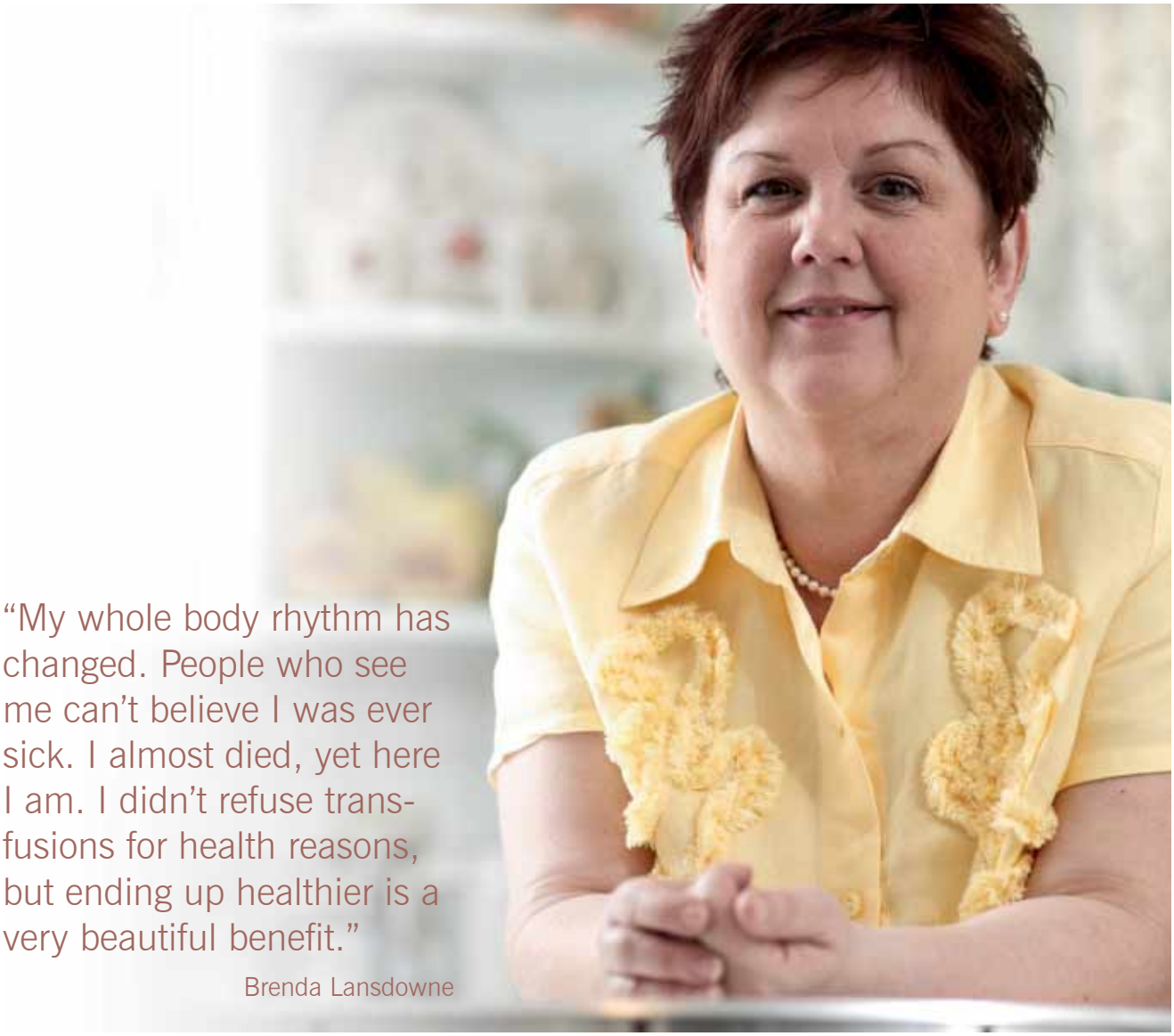
Finally, complex surgeries can be broken into component procedures performed at different times. This allows patients to rebuild their own blood over two to four weeks supported, if necessary, by medications that boost red blood cell production.

In the end, the key to better blood management is keeping blood loss at a minimum. Here, new tools are helping. The harmonic scalpel, for example, employs ultrasonic vibrations (the tip vibrates up to 55,000 cycles per second) to simultaneously cut and coagulate an incision. Another device, called an argon beam coagulator, hooks an electrical charge into argon gas, which can then be "painted" over large surfaces that need to be cauterized (such as in transplant surgery). "In the operating room, the idea is to have an awareness of blood loss and to modify surgical techniques whenever possible," notes Dr. Froimson.

"Boom! There it was," says Brenda Lansdowne of the sudden hemorrhage she suffered in February 2006. A native of East Palestine, Ohio, Lansdowne had been quietly working at home on her eBay business, selling jewelry craft supplies, when pain began hitting her in waves, "every five minutes like contractions of labor." She could feel blood leaking down her legs. "Not enough to bleed out," she says, "but it was very disconcerting." Lansdowne's son and secretary called an ambulance and she was rushed to Fairview Hospital, where a malignant tumor was found perched on her bladder. A Jehovah's Witness since age 14, Lansdowne refused blood transfusions to replace her blood loss.

Dr. Treat was on hand to administer aggressive anemia management using Procrit and iron to boost her hemoglobin, and an antifibrinolytic agent to prevent her body from breaking down clots. Two months later, James Ulchaker, M.D., of the Cleveland Clinic Glickman Urological Institute, removed Lansdowne's bladder in a seven-and-a-half-hour procedure.

Richard Treat, M.D.



"My whole body rhythm has changed. People who see me can't believe I was ever sick. I almost died, yet here I am. I didn't refuse transfusions for health reasons, but ending up healthier is a very beautiful benefit."

Brenda Lansdowne

"Dr. Ulchaker pulled me through without a drop of [stored] blood," Lansdowne emphasizes. She says her recovery has been rapid, considering how ill she was. "My whole body rhythm has changed. People who see me can't believe I was ever sick. I almost died, yet here I am. I didn't refuse transfusions for health reasons, but ending up healthier is a very beautiful benefit," she adds.

Increasingly, many of those who resist blood transfusions–up to 90 percent in Thomas' estimate–are doing so for health, rather than religious, reasons. Doubts about the safety of transfusing blood emerged in the 1970s and '80s with the transference of deadly diseases to transfusion recipients; first hepatitis B and C, then the even more lethal HIV/AIDS. During the height of the AIDS epidemic, patients sometimes refused surgery rather than risk transfusions; blood donors were too frightened to give blood; and even veteran nurses became terrified by accidental needle sticks. As a result, blood shortages became widespread.

According to the Centers for Disease Control and Prevention, more rigorous donor screening, virus-killing techniques and development of genetically engineered clotting factors have virtually halted the spread of HIV, hepatitis and other viral diseases through the nation's blood supply. However, no system is 100 percent safe. In 2003, cases of transfusion-transmitted West Nile Virus were found.

Additionally, a recent study published in both the *Journal of the American Medical Association* and *The Lancet* found that transfusions increased the rate of complications but did not improve survival rates. Other studies published in orthopaedic journals have shown a relationship between transfused patients and an increased length of hospital stay, as well as an increased number of post-operative infections.

"In general, although getting blood is safe, there may be an immunologic response that impacts a patient's response to stress and surgery," says Dr. Froimson. "Having studied the information, we're changing how we look at the trigger point when we would transfuse a patient."

"Not transfusing saves money, preserves the blood supply and generally produces better patient outcomes."

Joseph Thomas, R.N.

While the assessment of blood-management techniques has risen, wide adoption in the medical community has been slow and careful. To train other healthcare professionals on the advantages of better blood management, the Bloodless Medicine and Surgery Institute (BMSI) was created in 1997 and brought to Cleveland Clinic Fairview in 2004.

About every other month, five to 10 medical professionals from around the world attend a one-week seminar on integrated blood conservation. Within the hospital, they witness the spectrum of pre-, intra- and post-operative blood-conservation practices in daily use, with Joe Thomas focusing on pharmacology and Dr. Treat on surgical techniques. The goal is to have these professionals create and manage similar programs at their own institutions. For example, in Dhahran, Saudi Arabia, one student will be establishing the first blood-management program in the Middle East with the assistance of Thomas and Dr. Treat.

In the United States, the debate still churns. While the medical benefit is becoming clearer, some in the healthcare community worry that Procrit, clotting factors and other drugs involved are too expensive. Are the savings going to be greater than the costs? Thomas is clear: "In any program that's well run, yes."

Small community hospitals may use anywhere from 2,000 to 4,000 units of blood per year, but larger institutions can go through between 20,000 and 50,000 units in the same period. One unit of packed red blood cells, including acquisition, processing and storage, costs $600 or more.

"Overall, our cost savings, which is estimated to be hundreds of thousands of dollars each year, have clearly made up for any increase in cost associated with blood conservation medications or technologies," says Dr. Treat. And, by reducing the risk of post-operative infections, blood-management practices also shorten patients' length of stay, which further lowers costs to both patients and institutions.

Blood Counts

- **14 million** units of blood are donated annually. On average, an adult body has approximately seven to nine units of blood.
- **4 million** patients a year receive blood or blood components.

While Dr. Treat notes the importance of saving money, he underscores the fact that "blood is what's valuable. Blood is critical." In 2001, Fairview used 1,855 units of blood for all surgical services. In 2005, usage was down to 857 units, even though in many specialties the number of surgeries increased. That leaves more blood in the nation's supply to treat patients who really need it.

Meanwhile, Thomas continues to lecture at medical and nursing schools, hoping that blood conservation will one day become part of the standard medical school curriculum. "In the next five years, we have to embrace blood conservation in the broader medical community," Thomas says. "Not transfusing saves money, preserves the blood supply and generally produces better patient outcomes."

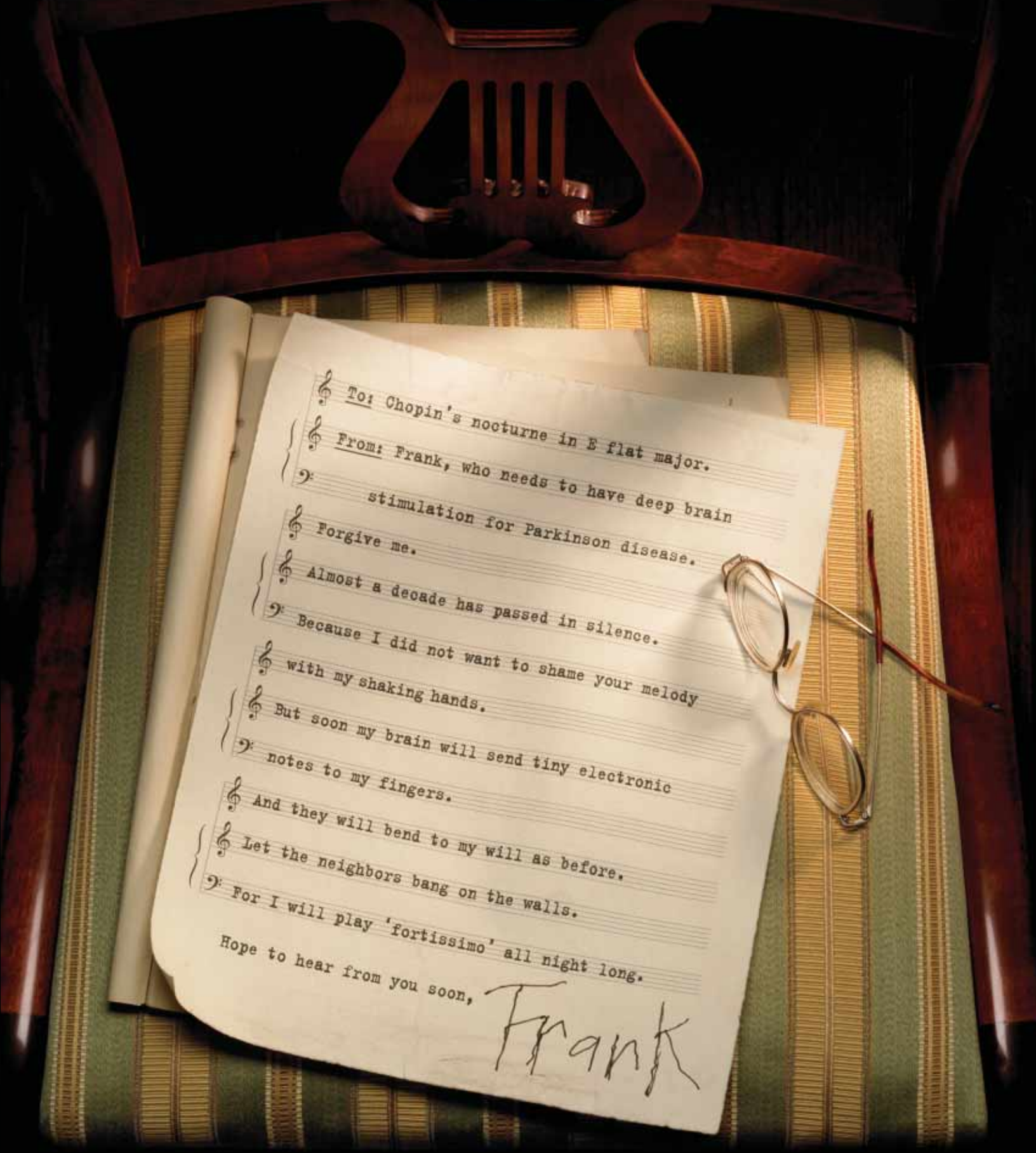
Adds Dr. Treat, "We're recognizing that better blood conservation and management is integral to everything we do."

Special Podcast: First successful human-to-human blood transfusion

On Aug. 8, 1906, Cleveland Clinic founder George W. Crile, M.D., and Harry Sloan, M.D., performed their first successful human-to-human artery-to-vein blood transfusion on the Miller brothers. Listen to an audio re-creation of this historic event, as described in Dr. Crile's autobiography published in 1947, by visiting **clevelandclinic.org/ccm.**

- **40,000 units** of blood are used each day in the United States.
- Someone needs blood every **three seconds**.
- **One in 20** Americans will require a blood transfusion at some point in their lives.
- **One person in 3** has type O+ blood.
- **One person in 167** has type AB- blood.

Source: bloodtransfusion.com



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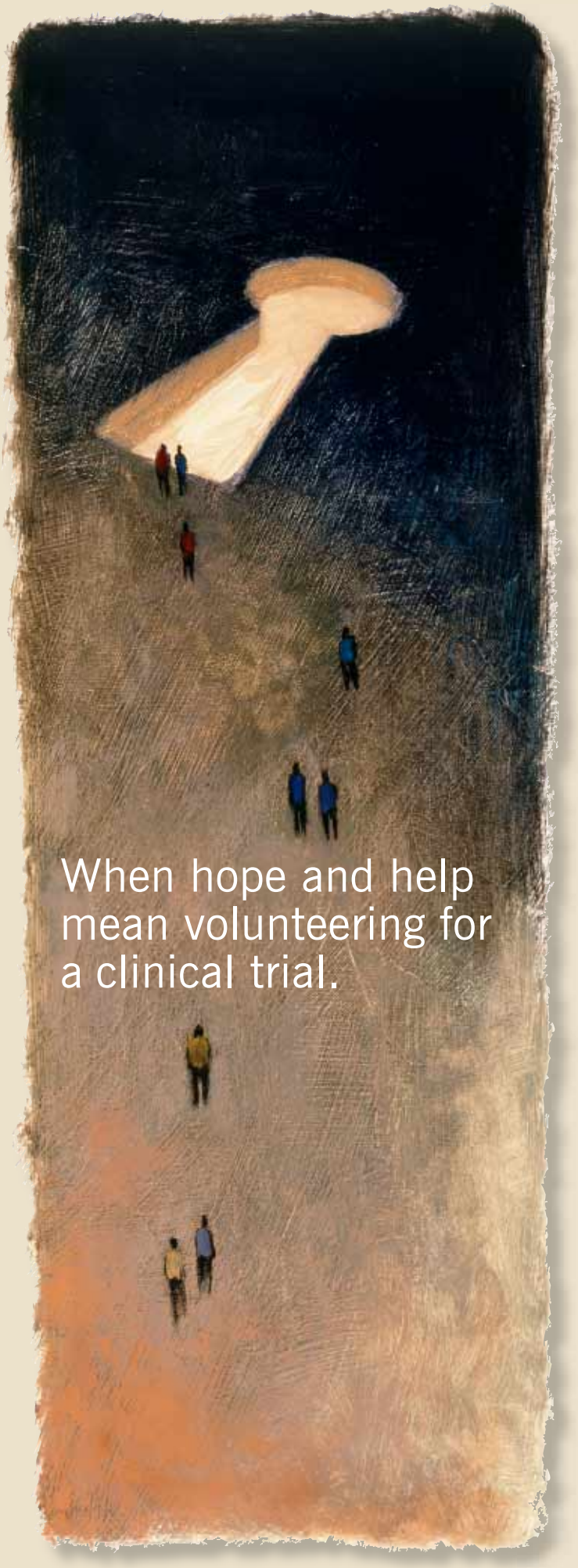
Cleveland Clinic

Trying a Trial

When hope and help mean volunteering for a clinical trial.



In "First, Do No Harm" (Spring 2006), we looked at how Cleveland Clinic's Institutional Review Board works to protect patients who participate in clinical research. In this article, we take a closer look at clinical trials and what they mean to you.

Eleanor Heffner was going blind. Slowly her sight was disappearing. First, the central vision in her right eye was replaced by a dark, fuzzy hole. A few years later, the same thing began happening with her left eye.

At 88, Heffner lived by herself and did things on her own. "I'm a do-it-yourselfer," she says. "I do my own laundry, cook my own meals, read my mail, pay my bills, and knit scarves for the U.S. soldiers over in Iraq."

Her independence, however, was being threatened by an eye disease called age-related macular degeneration (AMD). When her ophthalmologist asked if she would consider volunteering for a clinical trial, she was surprised, then thoughtful: Would she become a human guinea pig?

Clinical trials are research studies that use human volunteers and follow strict rules for volunteer protection. They are conducted to determine the safety and effectiveness of drugs, medical procedures or devices on people. In the United States, approximately 12,000 clinical trials take place annually. Medical trials cover everything from "Abdominal Injuries" to "Zollinger-Ellison Syndrome," with cancer, neurologic and cardiovascular-related studies being the most numerous. Some trials are backed by the government; others by pharmaceutical or biomedical companies. Still more are sponsored through medical research centers.

Clinical trials have been in existence for centuries. Most historical materials list naval surgeon James Lind as the "father" of clinical trials. In 1747, while at sea, Lind tested the effects of six different treatments then in use for scurvy, a disease distinguished by swollen and bleeding gums, loose teeth and bleeding under the skin. Lind examined the effects of each treatment through a controlled experiment based on observable fact rather than prevailing medical theory. Twelve sailors suffering from scurvy were divided into six pairs, with each pair receiving the same diet but a different treatment. Lind's research suggested that citrus fruits in the diet were more effective at eliminating scurvy than the other treatments he tested.

"Clinical trials are so important," says Elias Zerhouni, Director of the National Institutes of Health in a video interview with CNN news service. "There is no scientific medicine without clinical trials." Throughout the last century, clinical trials have found therapies to combat tuberculosis, HIV and many other diseases. They have proved penicillin and streptomycin, some of the most powerful antibiotics in the world, to be safe and effective.

Most patients learn about the possibility of participating in a clinical trial through their physician, although several Internet sites, such as ClinicalTrials.gov from the National Institutes of Health and MedlinePlus from the National Library of Medicine, list ongoing trials with contact information. Individual healthcare systems also may make public the various trials they are conducting. Currently, Cleveland Clinic is running more than 2,000 clinical trials.

Entering a clinical trial often produces mixed emotions and brings up myriad questions: What exactly will I have to do? Can I change my mind once I sign up? How closely are patients watched? What happens if something goes wrong?

In her well-lit office, Kathy Hammerhofer, Director of the Center for Clinical Trials at Cleveland Clinic, sits behind a desk blanketed with papers and neatly stacked files. Behind her is a shelf of books with such titles as *Designing Clinical Research, Clinical Research Law and Compliance Handbook,* and *Ethics and Regulations of Clinical Research.* Formerly the manager of an experimental therapeutics program and a research nurse, Hammerhofer has spent time in the research trenches. As part of her current role, she serves on a variety of committees designed to educate scientists about Cleveland Clinic research policies and to oversee enforcement of the regulations that guide research and protect patients.

Within an organization the size of Cleveland Clinic, the opportunities for researchers to conduct studies are infinite. So are the challenges of making those studies run smoothly. "For example, technology raises a lot of issues," says Hammerhofer. To ensure the accuracy of patient information collected for the clinical trial, independent companies are contracted. These companies receive clinical trial data, confirm their accuracy, and aggregate them to make them meaningful.

Says Hammerhofer, "We use electronic medical records, which contain a tremendous amount of information on each patient. Patient privacy is important. How much patient information does the third party need to see to do its job? We have to determine this before the trial gets under way, then make sure they only see what they need to see."

As well versed as Hammerhofer is on the topic of clinical trials, she says the public isn't far behind. "Because of the Internet and stories in the media, most people are aware that you can be in a clinical trial. Consumers have become savvier about their healthcare." She adds, however, that patients who are thinking about participating in a clinical trial need an additional level of information-gathering and option-weighing. "People need to understand what the scientists would like from them, as well as what the possible benefits and side effects of volunteering might be in a trial."

Entering a clinical trial often produces mixed emotions and brings up myriad questions, says Hammerhofer. Common questions include: What exactly will I have to do? Can I change my mind once I sign up? How closely are patients watched? What happens if something goes wrong? "Fortunately," says Hammerhofer, "among those questions and mixed emotions there is some form of hope. Hope for a better quality of life, a little more time or, best of all, a cure."

Hammerhofer says that patients enter a trial for many reasons. "Many people enter a trial to find a better medical treatment. But altruism also draws in a lot of volunteers. That desire to help unknown others in the future is quite strong. From my own experience, older individuals in particular tend to be altruistic. They often do clinical trials to help mankind."

Eleanor Heffner

For Eleanor Heffner, hope and a desire to help others were behind her decision to enter the SAILOR trial.

For patient Eleanor Heffner, hope for herself and a desire to help others were behind her eventual decision to enter the SAILOR (Safety Assessment of Intravitreal Lucentis for AMD) trial, one of several clinical trials assessing the effectiveness of the AMD drug Lucentis.

When Heffner's vision began its slow decline, her Greenville, South Carolina ophthalmologist spotted a problem in her right eye. "He didn't know what it was," she remembers, "but he thought I should see a specialist. That's when I found out that I had AMD." Heffner also discovered that she had the wet, or more severe, form of AMD. Wet macular degeneration involves new blood vessels developing underneath the retina, causing hemorrhage, swelling and scar tissue. For Heffner, this meant that her right eye would eventually have no central vision and, in time, she would only be able to see the edges of what she viewed.

Two years after her initial AMD diagnosis, Heffner–who now lives in Northeast Ohio–began losing some vision in her left eye. "I called my physician and he said that, since this is my second eye, I might want to consider other options," she recalls. "That's when he mentioned that Cleveland Clinic was testing a new medication in a clinical trial. He said I could be a candidate for it if I chose to be." Heffner contacted Cleveland Clinic, reviewed the trial information and decided she wanted to volunteer. But first, she had to be accepted into the trial.

"Not everyone who volunteers for a trial can be a participant," says Hammerhofer. "The physicians have strict inclusion rules they must adhere to. Only certain volunteers fit the trial criteria."

As part of the trial enrollment process, Heffner had to submit a detailed medical history along with a list of her medications to ensure that nothing would interfere with the drug being tested. Anyone who volunteers for a clinical trial also will be asked to sign a consent form that explains the purpose, procedure, risks and benefits of the trial. In the form, volunteers must indicate they understand and agree to the terms of the trial. Additionally, would-be participants undergo a certain amount of testing, which includes having a physical examination and blood drawn.

While she waited to hear about her application, Heffner also began to prepare herself for eventual blindness. She purchased a large-print telephone and had Braille instructions attached to her stove. "I did enough to take care of myself," she says. "I think it's the worst thing that can happen–losing your eyesight completely. Even if I joined the trial, nothing was guaranteed. Still, I was hopeful and ready to try."

Clinical trials that test new drugs commonly progress through four phases. In Phase 1, the medicine or treatment has been safely tested in lab work and is ready to be tested on humans. Phase I trials involve a small number of people who test the drug or procedure's safety, helping researchers learn everything from possible side effects to how much medicine should be given and how the treatment should be applied.

Scientists and doctors involved in Phase 1 testing have every reason to believe the drug or treatment is safe and will lead to successful or at least improved treatment, but entering a Phase I clinical trial is a risk for the patient. That is one reason why Laura Holody, a clinical trial coordinator, advises interested patients to "review the consent form, understand what they're doing, and don't be afraid to ask questions of the coordinator or the doctor. You need to be fully informed."

In her role as trial coordinator, Holody is the point person between the patient and the doctor. If the physician investigator can be looked at as the "pilot" of a clinical trial, Holody is the "navigator," ensuring the flight is a smooth ride and that nobody gets lost. She oversees the scheduling, paperwork, interviewing of prospective patients and the details that go into managing a clinical trial.

Holody says that a common misconception patients have about volunteering for a trial centers around the use of inactive substances, or placebos. Generally, trial participants do not know if they are getting the medicine or a placebo. "Although placebos are frequently used in clinical trials, they are not used in Phase I trials," says Holody. "Patients who enter Phase I trials are desperate for any benefit. They need that treatment."

In Phase II trials, investigators have determined that the medicine or treatment isn't likely to make patients worse. "In Phase II, the question for investigators and patients then becomes, 'Is the drug generating the effect you want?'" says Holody.

Phase III increases the number of people involved in the study, as researchers probe for side effects. For example, physicians may know that the medicine being studied treats blood pressure effectively, but if it raises cholesterol in the process, that effect may negate the merits of the drug. The SAILOR trial, in which Eleanor Heffner is participating, is a Phase III study. In that trial, the drug Lucentis is being studied for effectiveness and side effects in AMD patients, having done well in Phase I and Phase II trials.

By Phase IV, the medicine has been approved for wide distribution and is being sold, but studies still continue. In fact, drug studies never really end. For example, in 2004, data from an ongoing long-term study showed that Vioxx–a non-steroidal anti-inflammatory drug that was approved by the Food and Drug Administration in May 1999 for the relief of osteoarthritis, management of acute pain in adults and treatment of menstrual symptoms –potentially doubled the patient's long-term risk of heart attack or stroke. Though the drug had been sold for five years, the study results led the manufacturer to voluntarily withdraw it from the market.

Cleveland attorney John Carson knows he is at risk. Carson, 76, is one of 15 million people living with type 2 diabetes. In addition to the increased risk for blindness, stroke and complications related to poor circulation, people with type 2 diabetes die of cardiovascular disease at rates two to four times greater than people of similar age without diabetes. That's one of the primary reasons why Carson volunteered to participate in a five-year study called ACCORD (Action to Control Cardiovascular Risk in Diabetes). This National Institutes of Health trial, which has 10,000 adults participating at 70 clinics around the United States and Canada, is designed to test three complementary medical treatment strategies for preventing cardiovascular disease in people with type 2 diabetes.

"One of the things I wondered about before I volunteered was how much I'd be monitored," says Carson. He smiles, "I found out the answer–very closely."

During the trial, participants are connected to a network of medical professionals who are rigorously watching them. Everyone involved is aiming for the same outcome: improving the patient's health. To do that, and to ensure that success can be repeated for future patients, close monitoring is critical.

"I kind of enjoy it," says Carson. "They set the appointments, and you're seen right away. In my trial, they take your blood and your blood pressure. They review your medications with you and tell you what your glucose reading is that day. They let you know where they want your blood sugar to be, and they monitor your health closely. They also supply all of the medications related to the study."

Kathy Hammerhofer

Stages of a Clinical Trial

PHASE I: Researchers test an experimental drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range and identify side effects.

PHASE II: The experimental drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.

PHASE III: The experimental study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments and collect information that will allow the experimental drug or treatment to be used safely.

PHASE IV: Post-marketing studies delineate additional information including the drug's risks, benefits and optimal use.

Reprinted from ClinicalTrials.gov, a service of the National Institutes of Health.

Participants in the ACCORD trial will be treated and followed for up to eight years. Follow-up is scheduled to end in June 2009, with the primary results announced in early 2010.

One question volunteers often have is what happens when a trial ends? According to Clinical Trials Director Kathy Hammerhofer, the answer varies. If the trial has been to test a medication, FDA approval means patients can continue using the drug, most often by obtaining it through commercial channels. If the treatment is not approved, a new trial may be designed or, just as likely, developmental work on that drug will end.

In some cases, a trial may end with bad results overall, but the drug worked for a subgroup of people. In this situation, getting access to the medication for those who need it is much more problematic. Says Hammerhofer, "Every case is different. If a patient is seriously ill, and a helpful medicine isn't available any longer through a clinical trial, some drug manufacturers have a program known as 'compassionate use.' This allows the use of an investigational drug outside of an ongoing clinical trial for a limited number of subjects who are desperately ill and for whom no standard treatment is available."

Additionally, says Hammerhofer, the FDA now has an expanded access program (EAP), which makes experimental medications more widely available to severely ill patients who have life-threatening diseases. EAPs also can speed the review and approval of the applications of these drugs.

"Getting approval to use a medication that is not approved by the FDA and not in a controlled clinical trial is a complex process," notes Hammerhofer. "In those situations, the FDA must approve everything on a case-by-case basis. But it is an option for patients who have a life-threatening illness."

In June 2006, the FDA approved Lucentis, the drug Eleanor Heffner is taking as part of the SAILOR trial. That approval was based on the results of two different trials in which nearly 95 percent of the participants reported that they had maintained their sight, versus the 60 percent who received the placebo.

Continuing with the SAILOR trial, Eleanor Heffner says that she has definitely seen her vision, if not improve, at least stabilize. For now, she says, she has set aside her large-print telephone and she ignores the Braille instructions on her stove. She visits Cleveland Clinic every month for her Lucentis treatment and is closely monitored as part of the trial, which will end later this year. After that, if her eyesight continues to be stable, she'll receive her Lucentis treatment through her personal ophthalmologist, who will monitor her eye condition.

How does Heffner feel now about being a human guinea pig? She laughs, "Of course I'm glad I'm in this trial. I want to keep my eyesight as long as I can." Then she adds, "Some things you have to do. After all, where would any of us be if we didn't take a chance?"

For more information on clinical trials, go to clevelandclinic.org and click on "Research and Clinical Trials."

Learning the Language

Information on clinical trials abounds with jargon. Here's a quick primer on those unfamiliar words:

BASELINE: Information gathered at the beginning of a study that can influence an outcome. This information includes a volunteer's medical history, list of current medications and physical condition.

DIAGNOSTIC TRIALS: These are conducted to find better tests or procedures for diagnosing a disease or condition.

DOUBLE-BLIND STUDY: In the name of objectivity, these are studies in which neither the volunteers nor the staff know who is receiving the experimental drug and who is receiving a placebo or different therapy.

ORPHAN DRUGS: The cost of developing a new drug is high. To encourage drug companies to dedicate resources toward finding cures for rare diseases (defined as diseases or conditions affecting fewer than 200,000 people in the U.S.), the government offers tax reductions and a marketing monopoly on these drugs that lasts longer than the average 20 years of patent protection. This expanded time allows the company to recover its investment money and encourages it to invest in cures for other rare diseases.

PREVENTION TRIALS: These trials look for better ways to prevent diseases in people who have never had the disease. Expect a trial to contain anything from medicines to vitamins to minerals or lifestyle changes.

QUALITY OF LIFE TRIALS: Also called supportive care trials, these explore different strategies for improving the quality of life for people with a chronic illness.

SCREENING TRIALS: These look for the best way to detect certain diseases or health conditions.

TOXICITY: A negative effect produced by a drug that is bad for the participant's health.

TREATMENT TRIALS: These involve new treatments, drug combinations or approaches to surgery or radiation therapy.

Founder of Development Makes His Mark

F. Joseph Callahan's fundraising principles drive two influential campaigns.

When F. Joseph Callahan supports a cause, he works relentlessly. He approaches fundraising goals with carefully mapped strategies–ideas that have helped define two of Cleveland Clinic's most comprehensive campaigns.

"Joe often is thought of as the founder of development here," says Carol Moss, Acting Chairman of Institutional Relations and Development. "Many of the strategies he suggested in his tenure are used today."

In his 17 years as a force behind Cleveland Clinic fundraising campaigns, Mr. Callahan served as chairman of the *Securing the 21st Century* campaign, a $225 million drive to construct three world-class facilities: the Cole Eye Institute, Taussig Cancer Center and Lerner Research Institute.

He and his wife, Barbara, are honorary chairs of the current $1.25 billion campaign, *Today's Innovations, Tomorrow's Healthcare*. Embodied by four cornerstones–innovative patient care, basic and clinical research, medical and patient education, and a campus master plan–the current campaign seeks to support Northeast Ohio's economic development while strengthening Cleveland Clinic's resources.

"This requires requesting funds from outside the region," Mr. Callahan says. During his time as chairman of the 21st Century Campaign, Mr. Callahan advised the fundraising committee to broaden its geography when seeking board members. He adds, "If you're going to get anywhere today, you have to go all over the world."

While Mr. Callahan was executive vice president of Swagelok, he applied principles he learned as a submariner in World War II to business, insisting on quality people. This helped him grow the enterprise from $2 million to more than $800 million.

An entrepreneur, adviser, investor and philanthropist, Mr. Callahan sticks by his rule, "If you quit the rat race, the rats will win." This same fierce will to succeed trickles down to his passion to give back. He writes in his memoir, *Shoot for the Pin*, "I have always felt that it is important to give of your time and finances in support of worthy causes for the betterment of the community."

When his children were in school, he supported Junior Achievement and the Boy Scouts, and served as chairman of the board for Gilmour Academy. He also has served on hospital boards continually since 1978, starting at Marymount Hospital in Garfield Heights, Ohio. This evolved into a position on the board at Cleveland Clinic in 1990 and, since then, he has served on five different committees.

Barbara Callahan reflects on her husband's time at Cleveland Clinic after suffering a stroke six years ago. "He has just never given up," she says of his energy. "He has a ton of integrity and he's just very honest."

Mr. Callahan adds that he experienced how breakthrough science and development deliver the world-class care Cleveland Clinic promises to each patient–him included. Today, his twice-weekly physical therapy sessions are helping him get back into his beloved game: golf.

Shoot for the pin, Mr. Callahan explains, is his general life philosophy. "An objective, once determined, should be pursued relentlessly and without compromise. This has been my approach in business, fundraising and golf."

Philanthropy is New Career for Jane and Lee Seidman

Gift of $17 million creates Functional Neurosurgery Chair.

When businessman and philanthropist Lee G. Seidman spoke at the Cleveland Clinic philanthropy campaign launch, he opened by saying, "We've made a $17 million gift to Cleveland Clinic. The only problem is, we don't have $17 million."

When the laughter subsided, he more seriously shared his approach to philanthropy and his commitment to maximizing personal giving. "Many people under-give in relation to their worth," he explains candidly. "You can happily give more than you think you can, without impacting your chosen lifestyle."

A sincere desire to help people, coupled with a lifelong affection for the Cleveland area, are the driving forces for Lee and his wife, Jane. Born and raised in Cleveland, a graduate of Shaker Heights High School, with degrees from Cornell Hotel School and the Harvard Business School, Mr. Seidman started selling cars at a downtown Cleveland dealership in 1954. "They gave me a desk and a phone to begin my 'temporary' career," he smiles.

During the subsequent 52 years, Mr. Seidman has managed 35 different automotive franchises, primarily from Europe and Asia. In 1964, he founded, and still chairs, The Motorcars Group in Cleveland. Over the years, different members of his large, extended family helped him financially, and today he credits them as his philanthropy role models.

"Achieving financial success and independence can be a lot of fun, but at some point you realize that you've met the needs of you and your family. At that point, you hopefully will shift gears from accumulating to allocating," he states emphatically.

Through a friend, the Seidmans developed contact with Cleveland Clinic and in 2004 made a $1 million gift to the new Heart and Vascular Institute. They subsequently met neurosurgeon Ali Rezai, M.D. That introduction has developed beyond a strong friendship into a passion to support medical research. "We feel as though we're part of the Cleveland Clinic family. We want to help the Clinic's Heart-Brain Institute pursue medical advances that focus on diseases originating in the brain," Mr. Seidman says with passion.

When the Seidmans contemplated making a larger gift to Cleveland Clinic, they consulted with the hospital's development experts on the most effective way to structure their donation. The result is their $17 million gift.

As he approaches his 75th birthday, Mr. Seidman still spends part of each week in the automobile world, but he considers philanthropy his and Jane's "new career." He reads volumes on the subject and carefully studies the most effective philanthropic models. Although he has spent decades in the driver's seat of a business empire, Mr. Seidman finds great satisfaction in this second career. "I was taught to lead by example," he says. "Jane and I hope that others will step forward and follow our path."

Foundation Assists Physician's Cancer Care Study

Grants from the Elisabeth Severance Prentiss Foundation support bone marrow transplant patient care project.

The five board members of the Elisabeth Severance Prentiss Foundation are not easily impressed. Before a typical board meeting, they review stacks and stacks of funding requests.

However, when one of those stacks yielded a proposal from Brian Bolwell, M.D., Director of the Cleveland Clinic Bone Marrow Transplant Program, the board members immediately took notice. "We look for programs and projects that will have an impact on patient care for the people of Cleveland," explains board member Pamela Alexander. "Dr. Bolwell's proposal interested us because of its unique design and because, while it has great impact locally, it also has much broader implications."

Dr. Bolwell sought funding for a study that involves comparing the long-term outcomes of bone marrow transplant patients with and without consistent caregivers. "As we studied his proposal and his initial findings, we became convinced that Dr. Bolwell's work could lead to a breakthrough in the way medical professionals think about healthcare delivery," Alexander says.

Elisabeth Severance Prentiss, heir with her brother John to the Severance fortune, established the foundation that bears her name in 1939 after the death of her second husband, Francis Fleury Prentiss. Inspired perhaps by her first husband, renowned physician Dr. Dudley Allen, she specified that the Prentiss Foundation's sole mission and grant-making focus be to improve healthcare for Greater Clevelanders.

The foundation's original mission has endured, despite overwhelming changes in medicine and healthcare delivery. "Our focus today stays true to Mrs. Prentiss' vision 70 years ago when the foundation was established," Alexander states with pride. "Under the 'General Purposes' outlined in the original trust agreement, this specifically includes supporting programs that may not receive funding from other sources."

Dr. Bolwell's revolutionary work fits the bill, having received considerable attention in the field of cancer care but no federal funding to date. Earlier this year, the Prentiss Foundation gave $1.9 million to support his research. Dr. Bolwell hopes to replicate the results of his original retrospective study in which transplant patients with a consistent caregiver had much better three-month survival rates than did those without a caregiver.

"Understanding the impact of psychosocial factors is a vital aspect of cancer care," Dr. Bolwell says, explaining the focus of his research. "It's part of our commitment to treating cancer patients with empathy and understanding."

Dr. Bolwell's passion for the importance of the non-medical aspects of cancer treatment resonated with the Prentiss Foundation's board members, Alexander says. "Dr. Bolwell has an exceptional perspective on what makes a difference in healthcare, beyond the medical and technological. We believe that the foundation's support will help him take cancer treatment to the next level."

Campaign for Cleveland Clinic Will Raise Patient Care to New Levels

Today's Innovations, Tomorrow's Healthcare raises **$811 million** to date.

Philanthropy has many manifestations at Cleveland Clinic hospitals. It helps families battling cancer at Hillcrest Hospital find solace in surroundings dedicated to their needs. It supports Lerner College of Medicine students pursuing careers as doctors dedicated to seeking cures. And philanthropy is erecting the complex that will expand Cleveland Clinic's capacity by nearly 50 percent.

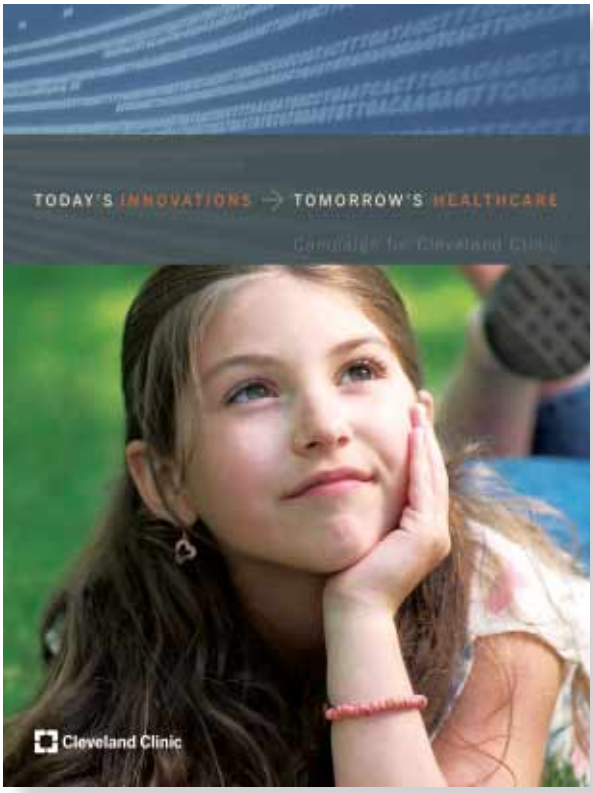
These initiatives are all made possible by supporters of *Today's Innovations, Tomorrow's Healthcare: Campaign for Cleveland Clinic*, one of the largest campaigns for a not-for-profit academic medical center in the United States.

At the end of 2006, *Today's Innovations, Tomorrow's Healthcare* surpassed $811 million in support for the campaign's four cornerstones: patient care, research, education and a campus master plan. The goal of Cleveland Clinic's public philanthropic campaign is to raise $1.25 billion by 2010.

"As we experience an enormous demand for services, this unprecedented public initiative will raise patient care to new and necessary levels," says Delos M. Cosgrove, M.D., CEO and President.

The Campaign for Cleveland Clinic offers patients, friends, and community-minded individuals and organizations an opportunity to show their support in a meaningful way.

For more campaign information or to make a donation, go to clevelandclinic.org/giving, e-mail campaign@ccf.org or call 216.444.1245.



Blood Test to Detect Thyroid Cancer

About 30,000 new cases of thyroid cancer are diagnosed annually, according to the American Cancer Society. In some cases, thyroid cancer is not easy to detect, even when a patient undergoes a biopsy. A simple blood test developed by Cleveland Clinic researchers, however, may significantly improve how the cancer is discovered and monitored.

Although fine-needle aspiration biopsies can detect about 70 percent of thyroid cancer cases, 30 percent of biopsies cannot confirm the presence of cancer cells. As a precaution, most patients whose biopsies are indeterminate undergo surgery to remove the thyroid gland that regulates metabolism. Post-operative testing on the gland, however, usually reveals benign cells, making the surgery unnecessary.

After more than six years of research, Manjula Gupta, Ph.D., a staff researcher for Clinical Pathology and Endocrinology, Diabetes and Metabolism, has developed a blood test that may someday reduce many of those unnecessary surgeries.

"We've known for years that some cancer cells can dislodge from a cancerous tumor or nodule, and slip into the bloodstream," says Dr. Gupta. "We needed a way to discern those cells. Our blood test can detect high levels of thyroid stimulating hormone receptors, which means there is a high likelihood that cancer is present."

In a study of 72 patients, the accuracy of the blood test in detecting thyroid cancer was 89 percent. Results of the study were published in the *Journal of Clinical Endocrinology and Metabolism* last year.

Dr. Gupta's blood test also can be useful in detecting the recurrence of cancer. Currently, doctors can monitor for cancer recurrence through a serum thyroglobulin test. However, about 25 percent of thyroid cancer patients have antibodies to thyroglobulin. These antibodies can interfere with thyroglobulin testing, leading to false results depending on the method used.

"We believe our blood test will add value in detecting cancer recurrence for those patients who have built up thyroglobulin antibodies," Dr. Gupta says. "This can help doctors more accurately monitor the recurrence rate."

New Virus May Be Linked to Prostate Cancer

Researchers at Cleveland Clinic, working jointly with investigators at University of California, San Francisco, have discovered a new human virus that may be related to prostate cancer. If the virus is found to be a part of the cause of prostate cancer, new research could lead to antiviral agents or vaccines.

The longstanding investigation of the gene RNaseL has led Robert Silverman, Ph.D., Cancer Biology, and Cleveland Clinic colleagues Eric Klein, M.D., Glickman Urological Institute, and Graham Casey, Ph.D., Cancer Biology, to identify the new virus XMRV–the first report of such a virus in humans.

Researchers found the virus by screening tissue samples from prostate cancer patients. A full report of the discovery, co-authored by the researchers, appeared in *PLoS Pathogens* in 2006.

For more than a decade, Dr. Silverman has been working with RNaseL, which defends the body against viruses. Drs. Silverman and Klein speculated that a virus might explain why men with mutations in the RNaseL gene have increased risk of developing prostate cancer. The investigators used a special virus computer chip, which is loaded with more than 20,000 snippets of genetic material from all known viruses, to check for the presence of any one of 950 different types of viruses in prostate tissue samples. The results were surprisingly clear: In tumor samples from 20 men with a specific mutation in both copies of the RNaseL gene, eight showed the presence of XMRV, while only one man in a group of 66 with at least one normal copy of the gene had the virus.

Drs. Silverman and Klein have discussed some implications of the finding of XMRV in tissues from prostate cancer patients. No one knows how humans acquired the virus, which is similar to a virus that causes leukemia in mice. Dr. Silverman says that "discovery of a new virus, especially in humans, doesn't happen every day." Although the collaborators "have not proven that this virus causes prostate cancer, these discoveries do ... open up a new avenue for prostate cancer research," he says. "If we can establish that this virus is part of the process leading to prostate cancer, then there are strategies that one could take to block the virus, such as antiviral agents or vaccines." It may take another five years to prove such a connection.

To Chemo or Not to Chemo in Breast Cancer

Not all early-stage breast cancer patients benefit from chemotherapy. The trick is to figure out who will benefit and who will not–before going through chemo. To make that determination, Cleveland Clinic is participating in a new nationwide breast cancer study, sponsored by the National Cancer Institute (NCI), called Trial Assigning Individualized Options for Treatment, or TAILORx. Researchers expect to enroll 10,000 women at 900 sites in the United States and Canada who have been diagnosed with breast cancer that has not spread to the lymph nodes and whose tumors are fed by estrogen. G. Thomas Budd, M.D., will oversee the TAILORx study at Cleveland Clinic.

More than 212,000 cases of breast cancer are diagnosed annually. It is the most frequently diagnosed cancer in women, according to the NCI. Almost 50 percent of these women have estrogen-positive, lymph node-negative breast cancer. For about 80 percent of those women, standard treatment includes surgery, as well as radiation and hormone therapy. Although chemotherapy also is recommended for most patients, the proportion of women who benefit from chemotherapy is small, reports the NCI.

Chemotherapy is more tolerable than it has been in the past, but it can still produce short-term side effects such as low blood counts, loss of appetite, fevers, rashes and long-term or more serious health problems such as organ damage, heart failure and susceptibility to other cancers, notes Dr. Budd. If the study determines which patients won't benefit from chemotherapy, unnecessary treatments and patient risk may be prevented.

TAILORx will use a molecular profiling test, called Oncotype DX, to help predict which patients are likely to benefit from chemotherapy. This test analyzes the expression of certain genes in breast tumors and can more precisely estimate a woman's risk of cancer recurrence than the standard characteristics physicians normally use to assess recurrence risk, such as tumor size, tumor grade and other characteristics of the tumor.

The Oncotype DX test results provide a recurrence score. For women with a recurrence score of 10 or less, there is a low risk for recurrence with hormonal therapy. For patients with recurrence scores of 26 or higher, the risk of recurrence is about 30 percent with hormonal treatment alone. That recurrence rate can be reduced by 10 percent with chemotherapy treatment.

However, for patients with midrange recurrence scores, from 11 to 25, it is uncertain whether chemotherapy is beneficial, says Dr. Budd. About 44 percent of patients are estimated to have a recurrence score within this range.

"Those midrange patients who participate in this research study will be randomized for treatment," Dr. Budd says. "This means that some patients will receive hormone therapy, and other patients will receive hormone treatment plus chemotherapy. We're hoping that this study will tell us which women will most likely benefit from chemotherapy and which women won't. The goal is to avoid as much unnecessary therapy as possible and to give the right treatment to the right patient."

Bruce Trapp, Ph.D.

Reversing Evolution to Cure Disease

About 400 million years ago, terrestrial vertebrates diverged from bony fish to start an evolutionary march out of the water, toward living on land and breathing air. That Paleozoic Era footnote turned out to be an important clue to Lerner Research Institute scientists who are investigating the function and protein composition of myelin, the membrane that encases, protects and nourishes nerve fibers, and that is often the target of human diseases.

The research was highlighted in the *Journal for Cell Biology* in 2006. It could lead to new therapies for the acquired and inherited myelin diseases, such as multiple sclerosis (MS) and Pelizaeus-Merzbacher disease, a degenerative disease of the brain caused by mutations in myelin proteins.

"The nervous system consists of billions of nerve cells interconnected by axons or wires," says Bruce Trapp, Ph.D., Chairman of Neurosciences with the Lerner Research Institute and principal author of the study. "Myelin is like the insulation around an electric wire. It increases the speed of the electrical impulses that travel down the nerve fibers, which move our muscles and control our thoughts." Without myelin, we would not be able to function or survive.

"Myelin also provides nutritional support that is critical to long-term survival of the nerve fibers," Dr. Trapp says. "Knowing this is important to understanding the cause of neurologic disability in diseases of myelin. For example, in multiple sclerosis, patches of myelin are destroyed by the immune system. Initially, the demyelinated axons survive and maintain function. But over time, because of the loss of nutritional support from myelin, the demyelinated axons degenerate. This degeneration causes the irreversible neurologic disability in MS patients." A better understanding of how myelin helps the axons to survive will allow researchers to identify new drugs that could delay or stop the degeneration.

What does all of this have to do with evolution? As the terrestrial vertebrates emerged from water, the chemical composition of myelin underwent a dramatic change. A new protein, called PLP, became the major component of central nervous system myelin. And the old protein, called P0, disappeared.

Dr. Trapp wondered whether the evolution of PLP might have brought a new function to central nervous system myelin that was related to the survival of axons. To address this possibility, the investigators essentially reversed evolution by producing a model that had the ancient protein P0 instead of the new protein PLP.

Dr. Trapp and his team found that models with P0 as the major component of central nervous system myelin (much like the bony fish) had diminished motor function and a higher mortality rate. They also found that disability was caused by the degeneration of myelinated axons.

"In short, we found that normal expression of PLP is essential for long-term survival of central nervous system axons in mammals," Dr. Trapp says. "Studying the evolutionary process and applying it to today's models allowed us to confirm PLP's critical role in nervous system function."

Several implications emerge as a result of this research. "Mutations in PLP cause certain diseases," Dr. Trapp says. "Replacing the PLP may be beneficial to those with these diseases. Also, if we can determine how PLP makes the axon happy, we may be able to develop therapies that mimic this effect. In other words, we could make the axon believe it's myelinated when, in fact, it is not."

Elasticity May Be Key to Female Prolapse

Giving birth is a life-changing experience for all women. But years after their pregnancy is over, many women can suffer from female pelvic floor disorders (FPFD), a group of conditions that include pelvic organ prolapse, incontinence and other abnormalities. Although FPFD is not life threatening, it affects at least a third of adult women and has a significant impact on their quality of life.

Prior research has established that genetics, aging and vaginal childbirth are risk factors for development of FPFD. However, researchers still don't fully understand why.

Assistant Professor Margot Damaser, Ph.D., Biomedical Engineering and the Glickman Urological Institute, wants to find the answer. "We are working on the basic science level to figure out what may cause FPFD and how we can treat it nonsurgically, or perhaps even prevent it from happening," says Dr. Damaser.

Female reproductive organs are rich in elastic fibers. Pregnancy and childbirth can damage these fibers, along with organs and structures of the pelvic floor. The elastic fibers must recover for the organs of the pelvic floor to regain their flexibility and shape.

Dr. Damaser is part of a research team that identified the protein, lysyl oxidase-like-1 (LOXL1), as essential to the formation and health of elastic fibers in female pelvic organs and tissues. She was co-author of the research report that appeared in *The American Journal of Pathology.*

During their research, scientists found that LOXL1 deficiency caused the reproductive organs in the models they used to be unable to replenish their elastic fibers after giving birth. Researchers believe this lack of elasticity can lead to FPFD.

Dr. Damaser surmises that some women may have a genetic disposition to a LOXL1 deficiency, which may prevent the elastic fibers from rebounding after birth. Researchers do know that LOXL1 levels remain unchanged in the lungs and aortas, but vary in pelvic organs in normal models during pregnancy. This suggests that the levels of the protein found in reproductive tissues may be regulated by the reproductive hormones in those tissues during pregnancy and birth.

"As we continue our research, we want to find out what it is about pregnancy and delivery that disrupts the tissues' elasticity and requires repair," says Dr. Damaser. "Could it be the hormonal changes of pregnancy or the vaginal delivery itself, or both?"

If women with FPFD have a LOXL1 deficiency, it's possible that a treatment to restore LOXL1 could be developed to recover lost elasticity. Dr. Damaser notes, "Even if no link between FPFD and LOXL1 is found clinically, an effective treatment might still be possible by boosting LOXL1 or elastin expression at the time of greatest need, such as just after delivery to prevent the development of FPFD at a later time."

"Forced Exercise" Might Improve Parkinson's Symptoms

Can exercise alleviate the symptoms of Parkinson's disease? Lerner Research Institute researchers are exploring the possibility.

Jay Alberts, Ph.D., Biomedical Engineering, is examining the effects of exercise using a specially designed tandem bicycle that independently measures and monitors patients' performance, power and pedaling rate.

Riding in tandem with an experienced cyclist increases the cadence of a patient with Parkinson's disease, which may in turn cause biochemical changes that improve disease symptoms. Researchers are looking at the possible mechanisms underlying improvements.

The study was inspired when Dr. Alberts observed a relationship between pedaling at a higher rate and improved motor symptoms in Parkinson's patients during and after a weeklong 450-mile ride across the state of Iowa. One rider said she felt like she didn't have Parkinson's at all during the ride and that the tremor in her hand was alleviated.

Most previous interventions using exercise in patients allowed them to set their own exercise rates, which yielded mixed results.

"Our initial data suggest that Parkinson's patients need to perform 'forced exercise,' in which they are forced to exercise at rates higher than they can achieve on their own," Dr. Alberts says. "With the tandem intervention, patients pedal at rates 40-60 percent faster than they can achieve on their own. We believe this driving of the central nervous system may be necessary to produce the underlying biochemical changes that need to occur to improve motor function.

"From a patient's perspective, this is a simple intervention that can be done with a spouse or any other able-bodied individual. The next steps are to understand the mechanisms underlying improved function." Dr. Alberts hopes to discover the minimum dose necessary for improvements to occur, if the effects are long-lasting and if forced exercise of this kind slows the progression of Parkinson's.

Fighting Inflammation With Fish Oil

Chronic inflammation is a leading marker for conditions such as stroke, Alzheimer's, diabetes, rheumatoid arthritis, Crohn's disease and many more diseases associated with aging. Every disease has inflammation as part of its process–even heart attacks.

Tanya Edwards, M.D., Director of the Center for Integrative Medicine, discusses managing inflammation using fish oil and an anti-inflammatory diet.

"I can't tell you how many things I've seen go away. I hate to make such blanket statements, after all, I'm a scientist and a skeptic, but fish oil is the best thing in complementary and alternative medicine."

Tanya Edwards, M.D.

WHAT CAUSES INFLAMMATION?

Inflammation comes in two forms: the kind you can see when you cut, scrape, bruise or burn your skin, and the more dangerous type known as chronic internal inflammation. This second kind of inflammation can be life-threatening. Inflammation has to do with the natural oxidation process of the body. Our bodies use food to produce energy. When food metabolizes, it causes the release of natural by-products called oxygen radicals. When we eat an excess of saturated and trans fats, which come mainly from animal products, our bodies produce way too many oxygen radicals, also called free radicals. These unstable molecules steal electrons from healthy cells. This can lead to inflammation.

HOW DOES DIET AFFECT THE INFLAMMATION PROCESS?

People really underestimate the damage caused by a lifestyle full of hamburgers and french fries. If you look at the eating history of the human species, you see that we've moved away from a diet where the ratio of omega-6 (primarily from red meat) to omega-3 essential fatty acids (from fish, plants and nuts) was 1-to-1. In the last 50 years, that ratio has gone anywhere from 16-to-1 to 25-to-1 depending on which research you reference. This increase is cause for concern.

HOW CAN FISH OIL SUPPLEMENTS AVERT THIS PROCESS?

Some studies show that getting the diet back to a ratio of 3-to-1 means a significantly decreased risk for everything from skin cancer to high blood pressure. Here's how it works: Proper diet and supplements with highly anti-oxidant properties donate an electron to free radicals, thereby eliminating the cause of inflammation. When we eat diets high in good oils–polyunsaturated and monounsaturated fats–the body turns them into anti-inflammatory molecules. Adding

a fish oil supplement ranging from 2,000 milligrams to 6,000 milligrams each day often can counteract the cell damage caused by free radicals. This means that many age-related diseases brought on by inflammation become less inevitable.

CAN YOU EVER EAT ENOUGH FISH TO GET A HIGH DOSAGE OF FISH OIL?

Probably not, although incorporating fish into an anti-inflammatory diet is recommended and healthy.

HOW HAS FISH OIL HELPED YOUR PATIENTS?

Here's a recent example: A patient of mine, a new mother, has a 6-month-old baby with a bad case of eczema. The baby was only taking breast milk at the time, and I thought it might be an allergy. Allergies also are caused by inflammation. I directed the mother to take fish oil supplements herself and continue breastfeeding. Within a few days her baby's eczema disappeared. Then, after she stopped taking the fish oil, the child's condition returned.

Another patient of mine lowered her blood pressure from 150/90 to 125/75 with the addition of fish oil supplements. A co-worker reduced her flare-ups of Crohn's disease from every week to none at all after a six-week regimen. It's also a good supplement to take for overuse injuries and chronic pain.

There are many examples out there. According to new research findings from Indiana University, reported in the January 2006 issue of the journal *Chest*, people suffering from exercise-induced asthma were able to reduce their symptoms below the threshold used to diagnose the disease by eating a diet supplemented with fish oil.

ARE THE MERCURY OR PCB LEVELS IN FISH OIL DANGEROUS?

Studies have shown that the processes used to filter the fish oil also filter out mercury and PCBs.

WHAT CAN YOU DO IF YOU'RE ALLERGIC TO FISH OR FOLLOW A VEGAN DIET?

Vegans can simply replace fish oil with blue green algae, which also are a good source of omega-3 for those with allergies.

WHERE CAN YOU BUY FISH OIL AND WHAT DOSAGE IS BEST?

The Food and Drug Administration just approved a new fish oil product. It has the highest level of omega-3, and you need a prescription. Other brands of fish oil also are available over-the-counter in drugstores. Whatever brand you buy, make sure you look for the highest levels of docosahexaenoic acid (DHA) and eicosapentenoic acid (EPA). The combined amount of DHA and EPA should make up more than 50 percent of the total milligrams of the dosage.

The New Face of AIDS

Senior citizens are contracting sexually transmitted diseases at an alarming pace. Cleveland Clinic Florida is working to reverse the trend.

Devastated. That's the word Lawrence Hakim, M.D., chooses to describe the look on his patients' faces when they are diagnosed with HIV/AIDS.

Dr. Hakim's patients have little resemblance to the AIDS patients of yesterday. Rather, they are classic grandmas and grandpas who remained sexually active well into their golden years. Some of them mistook their HIV symptoms for aging. Most of them didn't understand the risk of unprotected sex with multiple partners. All of them represent the new, more aged face of AIDS.

The rate of infection is growing at twice the pace among people 50 and older as those under 50.

"In the age of Viagra and penile implant surgery, more men remain sexually active into their 70s, 80s and even 90s," explains Dr. Hakim, a urological surgeon specializing in male and female sexual dysfunction at Cleveland Clinic Florida. "This is wonderful except that the risk of sexual disease is so much greater today than it was when they were young. They missed the sexual revolution of the 1960s, but they also missed the sex education wave of the 1980s and 90s–and they are contracting sexually transmitted diseases."

Every day, Dr. Hakim treats elderly HIV/AIDS patients in what he calls a sexually transmitted disease (STD) epidemic among seniors. The statistics support his view: According to the Centers for Disease Control (CDC), AIDS cases among the over-50 crowd have soared from 16,000 in 1995 to 90,000 in 2003–a 500 percent increase. Because older people don't get tested for HIV/AIDS on a regular basis, that number could be even greater.

With one of the largest senior populations in the nation, Florida is seeing an epidemic of regional proportions. Cleveland Clinic Florida is the epicenter for sexual dysfunction management and STD prevention and education in the southeastern United States, according to Dr. Hakim. His mission is to encourage seniors to remain sexually active, and to educate them about the myths and realities of STDs in the 21st century.

At the heart of the problem is the misconception–among physicians and seniors alike–that AIDS is only a threat to young singles and homosexuals. While it's true that these groups comprise the majority of HIV/AIDS victims in the U.S., the disease does not discriminate. The deadly virus targets all ages and races. This ignorance among the elderly community is largely responsible for the rapidly growing infection rates among this demographic. The rate of infection is growing at twice the pace among people 50 and older as those under 50.

"Since women associate safe sex with pregnancy prevention, and many of these seniors have gone through menopause, they may not insist that their partner wear a condom. In fact, studies show that most seniors do not use condoms," Dr. Hakim says. "Condoms don't guarantee the disease won't spread, but they certainly minimize the chances." Beyond a lack of health education, many other factors contribute to the rising risk of HIV infection in America's older people. Senior citizens are less likely than younger people to discuss their sex lives or drug use with their young doctors, Dr. Hakim explains. Doctors are often just as uncomfortable asking those tough, often embarrassing questions of someone who looks like their grandfather. However, he adds, open communication is a key to reversing the negative trend in any age group.

"We are working to reduce the stigma around discussing the sexual needs of these patients. We are physicians who need to communicate openly with our patients so we can promote safe sex and offer basic education about the risk of STDs," Dr. Hakim says. "We also need to educate them about the early warning signs of HIV/AIDS. Many of the patients I see are in the late stages of the disease and cannot be treated effectively."

Indeed, older people often mistake the symptoms of HIV/AIDS, including fatigue, weight loss, aches and pains and rashes, as a normal part of aging. That makes them less likely to get tested, the CDC reports. But this group is actually more prone to STDs because of physiological changes that come with aging. Ignorance, promiscuity and the natural aging process can lead to a deadly combination.

Also contributing to the rising numbers of elderly with HIV is the growing percentage of people who are living longer with the disease. People infected in their 30s and 40s are surviving with HIV thanks to "cocktails" of antiviral drugs, according to the CDC, and AIDS deaths have been declining since 1996. It can take 10 years or longer to develop AIDS after contracting HIV.

While intravenous infection is also part of the problem in this regional epidemic–aging Baby Boomers may still be doing drugs and diabetics could be sharing insulin needles–specialists believe this senior sexual revolution is the largest contributor to the rise of STDs. And while physicians also witness syphilis, gonorrhea, herpes, chlamydia and other STDs among the elderly, the focus remains on HIV since there is yet no cure, and older patients have much poorer prognoses for survival than their younger counterparts.

Compounding the problem, older patients may not have the support system younger patients do. Elder victims' parents are often deceased; they may also be widowed, or their children and siblings may react negatively in the wake of a HIV/AIDS diagnosis.

During the agonizing moments after Dr. Hakim breaks the news of an HIV/AIDS diagnosis to his senior clients, he has witnessed the complete range of emotions, from anger that their partners cheated on them, to depression in the face of death, to fear of excommunication from their social circles, to downright disbelief.

"Seniors are living longer and healthier lives, and they want to enjoy sexual intimacy," Dr. Hakim says. "We don't want to send the message that they shouldn't be sexually active. We want to send the message that they should take responsibility and minimize the chances of becoming infected with STDs or transmitting them."

Lawrence Hakim, M.D.

Letters to Tomorrow

Last year, Cleveland Clinic launched a new Web site for patients to post letters expressing their hopes for a better, healthier life. This Web site is intended to be an inspirational and motivational resource for other patients, their family and friends.

Here are just a few of the many "Letters to Tomorrow" our patients have written. To view more letters, or to write your own, go to **LettersToTomorrow.com.**

To: **My backyard**
From: **Dave, the guy with the achy legs**

This summer, you're mine.
For too long, I have had to pay others to mow you. I have been in too much pain to plant flowers, prune brushes, fertilize and mulch.
But as soon as Cleveland Clinic's vasular surgeons are done restoring full blood flow to my legs, I'm coming back.
Lawn mower, rakes and shovels: Your days gathering dust in the toolshed are over.
Shrubs: Stand up straight. You need a major buzz cut.
Weeds: Be afraid. Be very afraid.

To: **My unexpected self**
From: **Katy, with the new heart**

It was the only way I've ever known
I had only a distant thought of "normal"
Going through each day with half the beat,
Half the life, half the heart
Though I had twice the will,
twice the strength, twice the heart.
I then got a hope of someday reaching that distant thought "normal"
I have now reached it and find
I could have never
thought of this.

Katy

To: **My child of 3 years**
From: **Mommy, who needs back surgery**

I'm sorry that when you were one I couldn't raise you above my head to make you laugh and when you were two I couldn't lift you up for at least two hours in the morning after climbling out of bed–my back was so stiff and sore. But thanks to Cleveland Clinic–your third year will be an amazing one!

The very first thing I will do in the morning will be to scoop you up and give you the biggest bear hug!

I will give you all the piggyback rides in the world–even when it snows!

And when the sun goes down at the end of the day, I will carry you to bed and tuck you in without having to wake you.
I love you, my little boy.

I'll race you to the monkey bars!

Love,
Mommy
XXXOOO

To: **Cystic Fibrosis**
From: **Allyson, Lung Transplant Patient**

You thought you owned me.
You thought you could control my life.
You did.
But now I'm better, stronger.
You don't own me now.
I've got things to do:
Parties to plan, graduation to attend and a wedding to see.
You thought you could control me but you were wrong.
I'm a mom and I'm on a mission to live.

Ally

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TAKE OUR NEW READERS' POLL

Pricing Your Healthcare

More states are requiring hospitals to make pricing information available to the public. Recently a congressional bill was introduced that would require hospitals to publicly report information on specific inpatient and outpatient charges. The primary reason behind such "pricing transparency" is that it will help consumers make better choices about their healthcare.

Do you think pricing is an important factor in deciding where to go for care?

Tell us what you think at clevelandclinic.org/ccm

Get the results of our last poll, "Beyond Skin and Muscle: Face Transplantation" at clevelandclinic.org/ccm.

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