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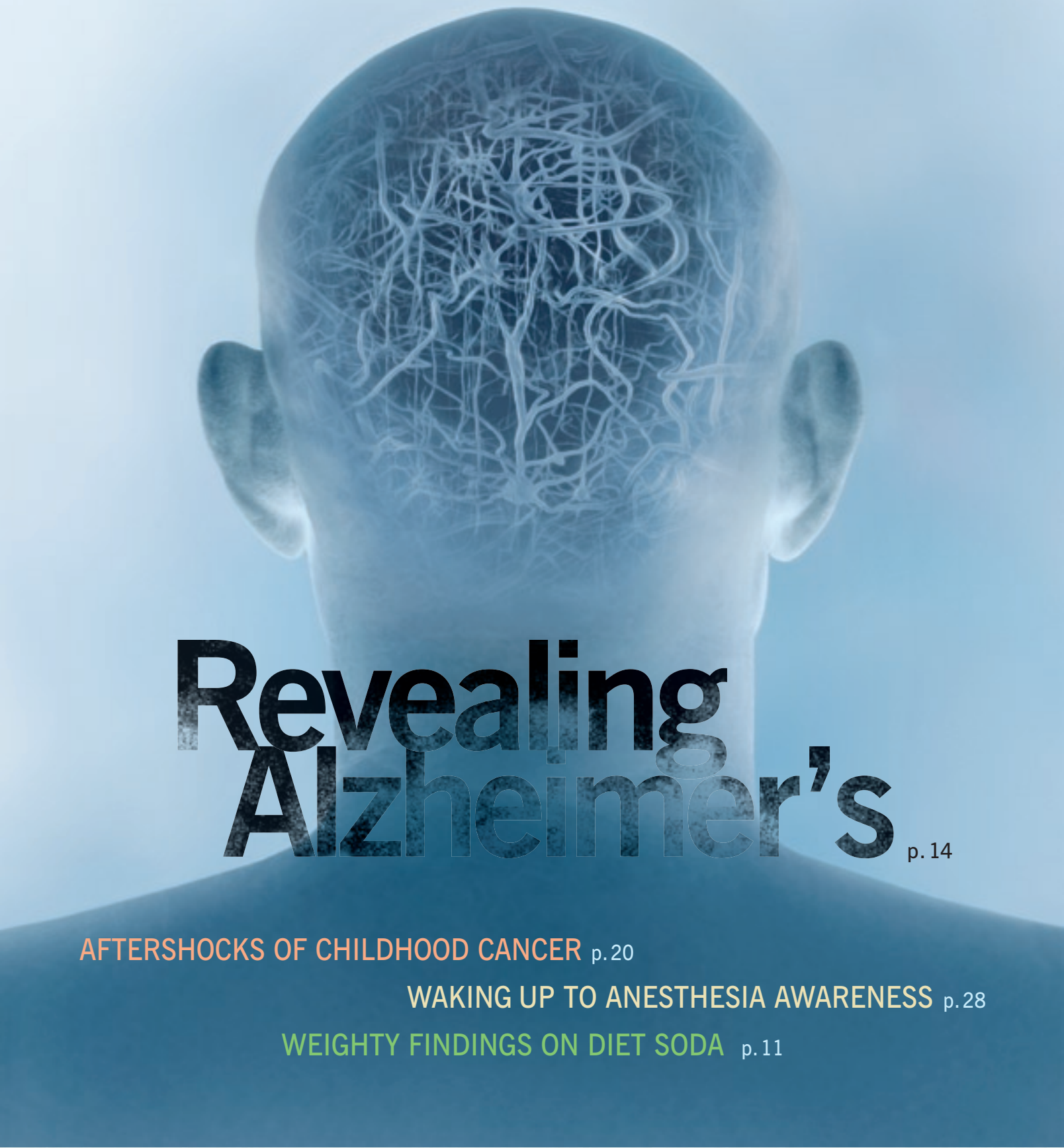

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Cleveland Clinic

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Cleveland Clinic

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We Need to Make 'Healthcare' About Health

A letter to our readers from Delos M. Cosgrove, M.D., CEO and President

I love old adages, particularly ones related to health. Remember "An apple a day keeps the doctor away"? Or "You are what you eat"? These pithy words seem to have been forgotten, which is a shame considering how true they actually are. I say it is time to bring them to the fore again.

American dietary habits have changed considerably over the past quarter-century. What this means is that we are eating emptier calories, and more of them. According to the Centers for Disease Control and Prevention, American obesity rates doubled between 1971 and 2000, and two-thirds of Americans are now considered overweight. This study was corroborated by a more recent study by the World Health Organization, which found that the United States ranks ninth in the world in the number of overweight people. This high rate of obesity puts Americans at greater risk for diseases, particularly diabetes, where America ranks third in the world with more than 19 million adults afflicted.

Diabetes, however, is just one health concern we need to worry about. Cardiac and respiratory failure, cancer and stroke are the top causes of death in the United States. While new treatments will continue to be developed for these diseases, the greatest impact will come from a grassroots approach in the form of wellness and prevention programs.

What do I mean by wellness and prevention? Healthy eating is certainly one aspect, but so are exercise, health promotion (such as smoking cessation programs) and wellness plans of care. All of these will play a significant role in improving survival rates. As an example, a National Heart, Lung and Blood Institute study found that you can reduce your risk of heart disease by up to 82 percent by making healthy lifestyle choices.

In other words, it won't be that red pill that helps keep the doctor away, but that red apple.

All of us need to change how we think about medical care. What we call our "healthcare" system is a misnomer, for our current system of care has little to do with health and more to do with sickness. Today, the treatment of chronic medical conditions comprises more than 75 percent of the nation's $1.4 trillion in medical expenditures. As a nation, we cannot afford spiraling healthcare costs and remain competitive at the same time.

Cleveland Clinic is well-known as a medical innovator, and we will continue to lead in the discovery of new treatments and cures. But we will also do more to help keep people healthier — and keep them out of the sick care system for as long as possible. This is good for our patients, our economy and our nation as a whole.

Wellness and prevention will be the keys to a future that is healthy, wealthy and wise.

What Lies Beneath

Ask surgeons what superpower would make their job easier, and they'll almost all say the same thing: X-ray vision. That's because, despite the array of imaging technology at their fingertips, surgeons still can't see what lies beneath opaque tissues.

"If we're looking for a tumor, we have to make a mental picture of what we've seen on CT and MRI scans before surgery. Then we have to recall that information from memory and apply it during the procedure," says Inderbir Gill, M.D. "That leaves a large gap."

BRAD YEO

Dr. Gill, Vice Chairman of Cleveland Clinic's Glickman Urological and Kidney Institute, is trying to close that gap for surgeries involving the prostate and kidneys. He has developed software that translates data from the patient's preoperative scans into real-time, 3-D images.

"What I want, and what this technology gives us, is a road map to help us navigate during surgery," says Dr. Gill.

The technology, called "augmented reality," is designed to improve removal of cancerous tumors. It could, Dr. Gill says, make surgery more precise and reduce the potential for complications. The software projects a virtual, 3-D image of the tumor and the surrounding blood vessels and nerves onto the site of the operation. The image reveals the exact location and depth of the tumor; as the patient breathes and the surgeon works, the virtual image moves with the natural movements of the patient's organs.

Augmented reality, which has been in limited use for several years for various procedures, can take different forms. Some require the surgeon to look through special goggles, while others show the tumor on a computer monitor.

Dr. Gill's software uses a color-coded system to precisely remove tumors in the prostate or kidneys, while preserving healthy tissue. The superimposed image glows red in the location of the tumor, revealing the target tissue to be cut. A software-created 5-millimeter yellow ring surrounds that area, and a 1-centimeter green ring surrounds the yellow. The green ring, like the "go" of a traffic light, tells the surgical team that they've removed all the cancer cells.

The technology could have other applications, says Dr. Gill, including the removal of tumors in other parts of the body.

"Very often, surgeons can't see how deep a tumor goes into an organ," says Dr. Gill. "With this technology, however, they can. It lets them look beyond what they can see."

— Tricia Schellenbach

Visit clevelandclinic.org/ccm to view a video demonstration of augmented reality technology.

Hip to a New Kind of Surgery

It's tough to be young and active with a painful, arthritic hip. Total hip replacement is a less-than-ideal solution because it often leaves the patient less mobile than desired. So younger patients often hold off on getting the surgery, enduring the discomfort and limitations as long as possible.

Now, an alternative is giving some younger, more active patients a chance to return to an energetic lifestyle. It's called hip resurfacing. "A year later, a patient can go back to all normal activities," says Cleveland Clinic orthopedic surgeon Peter Brooks, M.D. For some of his patients, that includes running marathons or climbing mountains.

Unlike hip replacement, which involves removing a portion of the healthy thigh bone, resurfacing shaves off only the damaged top end. As a result, it maintains the normal hip mechanics and bone thickness. There is less risk of uneven hip length or later dislocation.

Patients who have had both procedures done, one on each side of the hip, typically prefer the resurfacing side, according to Dr. Brooks. "They all say it feels more natural," he says.

So what is the catch? "You have to have good bone quality to be a candidate," Dr. Brooks says. The requirement excludes elderly patients and those with osteoporosis, or thinning bones. Another downside is that tiny amounts of metal from the caps placed on the arthritic thigh bone as part of the resurfacing procedure can leak into the blood. This isn't a problem for most healthy individuals, but it isn't good for patients whose kidneys do not function properly or for women of child-bearing age, because the metal could harm a developing fetus.

The procedure, available in Europe for about a decade, was approved in the United States only a year ago. — Laura Bonetta

Visit clevelandclinic.org/ccm to view a video about hip resurfacing.

JOHN HERSEY

ANATOMY 101: THE SPLEEN

For a small organ, the spleen is a busy body part. Tucked behind the stomach in the upper left portion of the abdomen and connected to the circulatory system, the spleen produces lymphocytes, the white blood cells that protect the body against infection.

It also filters the blood and destroys worn-out blood cells. The spleen can be affected by a host of conditions involving the blood or lymph system. Infection, certain types of cancer and liver disease can also cause problems, some of which require removal of the spleen.

Because of the spleen's role in protecting the body against infection, however, its removal should be carefully considered. For at least one illness, immune thrombocytopenic purpura (ITP), a bleeding disorder in which the body's blood-clotting platelets are being destroyed, new medications are making spleen removal less mandatory.

— Cori Vanchieri

Healing Rays

In fall 2006, Donna Boston and her husband were planning their 50th wedding anniversary celebration when she began having intense dizzy spells. "I would have to sit down on the couch, and the room would be spinning like an amusement park ride," says the 70-year-old Akron, Ohio, resident. "It got so that I was afraid to go out."

Her disappointment at postponing the festivities turned to fear when an MRI showed an acoustic neuroma, a benign but growing brain tumor near her left ear's auditory canal that would require surgery.

Uneasy with the prospect of general anesthesia, pain, potential complications and a long rehabilitation, she looked for alternatives to open-brain surgery. She learned about a noninvasive radiosurgery technique using a tool called the gamma knife.

It's not a scalpel, but a large machine that kills tumors using precisely aimed beams of gamma radiation. With each "shot," 192 separate, low-energy rays pass harmlessly through the patient's scalp, skull and overlying brain tissue, meeting at the exact site of the tumor, where their energy converges to deliver a powerful dose of radiation. The tumor is effectively killed, and over months the growth may shrink or completely disappear.

Ms. Boston was a prime candidate for the rapid procedure, which has been performed on some half-million patients worldwide. For patients with growths smaller than 4 centimeters in diameter and located away from critical parts of the brain, the gamma knife controls or eradicates more than 90 percent of most benign tumors and 70 percent to 80 percent of some malignant tumors, says Radiation Oncology Chairman John Suh, M.D., who performs the surgery at Cleveland Clinic, along with specialists in neurosurgery and otolaryngology. Ms. Boston's tumor was small, measuring 5 millimeters in diameter.

Ms. Boston's Aug. 1 gamma knife surgery, however, was unique. The machine used to perform the procedure is more efficient and effective than the traditional gamma knife and is in use at only a few medical centers in the United States, says Dr. Suh. With the new machine, Ms. Boston's procedure took just 10 minutes. She will have follow-up tests after three months, but, according to Dr. Suh, her prognosis is excellent. The dizzy spells have disappeared, she says, adding: "We celebrated our belated golden anniversary — with 100 friends and family — on Labor Day weekend." — Martha Frase

Watch a video about gamma knife surgery at clevelandclinic.org/ccm.

Giving the Voice a Hand

Walk in on Claudio Milstein, Ph.D., during an office visit and you're likely to see his hands wrapped around a patient's throat.

"I did have one patient leave the room saying, 'He choked me, he choked me and now I can talk again!' " admits the Cleveland Clinic laryngologist. Far from doing harm, however, Dr. Milstein was working to restore vocal function in a patient who had entered the room unable to speak. He treats patients who have problems with their voices, some of whom cannot speak above a whisper. How they've lost their voices varies from person to person, and often the reason is unclear to the patient.

Such was the case with Doug Macarthy, a veteran highway patrol dispatcher from Lorain County, Ohio. His voice was his livelihood, but then he lost it. "I have no idea what happened," he says. "All of a sudden, one day, I couldn't speak."

For 10 months, Mr. Macarthy could barely produce a whisper. He couldn't work, and his wife had to translate everyday conversations for him. He found himself visiting doctor after doctor and specialist after specialist with no success.

Mr. Macarthy's story is typical, says Dr. Milstein. "Some of these patients have been sent to psychiatrists because the condition is thought to be in their head," he says, pointing out that he can't always determine why his patients have lost their voices. What he finds, though, is that a procedure called digital laryngeal manipulation often helps them speak again.

Digital laryngeal manipulation does not involve computers, as its name might imply. Digital, in this case, refers to the pressure of fingers directly manipulating the larynx, which has become displaced in the neck, making it difficult to produce sound.

Dr. Milstein likens the condition to a muscle cramp. Tension in the neck muscles can "lock up" the larynx, altering the function critical to voice production. "By manipulating the neck, you can re-establish the balance in muscle tension," he says. The procedure is only performed after ruling out other potential causes of voice loss, such as lesions, tumors, infections or neurological problems.

Some patients experience discomfort during digital laryngeal manipulation, but any pain usually disappears after a couple of minutes. The procedure is not invasive and often takes place while the patient is sitting upright in a chair.

In most cases, the patient's voice improvement is long-term, says Dr. Milstein. So far so good for Mr. Macarthy, whose baritone is still booming over Lorain County walkie-talkies more than two years after his treatment. — Johnna Rizzo

ALIX MINDE/GETTY IMAGES

To see a video featuring Mr. Macarthy, visit clevelandclinic.org/ccm.

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Mastermind

Ali Rezai, M.D., a pioneer of deep brain stimulation surgery and research, talks about being amazed by results, what he would do if he were a patient and what it takes to be a brain surgeon.

YU KWAN LEE

►Deep brain stimulation (DBS), the procedure you're known for, involves threading fine wires into the brain to stimulate key areas. But you prefer the term "brain pacemaker" to DBS, is that right? Yes, because not everything is deep in the brain. It's also important to understand that we're not only talking about the brain. We're talking about using DBS and neurological pacemakers to influence the hundreds of nerves in your body outside your brain, your spinal cord and every one of your body organs that has a specific nervous system input.

►In August, a landmark study in the journal *Nature* reported one of your patients, a mugging victim in a minimally conscious state, had awoken. When you first started working with the patient, did you think you could help him? Based on our understanding from 10 years of research and our successes with Parkinson's patients and those with psychiatric disorders, we did expect to see improvements.

►Were the results better than expected? We've been pleasantly surprised by the improvements in this patient. From the first time we activated the brain pacemaker, he showed improvements in arousal, attention and behavior. The patient started opening his eyes and communicating. It was a defining moment for our team. And then we realized how much work was still ahead of us.

►So what's next? We'll be further developing the surgery for psychiatric disorders and brain trauma. We're also in the conceptual states of using brain pacemakers to improve cognitive recovery from traumatic brain injury, stroke and Alzheimer's.

►DBS is still a very novel idea for many people. Would you let someone perform it on you? This isn't the first avenue for treatment, but yes, I would consider it for myself or family if quality of life was compromised by a disease and medications and other approaches didn't provide relief. I think the answer is, you're living with this 24 hours a day, seven days a week, so why would you want to suffer and be limited and disabled when there is a technology that can help you?

►What do you do when you're not in the OR? I read, listen to music, exercise — some of the basic things most people do. But the vast majority of my time is spent at work, seven days a week. When not in surgery or seeing patients, our team is researching, learning more about the brain and nervous system. We're also coming up with more therapies.

►I guess no one can say to you, "It's not brain surgery." You mean, like "It's not rocket science"? There's a mystique about brain surgery. The brain makes you who you are and controls so many functions. And being a brain surgeon, it's a very serious responsibility that takes training, attention to detail and a great deal of good judgment. I don't take what I do lightly.

Dr. Rezai is Director of Cleveland Clinic's Center for Neurological Restoration. He holds the Jane and Lee Seidman Chair in Functional Neurosurgery.

To watch a video about deep brain stimulation, visit clevelandclinic.org/ccm.

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Rethink Your Drink?

Many of us live life with a diet soda in hand, confident we can have our cola and stay in shape. What could be bad about zero calories? But recent research casts doubt on that notion.

An analysis of 10 years of data from the Framingham Heart Study, a project of the National Heart, Lung and Blood Institute and Boston University, reveals that middle-aged participants who drank one or more sodas daily — regular *or* diet — were twice as likely as non-soda drinkers to develop a set of risk factors for heart disease and type 2 diabetes. Known as metabolic syndrome, the risk factors include abdominal obesity and high levels of blood sugar and LDL, or "bad," cholesterol.

The finding raises the obvious question: Should diet soda fans can their beverage of choice?

Soda reigns as America's most popular drink, accounting for almost a third of 2005 beverage consumption. That's more than bottled and tap water combined. Source: Beverage Marketing Corporation

THE BLAME GAME The study's senior author, Ramachandran Vasan, M.D., cautions against overreaction.

The findings don't suggest soda directly *causes* metabolic syndrome. The study of close to 3,500 people, published in the journal *Circulation* in July, merely indicates an association between the two — a link that may say more about people who drink soda than the soda itself.

In the study, people who drank more diet and regular soda had a greater intake of fat and sugar, and less intake of fiber in their diets, says Dr. Vasan. This finding squares with other studies. "Soda drinkers may also have a more sedentary lifestyle," Dr. Vasan adds.

Soda drinkers also may have a sweeter tooth than their non-soda-drinking brethren, says Cindy Moore, M.S., R.D., Director of Nutrition Therapy at Cleveland Clinic. She draws an analogy to people who consume a lot of salt.

"People can get so accustomed to food with high salt content that they think anything less salty tastes bland," explains Ms. Moore. "The same can happen with sweets, where you need higher and higher sweetness levels." And while your soda may be artificially sweetened, the cake and candy you eat isn't — helping to explain the higher rates of metabolic syndrome among soda drinkers, she offers.

Then there's the rationalization that diet soda drinking "allows" you to eat higher-calorie foods — an approach bound to backfire, says Ms. Moore.

Other theories pin more blame on diet soda itself. One intriguing possibility is that the caramel content in colas could promote insulin resistance, potentially leading to the dangerously high blood sugar levels of type 2 diabetes and metabolic syndrome. Research on animals indicates an association between insulin resistance and caramel additives, but the link has yet to be confirmed in people.

THE CHOICE IS YOURS Regardless of this latest study, the real weight-gain culprit is sugary soda, says Cleveland Clinic Florida endocrinologist Vineeth Mohan, M.D. Those who drink it should switch to diet, he says.

"When patients with diabetes drink diet instead of regular soda, I see their weight and blood sugar improve," says Dr. Mohan. "Unless I see more convincing data, I will continue recommending diet soda."

Meanwhile, everyone can benefit from drinking healthier alternatives, says Ms. Moore. "Other than hydration, what do diet soft drinks contribute?" she asks. She suggests instead reaching for nutrient-packed skim milk, or tea and coffee (without the cream and sugar) — both low in calories and high in antioxidants.

Better yet, she says, "why not pick water? It has no artificial sweeteners or additives, no calories — and costs next to nothing." — Bridget Murray Law

Take Our Online Poll: Is diet soda a health friend or foe? We want to know what you think. Visit **clevelandclinic.org/ccm** to vote and get results from last issue's online poll.

VEER GEORGE DIEBOLD/GETTY IMAGES

Double Dilemmas

Elizabeth Jones* was already dealing with a serious medical problem. The 36-year-old nurse had been diagnosed with ulcerative colitis five years earlier and was still struggling to get it under control.

Ulcerative colitis involves inflammation, ulcers, bleeding and pain in the lower intestine, perhaps activated by the person's immune system.

Then, in early 2003, came a nagging cough. "It wasn't much of anything to start with, but it didn't go away," says Ms. Jones.

Ms. Jones feared she had developed a whole other illness, and so began a series of visits to pulmonologists, or lung specialists, for another round of tests.

They all diagnosed the same thing, asthma, and prescribed inhalers and steroids that seemed to have little or no effect. Her colitis, meanwhile, worsened despite numerous treatments, diets and regimens.

Finally, at a medical convention in New York City, Ms. Jones began coughing up blood and found herself in an emergency room. "I knew that coughing up blood was not a symptom of asthma," she recalls. "And I knew I had to do something about my predicament, both about the colitis and the cough."

Back home in Georgia, she searched for answers and ultimately made her way to Cleveland Clinic's Center for Inflammatory Bowel Disease in April 2004. It was there that Victor W. Fazio, M.D., a specialist in colorectal surgery, performed a colectomy (removal of the lower part of the intestine), the definitive treatment for ulcerative colitis that is not responding to other treatments. "But there was still the cough," she says.

POSSIBLE CAUSES

By this time, the cough was nonstop. Ms. Jones had chronic rib and chest pain and brought up prodigious amounts of phlegm every day. Her voice had deteriorated to a raspy growl.

Tom Gildea, M.D., a specialist at Cleveland Clinic's Department of Pulmonary, Allergy, and Critical Care Medicine, was asked to evaluate Ms. Jones.

Dr. Gildea initially thought asthma might be the culprit, despite the consistent treatment failures. "People with ulcerative colitis do have an increased risk for asthma," says Dr. Gildea. "But there were the other major causes of

original diagnosis: ulcerative colitis
symptoms: ulcers, bleeding, lower intestinal pain

ILLUSTRATIONS BY TRACY WALKER

clue: **In early 2003 came a nagging cough. "It wasn't much of anything to start with, but it didn't go away."**

chronic cough as well, such as acid reflux, persistent postnasal drip or chronic sinusitis. These were all possibilities that had to be considered."

Dr. Gildea also thought Ms. Jones' symptoms might be an adverse reaction to any of her numerous medications. Further possibilities included heart failure or pulmonary hypertension (elevated pressures in the vessels that carry blood from the heart to the lungs). She had heart surgery when she was a teenager, and a CT scan of the lungs showed enlarged pulmonary arteries, which can be a sign of pulmonary hypertension.

As Dr. Gildea studied Ms. Jones' history and test results, he built a list of likely possibilities:

ASTHMA With an increased statistical association between ulcerative colitis and asthma, this remained high on the list.

ACID REFLUX, CHRONIC SINUSITIS OR POSTNASAL DRIP All common problems that, in Ms. Jones' case, might have been undertreated or incorrectly treated.

PULMONARY HYPERTENSION This could result in heart failure and may cause cough.

ENDOBRONCHIAL ULCERATIVE COLITIS Was Ms. Jones' colitis manifesting itself in a new way, outside her intestines?

DRUG REACTION If so, which was the culprit drug for a woman who had used many medications in myriad combinations over six years?

"When Elizabeth came back to see me, she had undergone the colectomy, but her cough was worse than ever," Dr. Gildea recalls. Acid reflux, sinusitis and postnasal drip had all been adequately treated. Asthma treatments hadn't worked. It was time for a bronchoscopy.

THE DIAGNOSIS

Examining Ms. Jones' lungs with the bronchoscope, Dr. Gildea had a diagnostic revelation. "There was a significant 'cobblestone' pattern of the airway," he recalls. "This is a classic extra-intestinal manifestation of ulcerative colitis." An "extra-intestinal" manifestation of colitis occurs when inflammatory cells similar to those seen in the colon invade the lining of the lung, causing swelling, irritation and sometimes permanent scarring of airways.

A biopsy confirmed the diagnosis, showing acute and chronic inflammation of the small airways due to ulcerative colitis. Her immune system had been overactivated, not only in her colon, but also in her airways, causing inflammation that led to the constant hacking.

Dr. Gildea treated Ms. Jones with immunosuppressive drugs and high-dose steroids. Her cough promptly came under control, and her medications were tapered.

Today, Ms. Jones is a nurse with a government agency. She had no difficulty passing endurance tests, running a mile or mastering the self-defense training her job required. And she walks more than 2 miles several times a week. "None of that would have been possible a few years ago," she says. — Richard Currey

**The patient's name and other details have been changed.*

By Tamar Nordenberg

Photoillustration by Ralph Mercer

Revealing Alzheimer's

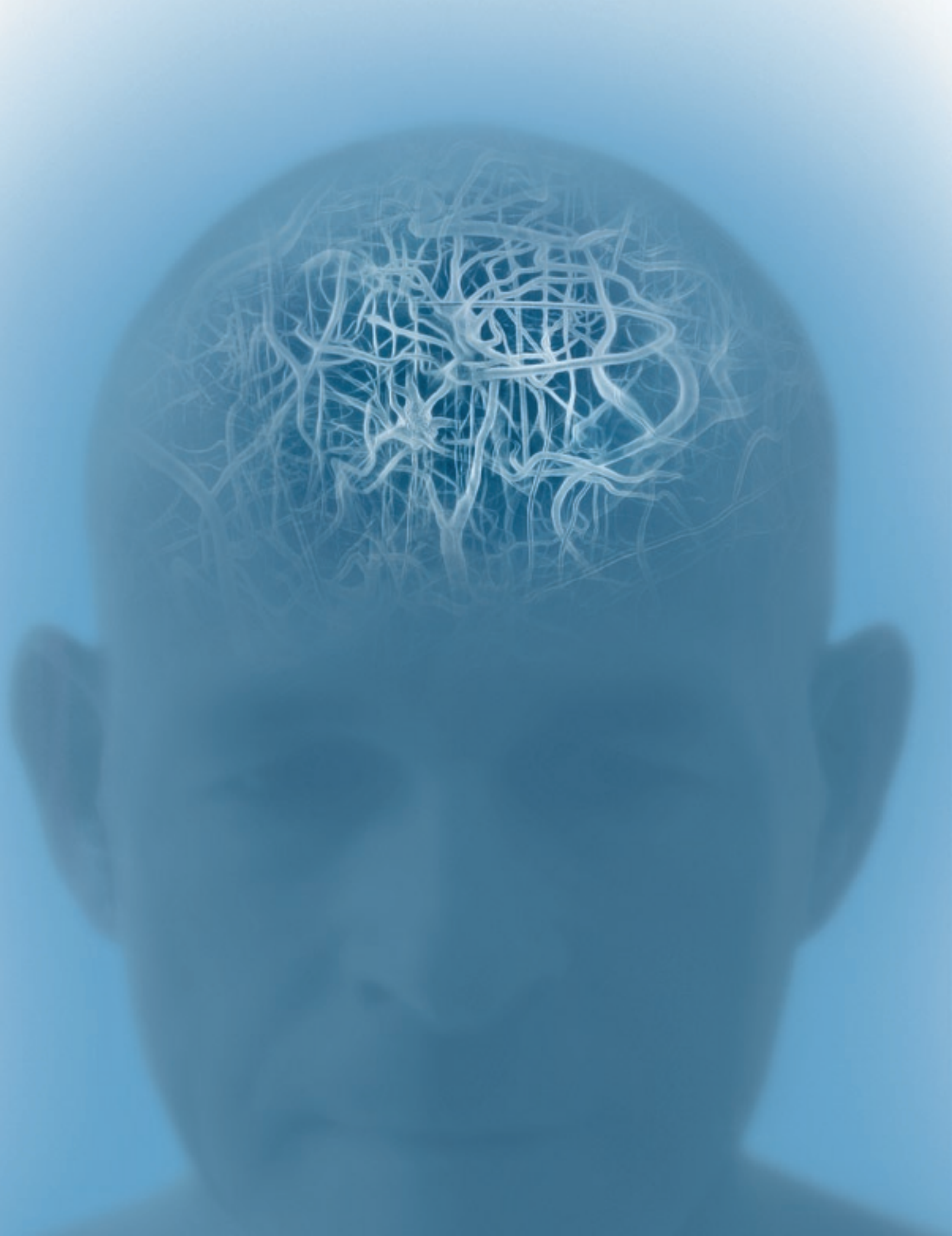
Forces I never knew existed have taken over places in my body. Alzheimer's works silently but its evil is steady, drilling through my brain until I no longer trust myself.

— *Thomas DeBaggio, in his 2003 memoir,* When It Gets Dark

By the year Thomas DeBaggio, a gardener and journalist living in Arlington, Va., wrote of his bleak showdown with Alzheimer's disease, scientists had accumulated some structural understanding of what must have been happening within the author's self-described "brain turned wild, drunk with death and destruction."

Clumps of a protein called amyloid beta, or Aß, were probably building up into large plaques outside his brain's nerve cells. Inside the same nerve cells, or neurons, twisted protein fibers called neurofibrillary tangles were doubtless taking root.

Plaques and tangles have long been the hallmarks of Alzheimer's, but scientists are murky on the role of these formations in the disease. Are they to blame for mercilessly snatching a patient's ability to think and remember?



Before treatments can effectively target the disease, scientists need to know more. "We want to know which brain changes *cause* Alzheimer's disease," says Sanjay W. Pimplikar, Ph.D., an Alzheimer's researcher in the Department of Neurosciences at Cleveland Clinic Lerner Research Institute. "We want to know how the offending changes can be stopped cold."

Today's medical therapies do little to challenge Alzheimer's disease. Though they provide patients a short-lived boost by regulating two brain chemicals called acetylcholine and glutamine, current drugs hardly stop the disease from progressing and fail entirely to reverse its tragic consequences.

Dr. Pimplikar and his colleagues at Cleveland Clinic, Riqiang Yan, Ph.D., and Bruce Lamb, Ph.D., are doing cutting-edge research that could lead to profoundly better options for treating or preventing Alzheimer's. "We're working on a way to really treat the patient, and not just alleviate the symptoms like drugs approved so far," says Dr. Yan, a leader in Alzheimer's research.

And there's no time to lose. More than 5 million Americans — most of them 65 and older — live with the disease, according to the Alzheimer's Association. With the so-called "graying of America," the association predicts that nearly 8 million in the United States could have Alzheimer's by 2025 unless treatment or prevention improves.

As Alzheimer's disease descends on the brain, the result is a steady deterioration in intellectual capabilities — starting with memory and judgment deficiencies during the disease's mild to moderate stages, progressing to trouble speaking and understanding speech, and finally advancing to a stage in which people cannot care for themselves or recognize even those closest to them.

For people watching a loved one with Alzheimer's, "the nightmarish part is the emotional disconnect," says Dr. Pimplikar, whose close family friend confided to him the

"In these early studies the vaccine not only prevented the development of plaques, it could even erase some signs of amyloid buildup in the brain. The possibility of stabilizing and preventing progression would be a huge step."

— Richard Lederman, M.D.

heartache of watching Alzheimer's take over her father's world. "Her dad doesn't know her anymore. The person who held her when she was a kid and stayed awake all night long when she had a fever — now Alzheimer's has stolen his personality. What's left behind is just a body."

By this advanced stage, rampant nerve cell death has caused the brain to shrink dramatically. A microscopic view of brain tissue reveals additional differences between a brain affected by Alzheimer's and a healthy one. For example, Alzheimer's-affected tissue has far fewer neurons, the cells that connect with each other and send signals that support memories, thoughts and feelings. Between the remaining neurons in an Alzheimer's-affected brain are plaques built up from the sticky Aß proteins that have clumped together.

Scientists have long viewed plaques as the primary culprits that shut down the brain. The "amyloid hypothesis" that fingers Aß and related plaques as the chief nerve cell killers in Alzheimer's remains a favored theory to explain the disease. Aß and built-up plaques rank as top targets for drug and vaccine developers.

HOPES FOR A VACCINE

Many scientists are pinning their near-term hopes on a vaccine against Alzheimer's plaques.

In one set of immunization studies, mice injected with Aß to mobilize their immune systems experienced complete elimination of plaques from their brains. "The results were stunning," says Dr. Lamb, who is studying Alzheimer's disease in mice in Cleveland Clinic's Department of Neurosciences. "The field was in complete shock, left with the million-dollar question, 'How exactly did it work?'"

A subsequent study of the same type of Aß immunization in people was stopped in 2002 because some participants developed encephalitis, a viral infection of the brain. Some people in the study, however, experienced small improvements in functions of daily living. There are now studies of modified vaccines that, at least preliminarily, seem to avoid the negative effects, says Richard Lederman, M.D., a neurologist at Cleveland Clinic's Neurological Institute who treats patients with Alzheimer's. "In these early studies the vaccine not only prevented the development of plaques, it could even erase some signs of amyloid buildup in the brain," he explains. "The possibility of stabilizing and preventing progression would be a huge step."

Meanwhile, new theories are evolving that consider other culprits. Dr. Pimplikar and others are coming to believe that Aß is not solely accountable for the assault on the brain. "If you look at all aspects of Alzheimer's disease and ask the question, 'Can every single facet of the disease be explained by Aß?' the answer is becoming a clear 'no,'" Dr. Pimplikar says. "Aß is definitely a prominent factor, but there is a lot more to the disease than this agent alone."

ON THE HUNT FOR OTHER CAUSES

Scientists are probing parts of the neuron that have barely been explored to find out what else might be behind the disease. For his part, Dr. Yan has improved the understanding of dystrophic neurites — nerve cell extensions that have become swollen and unable to carry messages between neurons as they are normally counted on to do. He wanted to know about these abnormal nerve cell extensions that are found surrounding the Aß deposits in plaques: Do they cause Alzheimer's disease? Or are dystrophic neurites merely a byproduct — a sign, but not a precursor — of Alzheimer's?

AN ALZHEIMER'S GLOSSARY

Amyloid beta (Aß): A protein found in clumps of tissue (called plaques) that appear in the brains of Alzheimer's patients.

Amyloid plaques: Unusual clumps of material found in the tissue between nerve cells. Amyloid plaques, which consist of a protein called amyloid beta along with degenerating bits of neurons and other cells, are a hallmark of Alzheimer's disease.

Amyloid precursor protein (APP): A normal brain protein that, in Alzheimer's, breaks down into three fragments, including amyloid beta.

APP intracellular domain (AICD): A second fragment of APP, which seems to prompt chemical changes that convert proteins, called tau, into the tangles.

BACE1: An enzyme involved in the creation of the plaques found in Alzheimer's patients.

Dystrophic neurites: Nerve cell extensions that become swollen and unable to carry messages between neurons.

Neurofibrillary tangles: Bundles of twisted filaments found within neurons that are found in the brains of Alzheimer's patients. These tangles are largely made up of a protein called *tau*.

RTN3: A protein involved in formation of dystrophic neurites.

Tau: A protein that is part of the cell's structural support and helps to deliver substances throughout the cell. In Alzheimer's disease, tau is changed in a way that causes it to twist into filaments that collect into tangles.

Source: National Institute of Neurological Disorders and Stroke, National Institutes of Health

Can You Reduce the Risk?

As with many degenerative diseases, prevention is likely the best medicine. While studies in mice have raised hopes that memories lost to Alzheimer's disease might be recaptured through exercises or drugs that help rewire the brain, some lost memories are likely gone forever.

Prevention may be as simple as eating right and exercising the body and mind.

The Mediterranean diet — lots of fruits, vegetables, legumes and cereals, plus good amounts of fish and little dairy and meat — is winning praise in Alzheimer's research circles. Recent studies show a reduced risk of Alzheimer's, even a reduced risk of death, in people who adhered to such a diet. "I tend to be a skeptic, but these studies are strong," says Cleveland Clinic neurologist Richard Lederman, M.D.

Several studies have suggested that physical activity and exercise — as little as 1.5 hours of walking each week — may protect the health of the brain, though researchers aren't sure how.

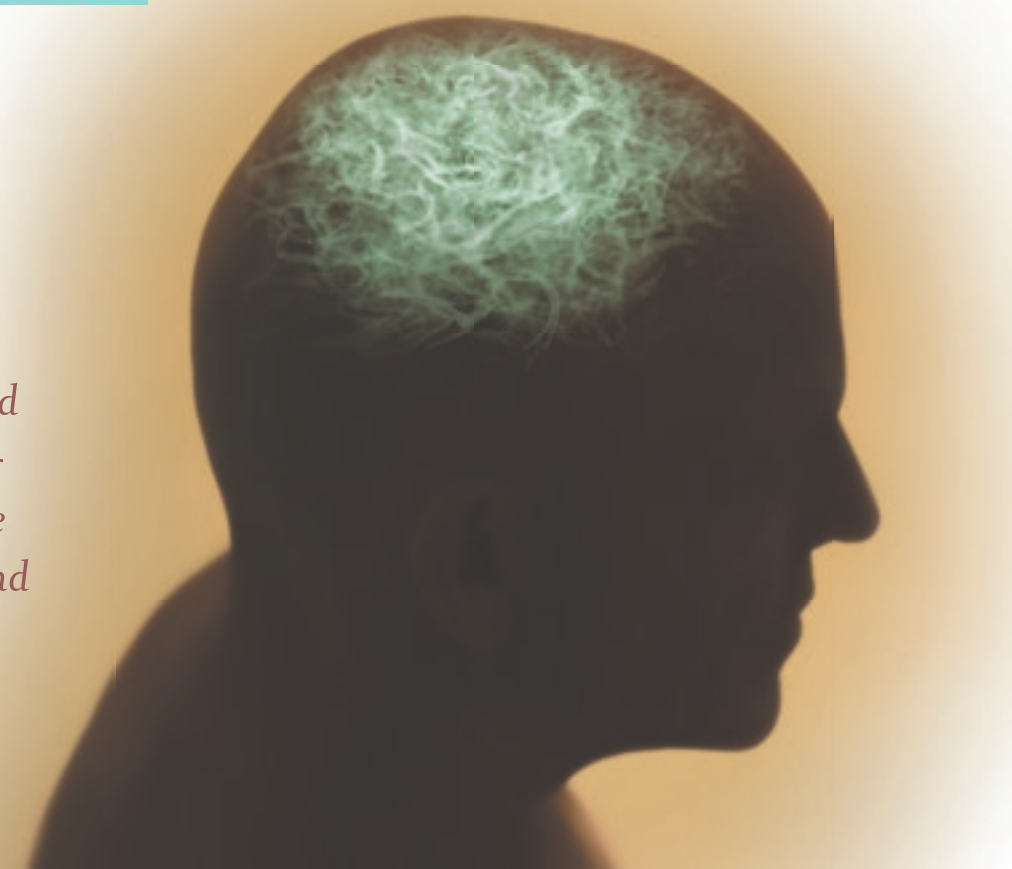
And mind-challenging hobbies, such as doing crossword puzzles, playing chess, playing an instrument or even listening to music, can help.

Dr. Yan's research team showed for the first time that dystrophic neurites can impair learning and memory — even in the absence of Aß deposits. In this study, published in the May 3, 2007, issue of *The EMBO Journal*, the researchers identified a promising target for new drugs: a protein called RTN3 that causes dystrophic neurites to form.

Dr. Yan's mouse study made an important connection between RTN3 and Aß production. Blocking the protein inhibited an enzyme called BACE1 that is necessary for creation of Alzheimer's plaques. "RTN3 may present a key to blocking plaques while at the same time blocking dystrophic neurite formation — that's our goal," Dr. Yan explains.

There's still more to learn, however. BACE1, which Dr. Yan co-discovered several years ago, is also critical to nervous system health. Blocking it could increase the risk for neurodegenerative diseases such as multiple sclerosis.

Another important clue being examined is the cause of the neurofibrillary tangles in the brain of Alzheimer's patients. The investigation starts with a large protein called amyloid precursor protein (APP), which helps neurons survive and grow. APP breaks down into three fragments in Alzheimer's patients, including the villainous Aß, but scientists remain baffled as to why this happens. After an unanticipated discovery in his lab several years ago, Dr. Pimplikar became intrigued by a second of APP's fragments, called APP intracellular domain (AICD). The surprising finding that revved his enthusiasm: AICD goes into a cell's nucleus and turns some genes on and others off.



"It's possible that, used much earlier, current Alzheimer's drugs and those in the works could arrest the early biological changes that set the stage for the disease and delay its onset."

— Stephen Rao, Ph.D.

Stop-Gap Therapies

Five Alzheimer's drugs are available by prescription, and all are considered to have modest benefits. All but one are cholinesterase inhibitors — they halt the unhealthy breakdown of the brain chemical acetylcholine, which supports memory and other mental processes. The other is thought to normalize the activity of glutamine, a chemical associated with learning and memory that can go amok in Alzheimer's disease.

Treatment…	Approved For…	Works On…
• Donepezil (Aricept)	• Mild, moderate or severe AD	• Acetylcholine
• ENA-713 (Exelon)	• Mild to moderate AD	• Acetylcholine
• Galantamine (Razadyne)	• Mild to moderate AD	• Acetylcholine
• Memantine (Namenda)	• Moderate to severe AD	• Glutamine
• Tacrine (Cognex)	• Mild to moderate AD	• Acetylcholine

Tests in mice by Cleveland Clinic's Dr. Pimplikar suggested that AICD is important to the hallmark tangles. AICD seems to prompt chemical changes that convert a brain cell protein called tau into the tangles. As they build up within the neuron, tangles wreck the system for transporting nutrients and other supplies that neurons need to survive.

Within five years, Dr. Pimplikar hopes to understand much more about the toxic effects of AICD. "Right now, AICD is just starting to creep onto the radar," he says. "But if AICD's contribution turns out to be very large, then the molecule may make for another valuable target for therapies."

IMPROVING DISEASE PREDICTION AND DIAGNOSIS

The early signs of the disease can be difficult to recognize, and current screening approaches for Alzheimer's rely heavily on psychological testing, which is slow to identify a cognitive deficit.

Disease prediction and early identification are major goals, and medical imaging may help. Researchers are developing imaging techniques using compounds that act as markers in the brain that "light up" on a diagnostic test called a positron emission tomography (PET) scan. "It allows scientists to see the abnormal amyloid plaques in the brain, which would allow a specific diagnosis of Alzheimer's — something we still can't do," explains Dr. Lederman. This technology may identify those at highest risk for developing Alzheimer's, which would be a big improvement, but this expensive technology is not likely to be used as a widespread screening tool.

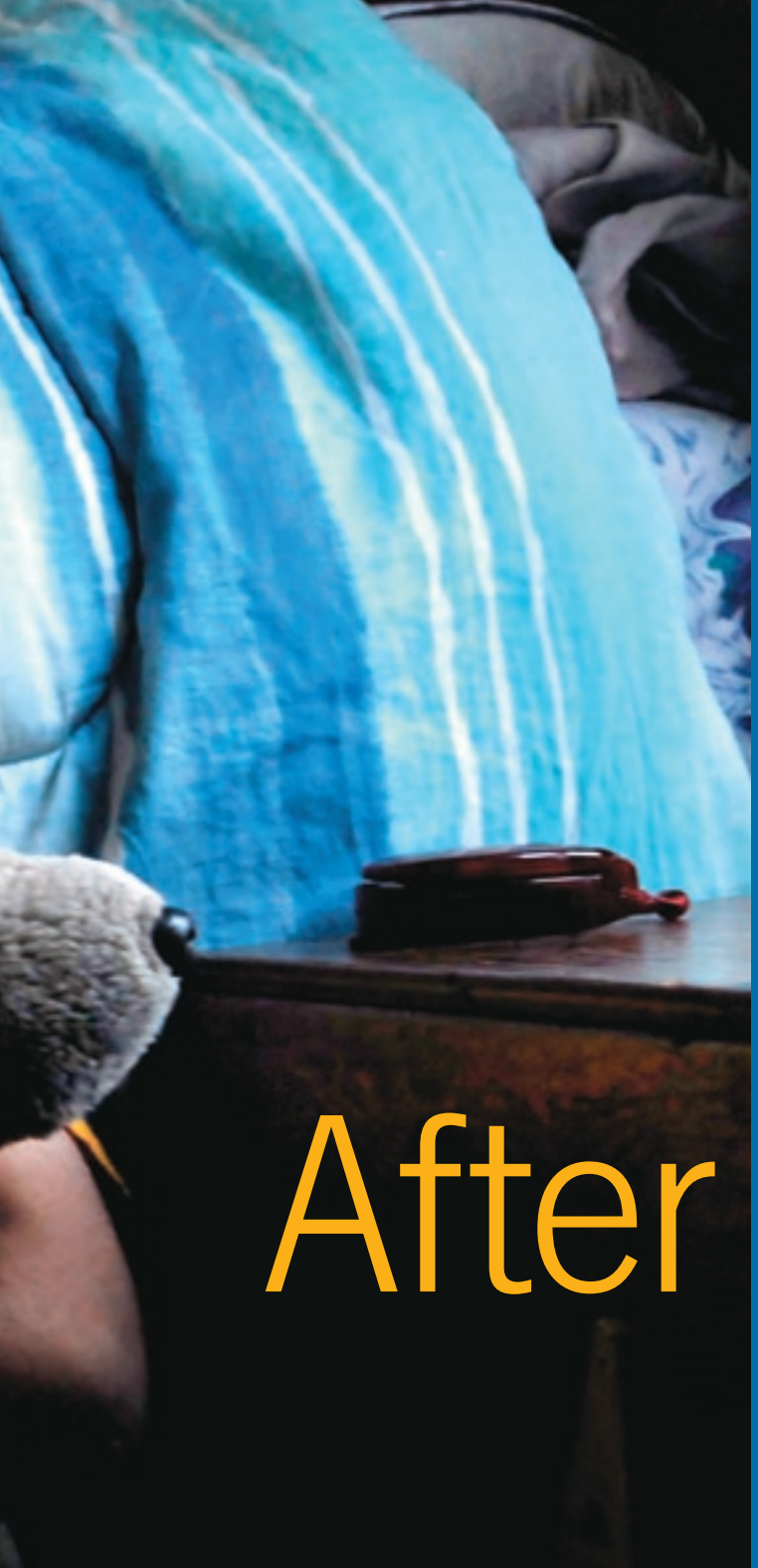
Others are working with more accessible technology, such as MRI, to pinpoint areas of the brain that show early signs of atrophy, or cell death. Stephen Rao, Ph.D., Director of Cleveland Clinic's new Shey Center for Cognitive Neuroimaging, is using a specific type of MRI, called functional MRI, to reveal brain changes consistent with the disease, in at-risk patients who do not yet exhibit symptoms. As the patient performs a task such as remembering, the MRI produces a brain map, which appears to be sensitive enough to detect preclinical stages of Alzheimer's. Though this is less specific than showing the amyloid plaques, scans like these are still an earlier marker for Alzheimer's than behavioral or clinical signs.

Another fascinating approach to detection, according to Dr. Lederman, uses the eye as the window to the brain. Scientists are looking at changes in the lens of the eye, detectable by a brief laser pulse that might indicate the earliest stages of Aß buildup. A blood marker may soon help as well. In October, researchers at Stanford University announced they have had preliminary success with a blood test that indicates which individuals with mild memory loss are most likely to go on to develop Alzheimer's disease two to six years later.

"Most of the current focus is on treating the disease after a diagnosis is made, which as things stand is probably too late," says Dr. Rao. "It's possible that, used much earlier, current Alzheimer's drugs and those in the works could arrest the early biological changes that set the stage for the disease and delay its onset." Because the disease most often strikes the elderly, delaying the disease by even five years, Dr. Rao points out, could slash prevalence by half. And a 10-year delay could "virtually wipe out" the disease.

And that will mean fewer fathers vanishing into inanimate shells, fewer authors regressing until they struggle to string together rudimentary sentences.

Tamar Nordenberg is a freelance health writer whose work has appeared in FDA Consumer magazine and on the WebMD and Discovery Health Channel Web sites.



Thirteen-year-old Holly Hofelich holds the stuffed animals she had with her at age 6 while undergoing radiation and chemotherapy for a brain tumor. Holly is one of roughly 300,000 long-term childhood cancer survivors in the United States. The photos in these pages offer a window into the daily life and posttreatment challenges of this middle-school student.

By Nancy Volkers | Photography by Greg Ruffing

TREATMENTS FOR CHILDREN WITH CANCER HAVE COME SO FAR THAT MOST CHILDREN SURVIVE THIS FRIGHTENING DISEASE. BUT THOSE AGGRESSIVE THERAPIES TAKE A TOLL ON THE BODY — SOMETIMES YEARS LATER. REGULAR, SPECIALIZED CHECKUPS, HOWEVER, CAN HELP WITH EARLY DETECTION AND CARE.

Aftershocks

Naomi Bartley has high blood pressure and cataracts. She also takes thyroid medication every day because her cancerous thyroid gland was removed three years ago.

These complaints might be typical for an older woman, but Ms. Bartley is only 27 years old. She can tie every one of these medical problems — and more — to the treatments that saved her life 20 years ago from a childhood cancer called acute myelogenous leukemia (AML).

In 1987, the London, Ontario, native became one of the first children in North America to receive a bone marrow transplant to treat her AML. Without the transplant, her outlook was grim — her bone marrow was churning out thousands of abnormal white blood cells that were crowding her healthy blood cells.

Total-body radiation and chemotherapy to destroy the rapidly dividing abnormal cells were followed by a bone marrow transplant to replace her faulty marrow with healthy cells. The donor was her older brother, Nathan. With this aggressive new treatment, Ms. Bartley became a survivor. Her story was chronicled in several newspapers and in a three-part special by the Canadian Broadcasting Corporation. She received hundreds of letters and gifts of encouragement, and she saved them in boxes she called "hope chests."

Today, Ms. Bartley doesn't like to complain, though she notes that she did have to schedule her wedding around her thyroid cancer treatments. Her mother, Ruth Hoffman, however, has a lengthy list of stories of how these late effects have made her daughter's life enormously challenging. "We are grateful that she's alive," says Ms. Hoffman, who is Executive Director of Candlelighters Childhood Cancer Foundation in Washington, D.C. "But many of these kids are not restored to prediagnosis health. You've traded an acute disease for a chronic one."

In 2006, the Childhood Cancer Survivor Study published in *The New England Journal of Medicine* confirmed that Ms. Bartley is not alone. Up to 25 years after their treatment, almost two-thirds of childhood cancer survivors have at least one chronic health problem. Of those, 45 percent are dealing with a disabling or life-threatening condition. Compared with their siblings, survivors are eight times more likely to have a serious health problem, such as a second cancer or congestive heart failure. And the risk increases as time goes on.

While researchers work to develop better treatments that target the cancer without causing long-term harm to the rest of the body, patient advocates and the professionals who care for young cancer patients are trying to educate

Cancer-free for five years, Holly today has the time and energy to devote to after-school activities, including drama club, left, and rehearsals for her church's Christmas play, below.

families about what they may face down the road and help them access regular follow-up care. This specialized care, often provided through what are being called "late-effects clinics," is crucial for detecting and successfully treating potential health problems.

"Nationally, there's a recognition that cancer survivors have unique health issues that need to be addressed," says Eric Kodish, M.D., a pediatric oncologist at Cleveland Clinic Children's Hospital's High Five Clinic, which cares for childhood cancer survivors. "We try to educate survivors as to the treatments they had and the effects they can expect. Knowledge is power."

THE GOOD NEWS — AND BAD

Until the early 1950s, cancer in children was almost uniformly fatal. That's changed dramatically. Today, nearly 80 percent of children are alive at least five years after diagnosis (some stubborn cancers, such as AML and certain brain tumors, have survival rates that are still lower than 60 percent). Researchers credit that improvement to the fact that the majority — 55 percent to 65 percent — of children age 14 and younger with cancer receive treatment in clinical trials sponsored by the National Cancer Institute, where they get leading-edge therapies.

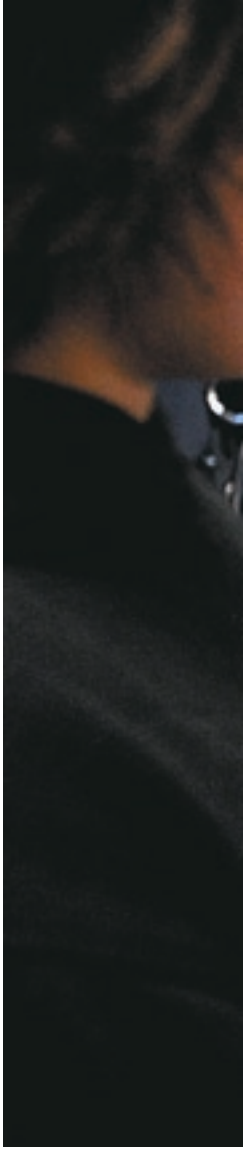
Most of these studies are conducted at more than 230 hospitals that are part of the National Cancer Institute-supported Children's Oncology Group. These hospitals, including Cleveland Clinic Children's Hospital, treat most of the children in the United States who have cancer. Over the years, the high participation rate of children in clinical trials (by comparison, fewer than 5 percent of adults with cancer take part in clinical trials) helped improve treatments and survival rates.

The intense treatments that boosted survival rates include chemotherapy with three or four different drugs, and radiation and chemotherapy combined. These same lifesaving treatments, however, can seriously affect children, whose bodies and brains are still developing. Depending on where it is aimed, radiation can lead to learning disabilities, short-term memory loss, growth problems, second cancers, delayed menstruation and infertility. Chemotherapy wipes out cancer cells, but also destroys healthy dividing cells. Some drugs induce early menopause or lead to infertility or leukemia. Others damage the lungs or heart, increasing the risks for weakened heart muscle and congestive heart failure.

EDUCATION AND MONITORING

Because of the high risk for health problems, long-term survivors of childhood cancer — there are about 300,000 in the United States — are increasingly being encouraged to seek specialized healthcare. Some might need certain screening

BECAUSE OF THE HIGH RISK FOR HEALTH PROBLEMS, LONG-TERM SURVIVORS OF CHILDHOOD CANCER — THERE ARE ABOUT 300,000 IN THE UNITED STATES — ARE INCREASINGLY BEING ENCOURAGED TO SEEK SPECIALIZED HEALTHCARE.



Holly also plays percussion in her middle-school band. The academic work itself can be a challenge, though. Holly has short-term memory problems, an effect of some childhood cancer treatments.

What's a Survivor to Do?

The potential late effects that a childhood cancer survivor might experience depend on many factors, including the type of cancer, treatments and dosages, and the survivor's gender and age at diagnosis. Late-effects clinics can help survivors learn about healthy lifestyles and receive ongoing monitoring of health status, early identification of late effects and timely care.

The Children's Oncology Group has detailed Survivorship Guidelines, which are written for health professionals to guide long-term follow-up care. They are available at survivorshipguidelines.org. It also offers patient-oriented fact sheets, called Health Links, which cover dozens of relevant topics, such as emotional issues, bone health and second cancers. Fact sheets provide general information about a health condition, along with risk factors specific to cancer patients.

For example, an introductory fact sheet notes that "a small percentage of survivors treated with chest radiation or certain chemotherapy drugs known as 'anthracyclines' (such as doxorubicin or daunomycin) have problems with the heart. This is most likely to happen in people who received higher doses of these medicines, and in those who received their treatment before their heart finished growing. Your healthcare provider may recommend tests to check your heart function, and may arrange for a cardiologist (heart specialist) to see you if the tests show any sign of these problems."

tests, such as early, frequent mammograms for women who had chest radiation, or annual echocardiograms for those who received the drug doxorubicin, which can be toxic to the heart. Some survivors need care from multiple specialists: an endocrinologist for thyroid issues, an ophthalmologist for cataracts, an oncologist for second cancers. And some may need counseling or medication to lessen the fear, anxiety or depression that stem partly from surviving a threat such as cancer.

Holly Kubaney, M.S.N., C.N.P., Coordinator at Cleveland Clinic Children's Hospital's High Five Clinic, says survivorship issues and follow-up care have been increasingly emphasized in recent years. "Primary prevention is a huge push in our clinic," she says. "There's so much you can do to avoid other health problems, most of which are the same things we've all been told: Don't smoke. Eat right. Exercise." But for some survivors, the rubric has more urgency. "If you've ever had radiation to the chest, the last thing you want to do is smoke," she says. "Damage from the radiation may have started lung cells on the road to becoming cancerous. Smoking will only accelerate the process."

Late-effects clinics also help patients deal with psychological and emotional effects, as well as issues raised by limb amputation, chronic pain and the search for healthcare and health insurance. "I think it is important for kids going through treatment to know that survivorship clinics exist and they will always be followed, long after they are off therapy," says High Five Clinic's Dr. Kodish.

Holly Hofelich was 6 years old when she was diagnosed with medulloblastoma, the most common childhood brain tumor. The Fremont, Ohio, girl traveled three hours round-trip to Cleveland Clinic for surgery, six weeks of radiation to her brain and spine, and a year of chemotherapy with the powerful drugs vincristine, cyclophosphamide and cisplatin.

Radiation and chemotherapy for medulloblastoma — a tumor that grows at the bottom of the brain, near the top of the spinal cord — have improved survival rates from 20 percent to about 80 percent over the past two decades. But they are not risk-free.

Now 13, Holly needs to take thyroid medication as well as growth hormone because her pituitary gland was damaged by radiation. The surgery to remove her tumor damaged a nerve in Holly's face, so her right eye has limited mobility. She also has short-term memory problems. Things she learned previously seem intact, but new knowledge, such as math facts, doesn't always stick. "It takes a lot of patience from a parental standpoint," says mom Tami Hofelich,

although, she adds, most people don't even know that Holly has a learning disability.

Holly visits Cleveland Clinic regularly to see an endocrinologist, an ophthalmologist, a neurologist and an oncologist. In December, she reached the milestone of being cancer-free for five years, but she will receive blood tests, MRIs and other care at least twice a year.

"There's a chance that other things could happen in the future," says Ms. Hofelich. "We plan to have her checked for the rest of her life."

Holly's mom says that the risk of late effects was not a priority during her daughter's treatment. "You don't think about that. You're thinking about survival," she says. "I've taken the attitude that whatever happens, at least we have Holly; she's here with us."

Joan Darling, who became a patient advocate after her own daughter's diagnosis, agrees. Alison Darling was diagnosed with alveolar rhabdomyosarcoma in 1996, when she was 13. The disease causes tumors in muscles, usually the arms, legs, shoulders and back. It's diagnosed in fewer than 100 children every year.

Ms. Darling, a Lincoln, Neb.-based environmental consultant, went into "research mode" to find out all she could. But when it came to treatment, "I remember saying, 'Throw everything at it and we'll worry about it later,'" she says. "Alison was given 50/50 odds, and we wanted to do whatever we could to get her into the 50 percent that survive."

Alison received 28 radiation treatments, four rounds of chemotherapy with three different drugs, and then eight rounds of chemotherapy with five different drugs. She also had surgery to remove the tumor.

After treatment, the family organized its own healthcare team of specialists to handle follow-up care. Ms. Darling also helped the Children's Oncology Group create the first set of guidelines for survivors of childhood cancer, which were updated in 2006. The guidelines, written for health professionals, offer advice on follow-up care based on the type of cancer and treatments received. "These guidelines should make a major improvement in the ability of survivors of all ages to find appropriate care to maintain their health throughout their lives," Ms. Darling says.

MORE HURDLES

Even though late-effects clinics are becoming more common — there are now more than 45 in the United States — few patients take advantage. Only 12 percent of the 14,000

The Hofelichs regularly make the hour-and-a-half trek from their home to Cleveland for Holly's follow-up care. Her cancer, diagnosed when she was 6, left her without full facial movement. "Other things could happen," says her mother. "We plan to have her checked for the rest of her life."

survivors in the Childhood Cancer Survivor Study reported getting care that specifically addressed possible late effects.

"Part of the challenge is to track these patients down and bring them back, even if it's only a one-time visit," says High Five Clinic Coordinator Ms. Kubaney. "Some don't want to come back, ever. Some say they're not having problems, so they don't come back."

Having access to a treatment summary can be key to receiving tailored healthcare after a survivor leaves for college, moves to another state or just decides to change doctors. But not only do most survivors lack such a summary, some don't even know they had cancer: They were so young that they don't remember it, and their parents may believe it's better not to discuss it. Others don't know the type of tumor, or the drugs they were given, or what part of their body was irradiated.

Ms. Kubaney says having a treatment summary is critical. It should contain the patient's cancer treatment history: type of cancer, radiation sites and doses, and chemotherapy drugs and doses. She develops summaries that include notes about possible late effects. "It might say: 'You received this dose of doxorubicin, which can affect your heart. So you need to have echocardiograms every year,'" she says.

Access to care can be difficult. Living in Ottawa, Ontario, after college, Ms. Bartley couldn't find a clinic that would see her after she left her pediatric oncologist. "That was one reason my secondary cancer was found at such a late stage," she says. "Follow-up clinics certainly are a step in the right direction, but I think there's still a long way to go in terms of educating the child, providing an accurate medical record, giving them information so they can go on."

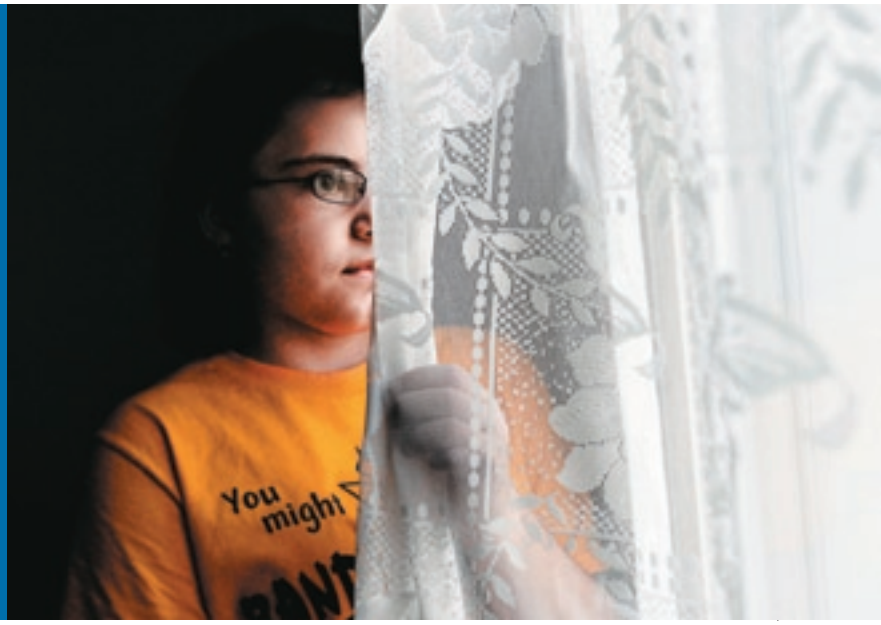
Ultimately, however, healthcare professionals would prefer that late-effects clinics weren't needed. They'd rather have treatments that offer a cure without causing later harm.

IMPROVING TREATMENTS

As survival rates for childhood cancers grew and late effects started to appear, researchers began trying to lower the toxicity of existing treatments without reducing the chances of survival. In general, radiation is now used less frequently and is better focused to spare nearby healthy tissue. This helps in the brain, for example, to reduce cognitive problems. Doctors can prescribe additional drugs to protect tissues such as the heart from the harmful effects of chemotherapy. Reducing toxicity has also led to fewer short-term side effects, such as infections or mouth sores. Toxicities have been reduced in treatments for Wilms tumor, Hodgkin's disease, neuroblastoma, medulloblastoma and some types of non-Hodgkin's lymphoma, among others.

Besides tweaking existing treatments, research continues into new ones. The Children's Oncology Group has 70 treatment trials designed to find effective treatments while minimizing effects on health.

ONLY 12 PERCENT OF THE 14,000 SURVIVORS IN THE CHILDHOOD CANCER SURVIVOR STUDY REPORTED GETTING CARE THAT SPECIFICALLY ADDRESSED POSSIBLE LATE EFFECTS.



Nevertheless, patient advocates like Ms. Hoffman are not satisfied with the pace of research and are concerned about the lack of new targeted therapies for pediatric cancers. Research dollars have long been an issue. Although cancer is the top cause of nonviolent death in children, most childhood cancers are still rare, making research unprofitable for pharmaceutical and biotech companies. For example, about 216,000 women are diagnosed with breast cancer each year. By comparison, about 425 children each year are diagnosed with rhabdomyosarcoma.

Ms. Hoffman believes the high overall five-year survival rate and the purported success of treating childhood cancer have backfired in budget meetings. "Money is going into targeted therapies for adults, but not for kids, because [childhood cancer] is considered to be 'cured,'" she says. "Adults need cures too, but you can't fail to provide research that leads to less toxic therapies for a 5-year-old who still has 70 years of life left."

To do her part, Ms. Bartley commemorated the 20-year anniversary of her lifesaving bone marrow transplant by hosting a November fundraiser called "Naomi's Hope for a Cure" at the National Building Museum in Washington, D.C. The night included a live auction of 15 hope chests, reminiscent of the ones that held all the supportive letters and cards she received when she was battling the disease. The chests were painted or signed by North American artists and supporters of childhood cancer research, including Robert Bateman, Lance Armstrong and former President George H.W. Bush and wife Barbara (whose 4-year-old daughter Robin died of leukemia in 1953).

Ms. Bartley hoped to raise $500,000 at the event for research into the molecular characterization of AML. She wants targeted therapies for the disease. "We can't offer much more hope for kids who are diagnosed with AML tomorrow than we could 10 years ago," she says. "Treatment really hasn't changed."

Ms. Bartley's original hope chests were destroyed a couple of years ago when her parents' basement flooded. Or so she thought. This past summer, construction workers found the letters, cards, newspaper clippings and photos. They were wrinkled, yellowed and somewhat musty, but all the important sentiments of hope were still there.

Nancy Volkers is a healthcare reporter who has written for the National Cancer Institute and InteliHealth News Service.

AWAKE

Anesthesia awareness is a rare experience that can have long-term, traumatic effects. The phenomenon is finally getting the attention of healthcare providers, who may have the power to do something about it.

Carol Weihrer recounts her nightmare:

Immobile on an operating table, music playing in the background, she hears a voice saying: "Cut deeper. Pull harder," as she feels extreme tugging on her right eye.

But this was no dream. Ms. Weihrer was actually awake and terrified during an operation — when she was supposed to be out cold — and no one else in the room took note.

Because of the drugs that kept her paralyzed, she was unable to move, unable to speak or scream.

"You literally are in a dead body," says Ms. Weihrer, describing her experience at a hospital in the District of Columbia. "A good phrase is 'buried alive,' because that's what you are."

Ms. Weihrer's experience is rare, but she's not alone. Multiple studies show that one or two patients out of every 1,000 experience some level of wakefulness during an operation. With some 21 million patients undergoing general anesthesia in the United States each year, the numbers become more striking, adding up to an estimated 20,000 to 40,000 incidents per year of anesthesia awareness.

POLKA DOT IMAGES/PUNCHSTOCK

ON THE TABLE

By Tracie L. Thompson

Ms. Weihrer, who says she eventually lost consciousness during the five-hour surgery to remove her eye, irreparably damaged by a severely scratched cornea that had caused years of pain, doesn't know whether she passed out or finally received more anesthetic. The experience was so traumatic that soon after her January 1998 surgery, she started the Anesthesia Awareness Campaign to bring attention to an issue that was not widely discussed.

"No patient should have to endure unintentional awareness during surgery. A lot of patients who have regional procedures that numb the arm or leg talk with an anesthesiologist or surgeon during surgery, but that is intentional," says Michael Roizen, M.D., former Chairman of Anesthesiology at Cleveland Clinic. "It is clear that unintentional awareness can be a devastating issue to those who have to face it."

Anesthesiologists are taking note of this issue, more aggressively exploring the phenomenon and studying the role of a technology that monitors the patient's brain activity to indicate how deeply sedated a patient really is.

DIFFERENT EXPERIENCES

Providing anesthesia for a patient during surgery involves more than just dampening consciousness. Drugs are used to induce temporary paralysis, which prevents involuntary muscle movements, which could result in more difficult, less accurate and even incorrect cuts during surgery. If the sedative wears off too soon and the body is immobilized by the paralytic drugs, the patient can't cry out or even wave a finger.

But anesthesia awareness isn't the same for everyone. Patients can experience varying degrees of wakefulness and subsequent trauma. A recent study from Sweden, reported in the journal *Anesthesiology*, evaluated 65 patients who had experienced anesthesia awareness at some point in their lives. Thirty patients had reported an acute emotional reaction, and while only one was classified as having post-traumatic stress disorder (PTSD), some 10 patients had experienced postsurgical nightmares, anxiety or flashbacks.

Janet Osterman, M.D., an associate professor of psychiatry at Boston University School of Medicine, has studied anesthesia awareness for a decade. "At the more benign end of the spectrum, there are people who will have a slight awakening and may hear conversation," says Dr. Osterman. "Some of these people will develop symptoms of post-traumatic stress disorder. The people who come in with severe PTSD symptoms are typically those who were fully awake during the entire procedure or suffered pain."

In 2001, Dr. Osterman published a study of 16 individuals who had experienced awareness and were willing to talk about it. There were a range of awareness experiences, and all but one patient had some sign of PTSD. More than half met the full diagnostic criteria for PTSD.

"Some postawareness patients are very difficult to treat because they had so much [physical] pain during the procedure," she notes. In addition, patients often refuse to go for any kind of treatment in hospital settings because of the flashbacks they experience while there.

Ms. Weihrer shares that aversion to hospitals, although she underwent surgery again shortly after her eye was removed because night terrors had caused her to reinjure the area. "My second surgery went fine, but going into it was just reliving everything that had happened and thinking, 'This is going to happen to me again.'"

She now needs additional surgery on her eye socket. "I just can't face it," she says.

> My second surgery went fine, but going into it was just reliving everything that had happened and thinking, 'This is going to happen to me again.'
>
> — Carol Weihrer, founder of the Anesthesia Awareness Campaign

Human error or equipment failure can occasionally cause the problem. But more commonly, awareness is a byproduct of the fact that "general anesthesia" describes a spectrum of unconsciousness: a continuum from light to deep that is deliberately tailored to the patient and his or her medical situation.

The lighter the anesthesia, the more likely awareness can occur. Lighter anesthesia is sometimes necessary in cardiac surgery, in emergency cesarean deliveries and in individuals undergoing surgery for severe injuries. In all of these cases, deeper anesthesia brings extra risks for the patient.

Other factors that can complicate the use of general anesthesia and lead to variations in consciousness include body weight and the effects of other drugs or substances used by the patient. People who have experienced a previous episode of anesthesia awareness are also at risk for another.

MOODBOARD PHOTOGRAPHY/PUNCHSTOCK

A WAKE-UP CALL

The real wake-up call for physicians came in 2004, when the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) issued an alert stating that anesthesia awareness is underrecognized and undertreated. JCAHO is the nation's main standards-setting and accrediting body in healthcare.

Dr. Osterman credits the 2004 JCAHO alert for opening the medical community's eyes on anesthesia awareness. "That sort of put it out there and said, 'We need to talk to people about this,'" says Dr. Osterman. "I think prior to that there had been what we might call a clinician's wish that it didn't happen, and if it happened, it wasn't bad."

By then, brain function monitors were on the market. They employ a form of electroencephalography (EEG) to record electrical activity in the patient's brain and generate

a numeric value describing a patient's depth of sedation. For most monitors, the number can range from zero (reflecting an absence of brain activity) to 100 (when the patient is fully awake).

The most commonly used monitor requires placing a single strip of electrodes on the patient's head once he or she is asleep. The patient's electrical brain activity is then monitored in real time by the anesthesiologist, who can adjust the anesthesia drugs accordingly. A value of 60 or lower in this device is considered best for preventing awareness during surgery.

About half of operating rooms nationwide have brain monitors, according to one company that makes the machines. But, they say, monitors are only used in 16 percent of eligible procedures.

Dr. Roizen says that in 1998, his predecessor, Fawzy G. Estafanous, M.D., started overseeing the installation of brain monitors in Cleveland Clinic cardiac surgery suites, where the likelihood of awareness incidents is greater because of lighter anesthesia and frequent use of paralytic drugs. In 2000, their use was made virtually mandatory or routine for all cardiac surgery procedures done with general anesthesia at Cleveland Clinic. "We wanted to assure people that we were going to do everything in our power to try and minimize awareness," Dr. Roizen says.

In 2005, the monitors were installed in all regular operating rooms at all Cleveland Clinic facilities.

"Brain monitoring is not in use everywhere. But it should be," says Dr. Roizen, who encourages routine use of the monitors. Anesthesiologists who choose not to use the monitor must provide a rationale — for example, because general anesthesia is not being used or because conventional monitoring is sufficient. "The anesthesiologist supervising the case has to either use it or make a conscious decision to not use the monitor," says Dr. Roizen.

"I use it virtually every time," adds Dr. Roizen, who spends one day each week in anesthesiology practice in addition to his administrative roles.

Using this type of brain activity measurement is a distinct departure from the traditional approach to anesthesia monitoring, Dr. Roizen notes.

"Until 1998 we did not have any monitor of brain function — or equivalent monitor of what you might call awareness — during surgery," he says. The standard approach, still used in conjunction with brain activity measurement, involves monitoring physiologic responses that are believed to be indicators of patient awareness.

"Almost all of us could judge — or thought we could — by sympathetic reflexes," says Dr. Roizen. "For example, how tense is the patient?" Other indicators include high blood pressure or fast heart rate. "If the patient is paralyzed — but aware of what's going on — you would traditionally expect him to have high blood pressure and high pulse rate. So you would expect to see that response in that patient."

But physiologic responses during surgery may not always tell the whole story. According to Dr. Osterman, researchers

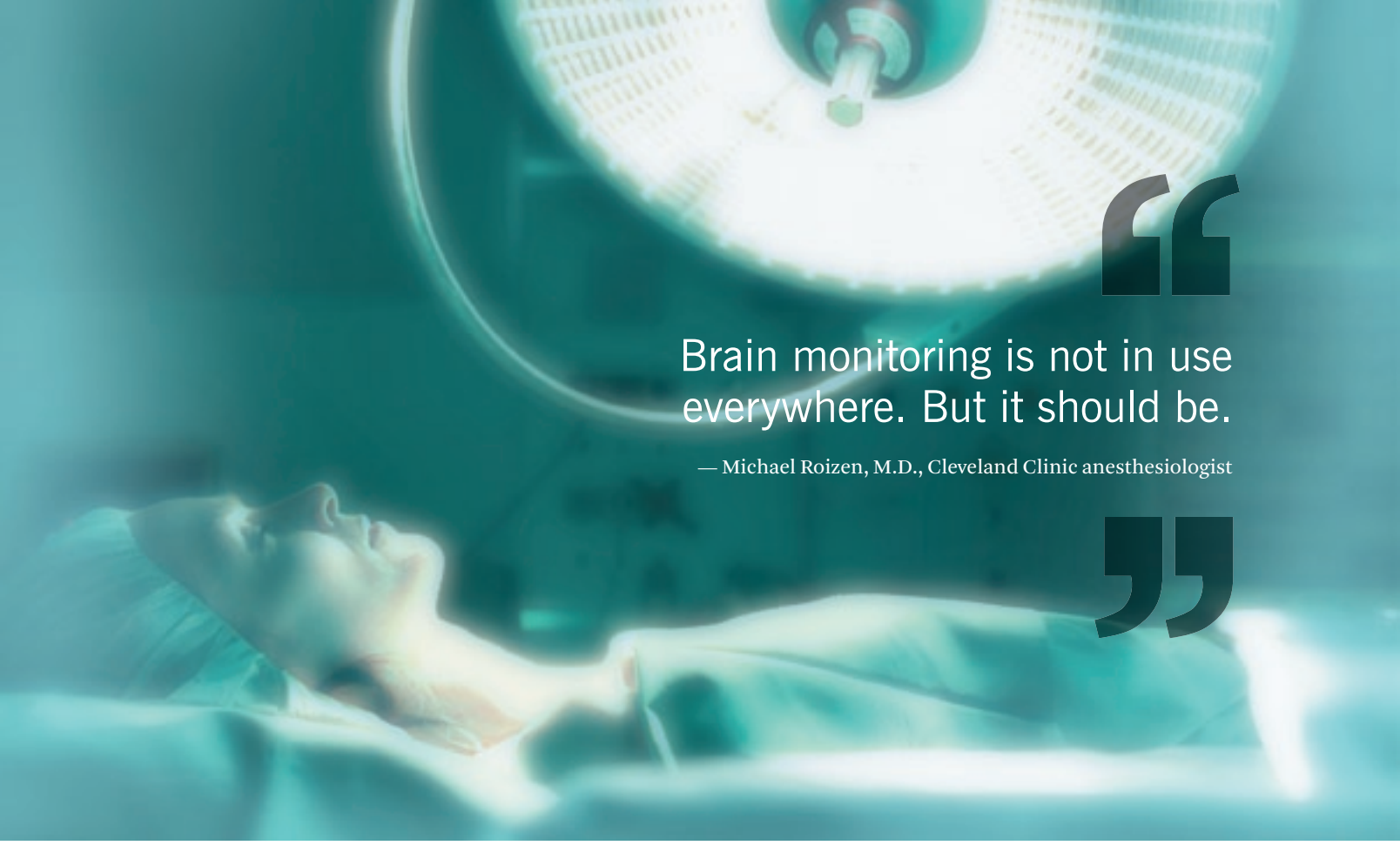
ANESTHESIA AWARENESS: What It Means

As with any shorthand expression for a complex topic, the phrase "anesthesia awareness" can be confusing. It does not apply to the use of local or regional anesthesia to numb a particular area of the body. Nor does it apply to the conscious sedation used for many procedures. In all of those cases, the patient is expected to be conscious and aware of what is happening.

To emphasize the point, Michael Roizen, M.D., a leading anesthesiologist at Cleveland Clinic, prefers and uses the phrase "unintentional awareness."

The American Society of Anesthesiologists and the American Association of Nurse Anesthetists also do not use the term "anesthesia awareness" in their patient education materials.

Instead, they talk about "awareness under general anesthesia," which they define as "a rare condition that occurs when surgical patients can recall their surroundings or an event — sometimes even pain — related to their surgery while they were under general anesthesia."



> Brain monitoring is not in use everywhere. But it should be.
>
> — Michael Roizen, M.D., Cleveland Clinic anesthesiologist

with access to patient medical records have found no correlation between a patient's recollection of awareness and their vital signs during anesthesia.

The American Society of Anesthesiologists (ASA) is now collaborating with the Anesthesia Awareness Campaign to create a database that includes the medical records in reported cases of anesthesia awareness.

NO CONSENSUS ON MONITORS

The American Society of Anesthesiologists has not endorsed brain monitoring or other equipment for anesthesia awareness. "At the present time, none of these new technologies has been perfected," states the ASA patient information on awareness. The organization released a statement in 2005 recognizing the devices as "a possible tool for monitoring selected patients, but ... the decision to use this emerging technology should be made on a case-by-case basis by the individual practitioner."

Dr. Roizen agrees that existing monitors are not a perfect indicator of awareness. But, he says, "We think that its use does correlate with decreased awareness." Two 2004 studies back up his thinking.

Studies from Sweden and Australia both found about an 80 percent lower risk of anesthesia awareness during surgery in patients who received brain monitoring. Both studies received funding from a monitor manufacturer.

Other studies have found significantly less postoperative nausea and vomiting among brain-monitored patients, likely due to lower drug doses. They also note earlier discharge from postanesthesia care units, and cost savings of up to 39 percent per patient from reduced use of anesthesia drugs.

In fact, Dr. Roizen notes, the evidence that brain monitors help reduce drug doses to patients who need less anesthetic is actually stronger than the evidence that it helps reduce awareness incidents among patients who need more.

Dr. Osterman, the Boston University psychiatrist, is in favor of further study to determine the best measures to prevent awareness. "We can develop a profile of people at high risk, but that doesn't mean it won't happen to someone at low risk," she observes. "I'm not an anesthesiologist, but my philosophy is, 'If we can prevent, then we should prevent.' If awareness does occur, it is important that the anesthesiology staff acknowledge the problem occurred and work with mental health clinicians to avoid extended trauma."

Ms. Weihrer is adamant: "I insist that people ask three questions [of their doctors]: 'Do you have brain activity monitors? Do you use brain activity monitors?' Then you still have to go one step further and say, 'Will you use one on me?' "

Tracie Thompson is a San Francisco-based writer and editor who specializes in medical and legal issues, contributing to publications including *California Lawyer* and the *Howard Hughes Medical Institute Bulletin*.

HANS NELEMAN/GETTY IMAGES

SEAT *of* HONOR

Some gifts never lose their luster. Their meaning and usefulness persist, often growing more valuable over time. Such was the case in 1502 when the mother of King Henry VII made a gift to the University of Cambridge in England, establishing the Lady Margaret Professorship of Divinity. The professorship, which remains today, began a tradition that still supports researchers and educators: the endowed chair.

Endowed chairs work in much the same way they did in the 16th century. An initial financial gift is invested to provide a permanent source of income that the chair holder uses to support his or her work.

At Cleveland Clinic, the first endowed chair was established in 1980. Today, chairs support the work of more than 70 physicians and scientists. In this issue of *Cleveland Clinic Magazine*, we meet the people who have provided for three of Cleveland Clinic's recently endowed chairs.

NEIL LANTZY

Gift of Learning

> "...we realized we had some resources of our own, and the best way to use those resources was to promote education, which we know is the key to a better life."

Growing up on a farm in western Tennessee, **John Brown** learned about hard work, discipline and responsibility. These were valuable lessons, but he had plans for the future that reached beyond the farm, and he knew that education was crucial to turning those plans into reality.

The man who is now Chairman of Stryker Corp., one of the world's leading medical technology companies, became the first member of his family to go to college. He attended Freed-Hardeman University, where he majored in chemical engineering and met his wife, **Rosemary**, who was studying to be a math teacher. The two later graduated from Auburn University.

Their meeting was the beginning of a life together that would champion education.

"We realized that education is important for everyone," Mrs. Brown says. They often combine their passion for education with their strong interests in health and medical advancement — interests that extend beyond Mr. Brown's leadership at Stryker.

About 30 years ago, Mr. Brown was diagnosed with mitral valve prolapse, a disorder in which one of the heart's valves does not close properly. Mitral valve prolapse often can go untreated, but by the mid-1990s, Mr. Brown's condition had progressed.

"With my condition and my interest in medical devices, I kept up on who was doing what," Mr. Brown says. "Cleveland Clinic had a reputation as the top institution for mitral valve repair."

Mr. Brown, a longtime Kalamazoo, Mich., resident, eventually came to Cleveland Clinic, where, in 2002, he had surgery. Over the course of his care, he developed a rapport with cardiologist Brian Griffin, M.D., and Delos M. Cosgrove, M.D., then a cardiac surgeon and now Cleveland Clinic's President and Chief Executive Officer. Their relationship inspired a $1.5 million gift to establish the John and Rosemary Brown Endowed Chair in Cardiovascular Medicine. The chair, which was dedicated on July 24, 2007, is held by Dr. Griffin and supports his work in cardiology and in educating other doctors.

John and Rosemary Brown

TOM MERCE

"We also train people from throughout the United States and from other countries so that they can go back and enhance academic and clinical cardiac services all over the world," says Dr. Griffin, who directs the cardiovascular disease training program.

The chair is endowed through the John and Rosemary Brown Family Foundation, in which the Browns' two daughters play active roles. The foundation supports a variety of education-oriented causes, from early childhood education to college funding.

"We grew up during the Great Depression," says Mrs. Brown, "so, of course, throughout our lives, we were saving money. Then we realized we had some resources of our own, and the best way to use those resources was to promote education, which we know is the key to a better life."

From the Heart


Chuck and Char Fowler

Vivid color and textures fill the walls of **Chuck** and **Char Fowler**'s home in Lyndhurst, Ohio, capturing local artists' unique paintings, eclectic glasswork and sculpture.

The homeowners, high school sweethearts married for 43 years, make a conscious effort to fill their home and their lives with what's most important. The Fowlers live by the motto, "do good, do well." They believe helping others will contribute toward life's successes, which motivates their generous support of community organizations focused on improving health and wellness, arts, education and children.

"If you feel it in your heart, it's the right thing to do," Mrs. Fowler says.

Mr. and Mrs. Fowler grew up in a small town in Indiana where, they say, everyone felt responsible for supporting the community and their neighbors. Their close-knit community upbringing inspired their desire to give back when the couple moved to Cleveland in 1988 to partner with William E. Conway, Emeritus Trustee of Cleveland Clinic and Chairman of Fairmount Minerals, a Chardon, Ohio-based industrial sand producer.

After arriving in Cleveland, Mr. Fowler, now President and CEO of Fairmount Minerals, attended Case Western Reserve University's Weatherhead Executive Management program. There he met classmates Joseph F. Hahn, M.D., Cleveland Clinic Chief of Staff; Robert Kay, M.D., former CEO of Cleveland Clinic in Florida; and Jeffrey Ponsky, M.D., former head of Non-Invasive Surgery at Cleveland Clinic.

His new study group partners introduced the Fowlers to Cleveland Clinic. Soon after, the Fowlers and employees of Fairmount Minerals began receiving yearly executive health examinations at the hospital.

In 2000, Mr. Fowler was referred to A. Michael Lincoff, M.D., interventional cardiologist, after his routine examination uncovered a heart problem. As a result, Mr. Fowler underwent septuple-bypass surgery to prevent a heart attack.

> "Dr. Lincoff is very passionate about his research, and he needs young medical people to continue the research."

Grateful for Dr. Lincoff's care, Mr. and Mrs. Fowler gave $1.5 million to Cleveland Clinic to establish the Charles and Charlotte Fowler Endowed Chair in Cardiovascular Research. Dr. Lincoff, Vice Chairman, Cardiovascular Medicine Research, is the first physician to hold the endowed chair.

Dr. Lincoff plans to use the endowed chair funds to support select graduate fellows' research and promising departmental studies, such as percutaneous replacement of cardiac valves, identification of genetic markers and therapy for heart disease, advancements in blood-thinning medications and improvements in stem cell therapy and lipid-lowering agents.

The Fowlers feel privileged to help Dr. Lincoff pursue his research goals and provide funds to support the next generation of innovators at Cleveland Clinic.

"Dr. Lincoff is very passionate about his research, and he needs young medical people to continue the research," Mr. Fowler says. "Our expectation for the chair is not only for him to continue current research efforts, but to expand as well."

Mr. and Mrs. Fowler are pleased to support research initiatives while they can still see the impact.

"We're glad to know where our finances are going," Mrs. Fowler says. "We made a choice that we feel good about and that we know will definitely help other people." Mr. Fowler adds, "We would much rather do this now while we can enjoy it, rather than be a name up on the wall."

YU KWAN LEE

Going the Distance

"We have a philosophy. We must give back at least part of what has been given to us, and the best way of doing this is through philanthropy."

Some people will go far to support the things they believe in. **The Mikati family** traveled almost 6,000 miles from Lebanon, where they live, to Cleveland Clinic. It's a trip the family makes several times a year to visit Nizar Zein, M.D., a specialist in liver disease and transplantation.

"Our relationship with Dr. Zein is twofold, you see," says patriarch **Taha Mikati**. "There is a family relationship — he is a relative. And there is a medical relationship: Dr. Zein saw our family through my liver transplantation, which was a difficult time that we were fortunate to overcome."

The Mikatis, who divide their time between London, Paris and Beirut, emphasize that good fortune is something they feel compelled to share with others.

"We have a philosophy," says Mr. Mikati. "We must give back at least part of what has been given to us, and the best way of doing this is through philanthropy."

The family's foundation gave $1.5 million to establish Cleveland Clinic's first endowed chair from an international family. Dr. Zein is the first physician to hold the chair, which was dedicated Nov. 14, 2007, and will support liver disease and transplantation research.

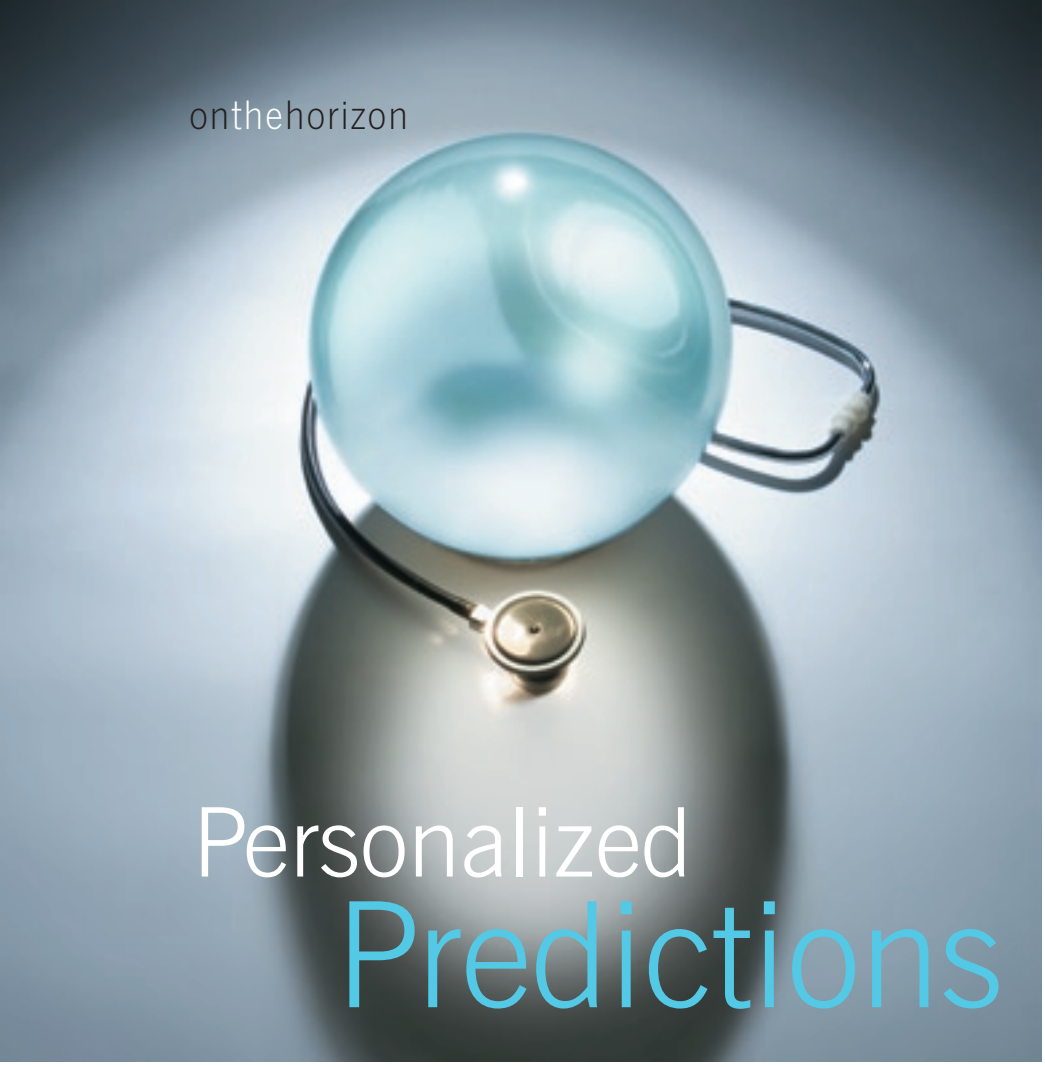
"Funds from the chair will support research into the factors that contribute to liver disease, as well as how to prevent liver cancer and how to develop novel, noninvasive diagnostic techniques," explains Dr. Zein, Chief of Hepatology and Medical Director of Liver Transplantation. "This will provide sustainable, long-term support for research."

"We believe that Cleveland Clinic is one of the leading institutions for liver disease care and research," says Mr. Mikati, Chairman of the diversified, family-owned company M1 Group. "We are convinced of the ability of Dr. Zein and his team to find solutions."

The Mikati Foundation, which supports various healthcare and education initiatives in Lebanon and abroad, was founded by Mr. Mikati and his brother, **Najib**, a former Prime Minister of Lebanon. In Lebanon, the organization is known as Azm & Saade and was named for the brothers' father and mother. "The names mean 'determination' and 'happiness,' respectively," says Taha Mikati. "It's a worthy namesake, we feel, for an organization that is determined to further the welfare and happiness of others. Our main goal is to make a difference in the lives of others."

Taha and Nada Mikati

TOM MERCE



Personalized Predictions

Michael W. Kattan knows firsthand why good predictions are so important in medicine: In 1990, while he was working on his Ph.D. at the University of Houston, he was diagnosed with Hodgkin's lymphoma. Chemotherapy seemed to eliminate the tumors that had spread throughout his chest, neck and ribs. But then the 24-year-old faced a decision: Should he agree to radiation therapy, which might kill any remaining cancer cells but might also damage his heart? Or should he decline the radiation and risk a recurrence of the cancer?

It was a tough call, says Dr. Kattan, now Head of Quantitative Health Sciences at Cleveland Clinic. His physicians told him the odds of various outcomes. But when he researched the matter on his own, he was appalled to learn that those predictions were one-size-fits-all generalities based on studies that lumped together patients of all conditions and ages.

Dr. Kattan wanted to know *his* odds. In graduate school, where he studied management information systems, he had learned that the business world had much more sophisticated methods for estimating risk. Why not medicine?

In the end, Dr. Kattan opted for the radiation therapy. Today he remains cancer-free and his heart appears undamaged. But after that experience, he vowed to help physicians and patients alike do a better job of navigating such decisions. Since 1999 he has been developing software that provides personalized predictions of the odds on various procedures — for example, a prostate cancer patient's specific chances of remaining cancer-free after surgery to remove the prostate versus his chances with radiation therapy.

"The difficult situations are where you're trading quantity for quality of life," says Dr. Kattan. "For example, prostate surgery might eliminate a tumor, but might also cause incontinence or sexual dysfunction. And that's where you really want to know the individual probabilities of good and bad so that the patients can know exactly what they are trading."

> "Patients today want to have more involvement in the medical decisions that affect them."
>
> — Michael W. Kattan, Ph.D.

Early in his career, Dr. Kattan and his colleagues developed prediction tools for prostate and eight other cancers. Now at Cleveland Clinic, he is moving beyond cancer to develop prediction software for diabetes, kidney disease, osteoporosis, endometriosis and cardiovascular disease.

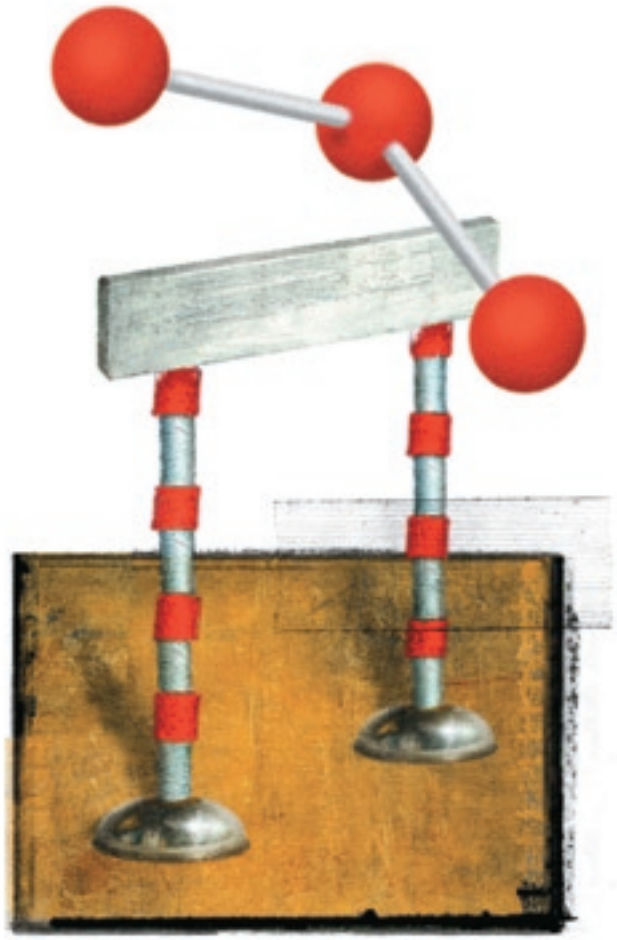
The tools are designed to be simple to use. Many physicians have downloaded the prediction software onto their PDAs, smart phones or desktop computers, he says. "With, say, a prostate patient sitting on the examining table, the physician enters data such as the patient's age, PSA [prostate-specific antigen] levels and clinical stage, which takes about 15 seconds. From there, the program takes a split second to calculate an answer," such as the statistical probability of survival after prostate surgery.

"Patients might also find the tools online themselves, print out the results and take them to their physicians," he adds. "Patients today want to have more involvement in the medical decisions that affect them, and this helps them participate."

— Mitch Waldrop

MICHAEL NORTHRUP

An Early Jump on Heart Disease



Study participants with higher levels of MPO were more likely to develop heart disease requiring hospitalization or to die of heart disease.

RICHARD BORGE/THEISPOT.COM

"How's my MPO?"

For those who are concerned about their heart disease risk, that question might someday be as important as "How's my cholesterol?"

Myeloperoxidase (MPO) is an enzyme produced by cells of the immune system as part of the inflammatory response. A Cleveland Clinic researcher has shown that elevated levels of MPO in the blood may help predict heart disease risk — years before symptoms appear.

"MPO is unique because it plays a direct part in the development and progression of hardening of the arteries," says Stanley L. Hazen, M.D., Ph.D., Head of Preventive Cardiology & Rehabilitation. Along with being a promising marker for future disease, MPO is a potential target for new treatments.

"MPO delivers a double whammy," Dr. Hazen explains. "It converts LDL, the carrier of so-called 'bad' cholesterol, to a form that deposits more cholesterol into cells of the artery wall and it modifies HDL, the carrier of so-called 'good' cholesterol, so that it no longer removes cholesterol as efficiently."

Dr. Hazen studied the potential for MPO as a blood marker for future heart disease in collaboration with S. Matthijs Boekholdt, M.D., Ph.D., and his team at the Academic Medical Center in Amsterdam, the Netherlands. They tested blood from healthy men and women in Norfolk, U.K.

At the beginning of the study, when participants had no symptoms of heart disease, the researchers measured MPO levels in their blood. Then the investigators determined who developed heart disease up to eight years later. Study participants with higher levels of MPO were more likely to develop heart disease requiring hospitalization or to die of heart disease, according to the results reported in the July 10, 2007, issue of the *Journal of the American College of Cardiology*.

Surprisingly, people with high levels of MPO had increased risk even if their HDL, LDL and C-reactive protein levels were favorable. While an FDA-approved MPO test is already in use for patients who have a history of chest pain, this new study could lead to routine MPO screenings to identify people who might be at risk for heart disease, even if they have no known risk factors.

"The predictive value of MPO is independent of HDL and LDL cholesterol," says Dr. Hazen. "Current risk-screening strategies have a very cholesterol-centric view, but this can only account for a portion of cardiovascular risk."

While some studies have shown that certain medications, called statins, effectively reduce MPO levels, more research is needed to determine whether general risk-reduction measures, such as exercise and weight reduction, can do the same.

— Jacqueline Houtman

Back to the Future

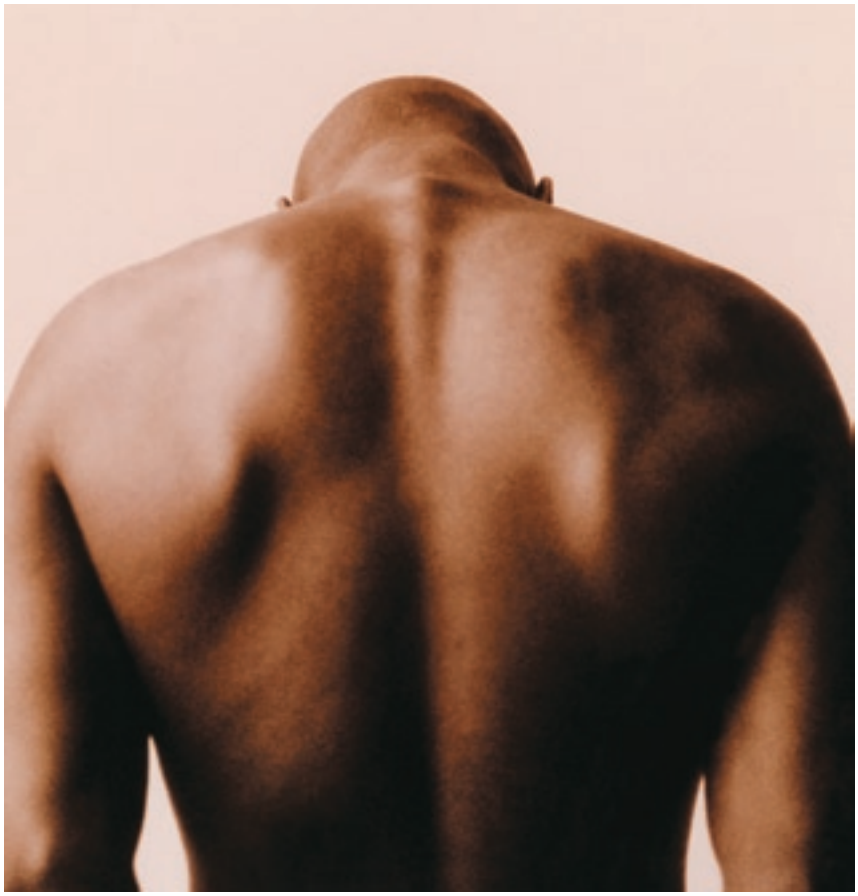
It sounds like something out of *Star Trek*: A tiny chip implanted in the body sends information about injury and postsurgical healing to a handheld device, giving doctors a clearer idea of what's wrong and how to fix it.

The idea is no longer the stuff of fantasy. Biomedical engineers at Cleveland Clinic are partnering with spine doctors to develop tiny sensors, measuring about a tenth of an inch, for placement between vertebrae. The sensors are intended to help doctors better determine the source of back pain, monitor healing after treatment and help prevent further injury.

"Back pain can be tricky to diagnose," says Edward Benzel, M.D., Chairman of Cleveland Clinic's Spine Institute, who is developing the technology with colleagues Shuvo Roy, Ph.D., and Aaron Fleischman, Ph.D. "X-ray and MRI images don't always tell the whole story."

Standard imaging devices can't provide information about load fluctuations on bones, artificial discs or plates used to fuse vertebrae together. Pressure data from the chip would reveal whether the body's delicate balance remains intact or if it has been thrown off. Doctors would be able to track the location of a patient's injury and assess how a patient is healing after surgery.

The sensors, called MEMS or microelectromechanical systems, are designed to function inside the body for as long as needed, providing information as the patient moves through various physical situations. The devices ultimately will be wireless, dispatching pain information straight to the doctor's handheld computer — or, possibly, the patient's own handheld device for self-monitoring. Implantation would occur with a catheterlike device during minimally invasive surgery.



The technology is still in development, with testing expected to begin in patients by early 2009. "Our hope is that physicians could start using this technology within a couple of years," says Dr. Roy.

And spine care is just one application doctors foresee. "We could monitor healing after joint replacement, decide if someone needs a hip or knee surgery and guide athletes' rehabilitation," says Dr. Benzel. "This is the kind of routine care that has the potential to be made much more precise."

— Tricia Schellenbach

Back pain is the most common cause of job-related disability and a leading contributor to missed work.

Source: National Institute of Neurological Disorders and Stroke

To view a video about spine sensor technology, visit clevelandclinic.org/ccm.

LISA SPINDLER PHOTOGRAPHY INC./GETTY IMAGES

Using Magnets to Improve Cancer Care

Separating the wheat from the chaff. In essence, that's what cancer researchers want to do as they look to a patient's blood to learn whether a treatment is working. It's also what they'd like to do as they try to "hand pick" cells that may be the key to the patient's recovery.

Now a team at Cleveland Clinic has developed a device that uses magnets to single out key cells. The device, known as a magnetic flow sorter, is still in development, but preliminary results are promising and the researchers hope to have a prototype ready for testing next year, says Maciej Zborowski, Ph.D., a biomedical engineer at Cleveland Clinic's Lerner Research Institute who is leading the development of the device with researchers at Cleveland Clinic's Taussig Cancer Institute and The Ohio State University in Columbus.

After drawing a blood sample from a patient, Dr. Zborowski's team treats the sample with a type of protein called an antibody. Antibodies are designed to zero in on and attach to specific cells of interest — for example, stem cells from the bone marrow or tumor cells. To make the target cells magnetic, the antibodies carry iron-containing nanoparticles.

By running the blood sample through the device's magnet, the magnetized cells are rapidly sorted out from other cells and blood components. They can then be counted or saved for later use.

The device could enable physicians to measure levels of tumor cells circulating in the blood, which would indicate how likely the cancer is to recur. Knowing whether levels of these cells are decreasing or increasing could also help physicians assess how a patient is faring on chemotherapy and plan how aggressively to treat the cancer.

Using magnets in this way to sort specific cells in the body — whether to kill cancer cells, monitor therapy or protect healthy cells during cancer treatments — is part of a larger movement toward targeted therapy for cancer patients.

Cancer isn't one disease. It's many with one thing in common: out-of-control cell growth that can be deadly. To halt unwanted growth, patients often undergo chemotherapy or radiation, which can kill good cells along with the bad.

Researchers are striving to add to a class of "smart drugs" that more effectively target each individual's cancer — because even within the same type of cancer, there are variations. For example, some women have breast cancer that responds well to certain drugs and others don't. New approaches to treatment and prognosis target receptors on specific cancer cells, allowing doctors to kill only those or at least find where they're hiding.

The magnetic flow sorter developed by Dr. Zborowski's team could possibly also be used to separate out adult stem cells, which are necessary to rebuild the immune system and other tissues, but are prone to destruction by chemotherapy. The team is testing whether the device could preserve the stem cells so they can then be injected back into the patient to aid the body's recovery after treatment is complete.

"The long-range hope is this type of device could be used for isolating adult stem cells, which could potentially be used for regenerative therapy for repairing bone, muscle, the heart or even brain tissue damaged by Parkinson's disease," Dr. Zborowski says. — Steve Mitchell

GEOFF SPEAR/VEER

A Menopause Survival Guide

Holly L. Thacker, M.D., charts the way through The Change

Are the changes that often come with menopause — weight gain, waning energy level and diminishing sex drive — a normal part of aging? Are hormones a good idea or something to avoid? Women have plenty of questions as they enter midlife, and they don't always get the best answers, according to this Cleveland Clinic women's health specialist.

What happens to a woman's body during menopause?

▶ A woman's body can go through major changes, many due partly to the drop in estrogen levels. The classic hormone-deficiency symptoms include hot flashes, night sweats, interrupted sleep, dry vagina, changes in skin and hair, and bone loss. For some women, these symptoms wreak havoc. Other women have zero symptoms, but may still be rapidly losing bone. Menopause is a normal life event, but as with childbearing, which is also natural and normal, women may need assistance and attention.

How can women in midlife avoid "if I knew then what I know now" in their later years?

▶ Having a strong focus on cleaning up their lifestyle — increasing exercise, improving diet — and knowing their numbers: BMI (body mass index), blood pressure, cholesterol, bone density. One in two women has low bone density and will suffer bone breakage, which is directly related to loss of female hormones at menopause. Taking calcium and vitamin D3 (often identified as cholecalciferol on the packaging) is necessary, but may not be enough. Lots of women have healthy lifestyles and take vitamins — then they're surprised to learn they are rapidly losing bone. And certainly, by the time a woman is 50, she should see a doctor every year. There is a lot we can offer in preventive care.

What was your reaction to the August report in the *New England Journal of Medicine* that most older Americans are still enjoying a robust sex life?

▶ A good sex life is a strong marker for health. But almost 40 percent of the women in the study reported vaginal dryness or inability to climax. Universally, the vagina and vulva shrink with loss of estrogen. It happens so gradually that women don't always link it to menopause. Then, by age 55 or 65, they lose tissue elasticity and some sensation. I see daily suffering — an epidemic of untreated vaginal atrophy. But there's no reason a woman can't have a healthy vagina. Localized hormone treatments can help. We have so many nice options for delivering estrogen directly to the vaginal area: creams, a vaginal tablet or a vaginal ring. Both the tablet and the ring are inserted into the vagina by hand. These low-dose estrogen products have little, if any, systemic side effects and can be used in women, such as breast cancer survivors, who might not choose to use systemic estrogen therapy.

Most women gain 10 to 15 pounds after menopause. How can they avoid that particular health risk?

▶ Women in midlife have to exercise more and eat less just to stay the same weight. It's just a fact. When my patients are reaching their early to mid-40s, I bring it up. When you were younger, maybe your body could withstand certain abuses, like overeating or not exercising. But not anymore. Here's another instance where estrogen may help. It's not a panacea, but women on hormone therapy gain less weight than women who take no hormone therapy.

What have you found motivates people to change?

▶ We've had good success with shared medical visits. Women have their individual appointment with a group of a dozen or so women who have similar concerns. It's very empowering and motivating to be in the presence of a woman who is no longer suffering with menopausal symp-

Holly Thacker, M.D., here leading one of her group medical visits for women, is Director of Cleveland Clinic's Women's Health Center and Associate Professor of Surgery, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University. Her new book, *Women's Health: Your Body, Your Hormones, Your Choices, A Cleveland Clinic Guide*, was published in 2007.

toms or who has shed extra weight or who is back to having an enjoyable sex life. Hearing it from another woman makes a big difference.

Does your position on hormones put you in the minority?

▶ Among true menopause experts, I am not in the minority. Also, other doctors are realizing that misapplying studies done on much older women without menopausal symptoms is not helpful to younger women who do have symptoms. For menopausal women with symptoms, hormones are far safer than people were led to believe five years ago.

Why has the use of hormone therapy to replace estrogen dropped so dramatically — from 61 million prescriptions in 2001 to 21 million in 2004?

▶ Ever since the federal government's Women's Health Initiative reported in 2002 that hormone replacement therapy can be harmful, women have been petrified of hormones. They have a highly exaggerated sense of risk, so they don't seek treatment for their symptoms. With any prescription medicine, there are risks and benefits. While you might not use high doses in a woman in her 60s with no symptoms, to translate that to a woman in her 40s or 50s is really a crime. And that's what's happened. We've lost a generation of women who may be helped by hormones.

The key is to tailor hormone therapy to each woman's individual needs, and there are many good options. But I'm concerned that women are being hoodwinked by people cashing in on this fear of hormones. They're turning to alternative products that are custom-compounded, or custom-mixed, by pharmacists and contain various hormones in differing amounts based on the individual's needs. Now, that may sound good, but there are risks associated with these mixtures because their safety and quality are not monitored or approved by the FDA. However, there *are* hormone medications tailored to individuals that are available by prescription and therefore regulated.

Read an excerpt from Dr. Thacker's book at clevelandclinic.org/ccm.

GREG RUFFING

BY TERESA MARTENS, as told to *Cleveland Clinic Magazine*

Good Catch

There I was: standing at the stove, making Thanksgiving dinner when, suddenly, my legs disappeared. Chad, my fiancé, was at the counter chopping vegetables when I started to fall. He caught me — I don't know how — and lowered me to the floor, where we waited nearly 15 minutes for the sensation in my left side to return.

I thought it was stress. At 21, I was finishing my bachelor's degree in sociology while living six hours apart from Chad. We were planning to marry in just seven months, and I had a lot to do. Anyone who has ever planned a wedding knows just how over the top things can get. Between visits to the florist, dress fittings and deciding where to seat your father's co-workers at the reception, real life takes a backseat. It just happens.

But my "episodes" kept happening, too. One snuck up on me at a friend's birthday party. They had become so common at that point that I just sat down on the floor and said I was dizzy. Another time, at the mall, I felt an attack coming and tried to make it to my car. I ended up dragging my left leg across the parking lot.

Maybe I should have taken it more seriously, but in the shadow of my planning and schoolwork, the attacks were a small thing, an inconvenience. The fact that I bounced back fairly quickly after each episode made them easier to ignore.

In late March, I had an appointment with the eye doctor and casually mentioned what had been happening. I was making small talk, but the optometrist was horrified. How long had this been going on? Why hadn't I seen a doctor? But it wasn't her concern that sent me looking for help. It was a story from years ago that suddenly came back to me about a man whose diabetes was discovered in his eyes during a vision exam. The man ended up losing part of his sight, but if he had let his condition go much longer, he could have lost it all.

I was instantly worried that I had put this off for too long.

Things happened quickly after that. A flurry of referrals, a flight to Cleveland, a barrage of tests and, suddenly, my episodes had a name: Moyamoya. Moyamoya is Japanese for "puff of smoke," which describes the look of the tangled blood vessels that were blocking the arteries at the base of my brain. Far from a stress disorder, Moyamoya is a rare condition that affects the blood supply to the brain. It is more common in Asians, and I was born in South Korea.

The disease is treatable with surgery, but by letting it go — even for four months — I had run the risk of permanent brain damage.

I was crushed. I don't know what I expected the doctors to find or what treatment I'd hoped they'd recommend, but brain surgery was not on my agenda — not at this point in my life. I didn't have much choice, though. My plans had to adjust.

On April 10, 2007, 10 days after my family and I arrived at Cleveland Clinic, I had surgery. My parents, Chad and his parents waited 15 long hours before they could see me. At the end of it, though, I was recovering well, and we were making plans for home. My episodes, or ministrokes as I had learned to call them, were gone, and it was unlikely they'd ever return. I should have been relieved.

That's not how I saw it, though. I was worried that I wouldn't graduate, and I still had a wedding to coordinate.

In the end, everything I'd hoped for took place, even if it didn't go exactly as I'd planned. I spent most of spring semester away from campus, but, somehow, on May 13, I walked across the stage with my friends and accepted my degree. On July 14, Chad and I said our "I do's" on a day that was chaotic but perfect and ended with a beautiful result — we were married.

It turns out you find time for the things that matter.

Teresa Martens graduated in May from St. Ambrose University in Davenport, Iowa. She is now a youth specialist at a behavioral rehabilitation center for boys, and she and her husband live in Higginsville, Mo.

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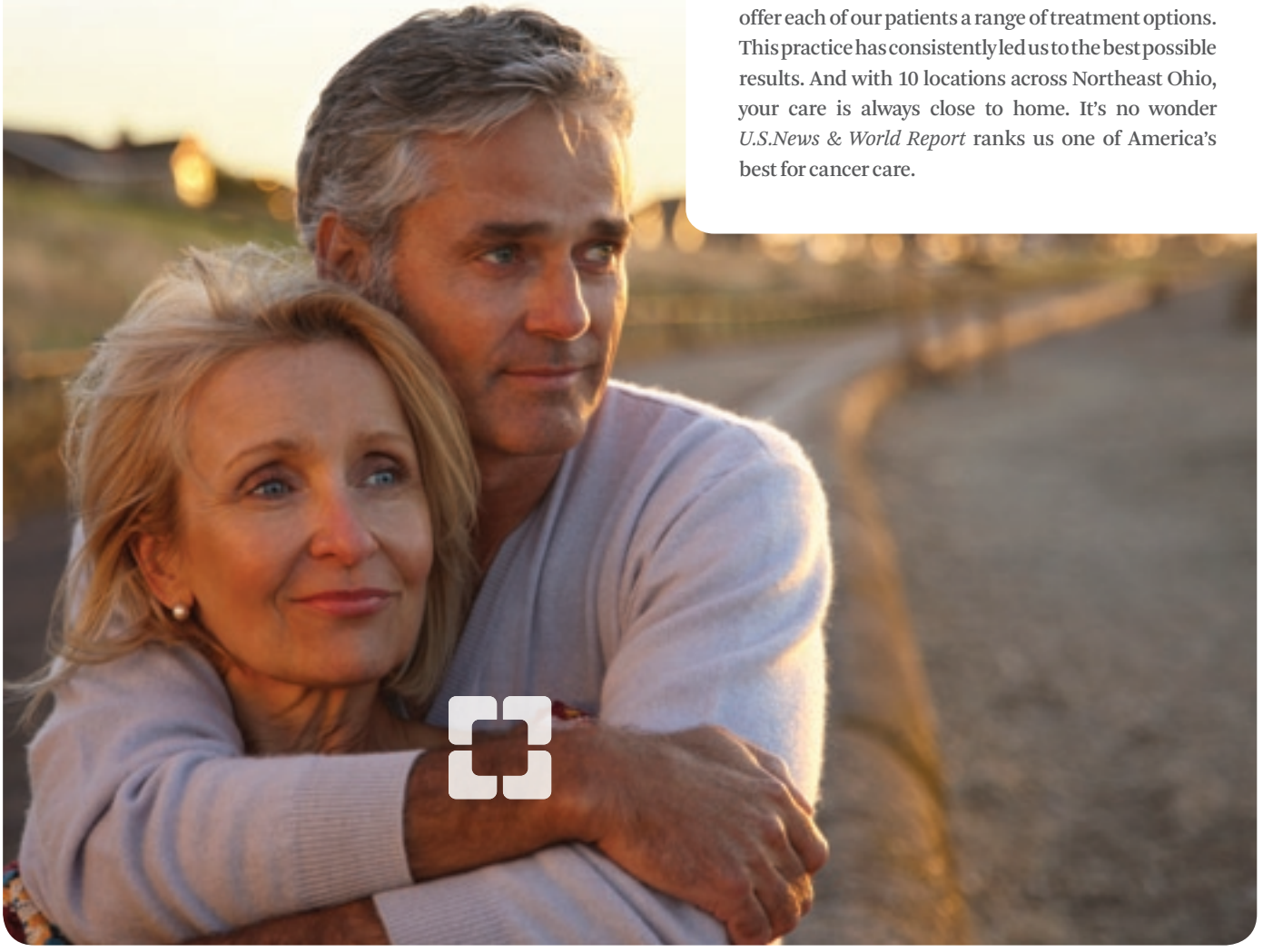

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