Michael Waters, MD, PhD, utilizes Cedars-Sinai's state-of-the-art 64-slice CT scanner for emergency imaging of acute stroke patients.

SILENCING THE SILENT KILLER

BY IDELLE DAVIDSON

Every 45 seconds, someone in the United States suffers a stroke. The acute stroke team at Cedars-Sinai knows a good fight. Their strategy? Award-winning quality patient care and education; researching stroke-causing gene mutations; and investigating the life-saving potential of clinical trials.

THE TWO WOMEN SIT IN A CAFÉ NEAR THE OFFICE. They are having lunch. One drops her fork into her salad and stares at her hand. It is trembling. Her entire right side suddenly feels numb, and she can't see out of one eye. When she tries to speak, her friend can't understand her. "I feel funny," the woman says, her voice a slur, her face drooping.

The paramedics arrive within minutes. They suspect a stroke and transport the woman to Cedars-Sinai Medical Center. While en route, they call a "code brain," activating the pagers of the stroke team. The team prepares for arrival.

"At this point, it is a well-oiled machine," says Laurie Paletz, RN, nurse coordinator for the Cedars-Sinai Clinical Stroke Program. "We do a very thorough neurologic exam and history. Can they speak? Answer questions? Move their extremities? This is all happening while the blood is being run, they have their CT scans, and their IVs are started."

Stroke is the third-leading cause of death in the United States. These "brain attacks" occur when an artery bursts (a hemorrhagic stroke) or becomes blocked (an ischemic stroke), cutting off oxygen to nerve cells. More than 80 percent of strokes are ischemic. Within moments, the cells die. Waiting too long for help can mean the difference between recovery and permanent brain damage.

"Every minute counts," says Paletz, who is her own energy force as she talks at warp speed and blasts from office to clinic to consult with patients in the ER. "There is an area around the brain that remains viable for about three or four hours after the stroke occurs. If we can restore blood—which has oxygen and nutrients—to the area, the stroke will be significantly smaller." Their goal is to administer tissue plasminogen activator (tPA) to all appropriate ischemic stroke patients. The clot-busting drug can save lives—but it must be given within the three-hour window.

The engine that drives the staff's brisk, methodical pace is Get With the Guidelines (GWTG), an American Heart Association and American Stroke Association in-hospital quality improvement program. GWTG sets national standards for timely treatment and discharging practices. In addition, the program educates patients on secondary stroke prevention. "Everything we do goes into a database," says Paletz, who started GWTG at Cedars-Sinai last year. She coordinates the program with Vladimir Royter, MD, a research stroke fellow. "It allows us to compare our performance to other stroke centers across the country." The team has been so effective in delivering rapid care that in March they received one of the Stroke Association's top compliance awards, The Initial Performance Achievement Award.

But critical care and education are just one part of a concerted effort to wipe out stroke. Michael F. Waters, MD, PhD, heads the Clinical Stroke Program, including GWTG. He also partners with a team of neurologists, neurosurgeons, neuroradiologists, vascular surgeons, and rehabilitation specialists. Dr. Waters believes a critical

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element to stroke prevention lies in cutting-edge research and clinical trials.

"For me, the brass ring is being able to go back into a clinic and tell a patient, 'I think I've got something for you, something that is going to help you,'" he says.

As Waters sits at his desk, hands folded, he speaks slowly, measuredly, in a deep radio-announcer's voice. He is completely focused on explaining the nuances of one of the most promising areas of scientific research.

That area is the study of cerebral cavernous malformations, or collections of blood vessels in the brain that grow into one or more non-cancerous masses. The capillaries within these vessels are weak and lack supportive tissue, Dr. Waters explains. Therein lies the problem.

"They have devastating effects when they rupture and bleed, because then they will cause a stroke," says Dr. Waters. They can also result in migraine headaches or seizures. These malformations affect some 30 million people, or 0.5 percent of the world's population.

Scientists now know that genetic mutations in genes—identified as CCM1, 2 and 3—cause these masses. Patients with multiple malformations have usually inherited a faulty allele. In what is called an autosomal dominant pattern, if one parent carries the mutation, the child has a 50 percent chance of inheriting it. But those with a single mass would have developed the mutation during their own growth and development.

"We found that most patients who have a malformation have a single lesion. So it is more rudimentary to manage them with medication, especially if their symptoms are minor," says Dr. Waters. "But every once in a while, you find patients who have multiple lesions and sometimes a dozen of them throughout the brain and spinal cord. That can be deadly." Once the masses start to bleed, they can affect motor skills or cognition, or cause paralysis. Sometimes surgeons can remove them.

In 2005, Dr. Waters identified a new mutation in the CCM1 gene. His work resulted in a diagnostic DNA-based gene test that is now offered to patients. At least in one family, the test changed the course of two women's lives. Their brother had been diagnosed with the mutation and multiple cerebral cavernous malformations. He had migraine headaches, then a hemorrhagic stroke. Ultimately he suffered acute paralysis on one side of his body. The women lived in fear of developing the defect and passing it on should they have children. Each year they underwent brain imaging tests at no trivial cost to themselves and to the healthcare system.

But finally there was a way to screen them. Technicians drew their blood. Then Dr. Waters sequenced their DNA. He discovered that their risk was no greater than that of the general population. He told them: "Don't worry about it. Get married. Have your kids. Be happy."

Of course, in some families the genetic test confirms a patient's worst fears. "Many families want this information," says Dr. Waters. "At least they know what they're dealing with, and it helps us manage their care."

Dr. Waters added the CCM1 variant to a database that catalogs disease-associated mutations. Now when doctors sequence someone's DNA, they can cross check the results with the registry.

FOR MANY PATIENTS, AVOIDING ANOTHER stroke is their main concern. Some see clinical trials as lifelines. "This is all about patient education: learning risk factors, cutting out smoking, taking the right medication," says nurse Paletz. "By the time the patient is seen in the hospital, we are unable to prevent the first stroke, but we can certainly do something about preventing the second one."

At Cedars-Sinai, Dr. Waters oversees several important clinical trials. One, PROFESS, or Prevention Regimen for Effectively Avoiding Second Strokes, involves 20,000 patients worldwide. The trial compares the safety and effectiveness of several antiplatelet agents vs. a placebo. "There is strong evidence that these agents may provide protection against recurrent stroke," says Waters.

The IRIS clinical trial, or Insulin Resistance Intervention After Stroke trial, targets patients with insulin resistance, a metabolic disorder in which the body can't process insulin efficiently. Insulin resistance is associated with fat buildup in arteries and blood vessel disease. It generally leads to adult-onset diabetes. If that isn't frightening enough, people with diabetes are at a higher risk of developing heart disease and stroke.

So what if neurologists could work backwards: treat people with insulin resistance to prevent stroke and heart disease? "That is the question we ask ourselves," says Dr. Waters. "Will the same medications that are effective in treating diabetes be just as effective in preventing a secondary stroke before that person develops full-blown diabetes?"

Dr. Waters and the other scientists behind IRIS aim to find out. Patients at Cedars-Sinai have joined others around the world in clinical trials to test Pioglitazone, a medication that reduces insulin resistance. They will remain on either the drug or a placebo for four years while researchers investigate the number of recurring strokes and heart attacks between the two groups.

And, finally, a trial conducted within the service area of the L.A. County Emergency Medical Services Agency is studying a patient's long-term outcome when paramedics in the field administer intravenous magnesium sulfate within two hours of stroke symptoms. Magnesium sulfate is a promising neuroprotective agent.

"The advantage here is that EMS technicians administer the agent while in the ambulance, even before a doctor sees them," says Dr. Waters. "We are trying to tilt the scale in a sense, in order to have those neurons survive, rather than die."

Dr. Waters expertly juggles his time between managing these clinical trials, directing a clinic, overseeing a lab, and writing and reviewing scientific papers. But patients come first. "Once I've made a commitment to establish a relationship with a patient," he says, "that becomes the most important thing to me."

THE BRAIN'S BREAKING POINT

A brain aneurysm is a bulging, weak area in the wall of an artery that supplies blood to the brain. In most cases, a brain aneurysm causes no symptoms and goes unnoticed. In rare cases, the brain aneurysm ruptures, releasing blood into the skull and causing a stroke.

Ruptured brain aneurysms are among the most life-threatening neurological diseases. One in eight people who have them die before reaching the hospital, and 50 percent of those who make it to the emergency room die within two weeks.

By studying the root causes of bleeding aneurysms, Cedars-Sinai researchers are helping to find ways to treat aneurysms early in their development and to prevent hemorrhages.

Preliminary results show that patients diagnosed with a common valve defect in their hearts are about ten times more likely to suffer from a brain aneurysm than the general population, says Dr. Wouter Schievink, director of the neurovascular surgery program in the Department of Neurosurgery.

"It is one of the most dangerous diseases that we work with as neurosurgeons," Dr. Schievink explains. "But we have learned that if we are able to discover an aneurysm prior to it bleeding, treatment can be very effective and a lot safer than after the aneurysm has burst."

Next, Dr. Schievink and his team will be screening large numbers of people who have bicuspid aortic valve for the presence of a brain aneurysm. "This is something we are all very excited about because we could have a fairly significant group of people in the United States who might benefit from having this noninvasive screening done. It is a great opportunity to prevent some deadly brain hemorrhages."

—Laura Randall