ast weekend I took care of a 23-year-old woman with an acute, disabbling stroke—the unwanted surprise of her life," Creed Pettigrew says, as he talks about his work. "Stroke is not simply Grandpa in a wheelchair who can’t move one side of his body."

To further make his point, Pettigrew shares some statistics: of the nearly 600 people admitted to the UK hospital for stroke each year, 25 percent are under the age of 55.

Every 45 seconds, someone in the United States has a stroke; every three minutes, someone dies of one. Stroke is the nation’s third-leading cause of death and the leading cause of long-term disability.

Stroke is a “brain attack”—it’s like a heart attack, only it affects the arteries leading to and inside the brain. And every second counts. As the American Stroke Association’s motto puts it: “Time lost is brain lost.”

The University of Kentucky is battling stroke, and devastating after-effects like dementia and language problems, on a number of fronts. Pettigrew and his colleague Anand Vaishnav are finding out if aspirin, a prescription blood thinner, and rigorous blood pressure control will prevent future strokes more effectively than aspirin alone. Pettigrew just wrapped up a study on the role of folic acid and vitamins B6 and B12 in preventing second strokes and first-time heart attacks. And Lee Blonder is analyzing videotapes to see if targeted language therapy can help stroke patients improve language skills or re-energize the emotional content of their speech.
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These projects all have one thing in common: they focus on disabling results of stroke that up to now haven’t received much attention in clinical research. Pettigrew talks about a major enemy in the battle against stroke: time. In the next few pages, you’ll read about a clinical trial in which scientists at UK and around the world are testing a new drug, based on a clot-busting protein found in vampire bat saliva. This drug could spare thousands of stroke patients from brain damage by extending the treatment window from three hours to up to nine hours after the onset of stroke symptoms.

First, some basics. Pettigrew points out that there are two types of stroke. Hemorrhagic strokes are caused by a ruptured artery, and ischemic strokes—the most common kind—are caused by blood-clot barricades inside an artery. In ischemic strokes, the goal is to remove the obstruction and restore blood flow, something called reperfusion. And the faster you reperfuse brain tissue, the more brain you can save.

Right now the only FDA-approved treatment for stroke is tPA (tissue plasminogen activator), and this drug must be administered, by IV injection, within three hours of onset of stroke symptoms. Because many stroke victims don’t seek treatment within that limited window of opportunity, Pettigrew says, “It’s estimated that in the U.S. no more than 2 percent of all eligible stroke patients get tPA.

“Stroke is very much like a heart attack in that, first
of all, it’s a matter of irrigation. The brain is exquisitely sensitive. It needs a continuous, fresh supply of blood with oxygen and sugars, and without those nutrients the tissue cannot survive. The first line of treatment is reperfusion.

“If we’re lucky enough to beat the clock—which is what happened with this 23 year old I saw last weekend—tPA works pretty well,” says Pettigrew, director of the UK Stroke Program, who, as a member of the 24-hour Stroke Response Team, sees firsthand stroke’s devastating after-effects.

Pettigrew and two other physicians take phone calls to consult about patients, admit patients and supervise their care. This is one of the clinical outreach efforts of the UK Stroke Program, part of the Sanders-Brown Center on Aging.

Because of tPA’s time crunch and other serious drawbacks, researchers around the world are looking at new, more targeted “clotbusters.” One of these is called Desmoteplase. This synthetic protein was derived from a natural compound in vampire bat saliva that keeps the blood from clotting while the bat is feeding. Here’s a fun fact: A bat’s “meal” can take up to 30 minutes. The blood of the bat’s sleeping prey begins to clot just a few seconds after the skin is punctured. A string-like substance called fibrin forms a “screen” that slows, and eventually stops, blood flow. This special compound in bat saliva digests fibrin.

Pettigrew lists several advantages of Desmoteplase over tPA: “Desmoteplase lowers the risk of systemic hemorrhage. When you inject a drug that purposely busts the ‘trouble’ clot, you get an undesired, but unavoidable, side effect: you impair the body’s ability to form normal clotting. What that creates is a propensity for complications like gastro-intestinal hemorrhages.”

He pulls out some stats: “tPA has a 6.4 percent risk of associated hemorrhage, compared to 0.8 percent in patients who do not get tPA.” The German drug company PAION GmbH launched two parallel studies of Desmoteplase. The U.S. study is still ongoing, but the European Phase II clinical trial, which wrapped up in February 2004, found the risk of hemorrhage with Desmoteplase
was 3.3 percent. The European study also determined an effective dose of Desmoteplase and showed that the drug could safely restore blood flow to damaged brain tissue six to nine hours after onset of stroke symptoms.

“The trouble with any of these clot-busting agents is that there is a constant balance between the risk of hemorrhagic complications and likelihood of advantageous reperfusion of the brain.

“Desmoteplase binds avidly to the fibrin in the clot, which means it’s better targeted.” Pettigrew explains targeting is important because you can give much smaller doses of this protein than tPA, thereby lowering the risk of hemorrhage.

“Desmoteplase doesn’t deplete the body’s pool of clotting factors like tPA does, it’s better targeted, and it can be given in lower doses for delayed periods of time.” And Desmoteplase works in two minutes—“that translates into thousands of brain cells salvaged per minute,” Pettigrew says. It can take up to an hour for tPA to have an effect.

UK was one of only 12 sites in the U.S. Desmoteplase study, and Pettigrew led UK’s recruitment effort. Only one patient at UK was enrolled in the study, although Pettigrew’s research team screened more than 50 stroke patients. (To qualify the patient could not have already been treated with tPA, had to arrive at UK within nine hours of stroke-symptom onset, and could not have had recent surgery.) “These exclusionary criteria were set up to limit the risk of hemorrhage,” Pettigrew says.

“We were pleased to be a part of this and look forward to seeing the results of the U.S. study.”

Alzheimer’s disease is the most common cause of the mind-robbing malady dementia, but, as Pettigrew points out, most people don’t realize vascular disease caused by stroke is the second: “Dementia is a silent, underappreciated, but catastrophic, secondary outcome of stroke.”

In the course of his clinical rotations in the UK hospital, Pettigrew estimates every fifth stroke patient he sees suffers from vascular disease-related dementia. “It’s crushingly common. In an MRI, these patients will have multiple areas of abnormal signal intensity—‘bright’ lesions—that are clustered in the complex network of nerve fibers called ‘white matter’ in the brain,” he explains, noting an MRI is only a supportive laboratory test to a clinical diagnosis of dementia.
That final diagnosis requires a formal neurological assessment, something Pettigrew explains is built into an exciting new study called SPS3 (Secondary Prevention of Small Subcortical Strokes).

This five-year study, led by Anand Vaishnav, is looking at a common, preventable type of stroke called lacunar stroke. “Lacunar” comes from the Latin word meaning “hole.” These tiny, round lesions are less than 1.5 centimeters across and usually occur deep within the brain. Forty percent of the patients admitted to the UK Hospital with ischemic strokes have lacunar strokes.

“And the main risk factor for this type of stroke—in 70 to 80 percent of cases—is hypertension,” says Vaishnav, an assistant professor of neurology who’s worked with Pettigrew in the UK Stroke Program for two years. SPS3 is looking at two key questions: Is aspirin plus Plavix (an FDA-approved blood thinner) better than aspirin alone at preventing recurrent lacunar stroke? What should the target blood pressure range be to reduce the chance patients with lacunar stroke will have a second stroke and lose their memory?

“We know that modifying blood pressure is definitely going to decrease the stroke risk, but to what extent should we go to decrease the blood pressure?” Vaishnav says. “The second aim of the study is to determine whether we should be very aggressive in treating blood pressure, keeping systolic less than 130, or less aggressive, keeping it between 130 and 149.”

The University of Texas Health Science Center in San Antonio received National Institute of Neurological Disorders and Stroke (NINDS) funds for this study and recruited Vaishnav as principal investigator, and Pettigrew as co-investigator. Pettigrew says, “They asked us to participate based on the numbers of patients we’ve enrolled in other trials.” Since 1990, the UK Stroke Program has participated in more than 30 clinical trials. “We’ve marketed ourselves aggressively, and we’ve had great success in attracting clinical trial participants.”

“We’ve been enrolling patients in the study for the past six months, and we expect to enroll more in the next three years. The last patient will be followed for at least a year and a half,” Vaishnav explains.

“One of the important features of SPS3 is that it was designed to see what therapeutic interventions can do to prevent dementia from occurring,” Pettigrew says, adding that the study involves a psychologist who will conduct a battery of standardized psychological tests to look at language usage and intelligence, and who will be mapping changes in those areas over time. “SPS3 is going to be unusually comprehensive. Unlike most studies, this is not simply a matter of ‘did you prevent another stroke or not?’ We’re asking, ‘Does the therapy keep Mr. Jones from becoming demented?’”
Lee Blonder (right), a faculty member in the UK Stroke Program and professor in the Department of Behavioral Science with joint appointments in neurology and anthropology, leads a team that is analyzing videotapes to see if targeted therapy works for stroke patients with language disorders. Jane Meara (left) transcribes and edits each videotape down to 60, 10-second clips, and Teri Cox watches each clip and rates facial expressivity.

Once Mr. Jones has had a stroke, there's a significant increased risk he'll have another. But as time passes after the first event, his threat of a future stroke goes down. Lowering blood pressure and cholesterol are the primary risk-factor targets for doctors in stroke prevention. But based on a study UK participated in called VISP (Vitamin Intervention for Stroke Prevention), physicians may soon add high homocysteine levels to their stroke-risk checklist.

The goal of the VISP study, funded by NINDS and led by Wake Forest University, was to find out if a special vitamin cocktail can prevent second strokes and first-time heart attacks. The study compared high- and low-dose vitamin combinations (folic acid, B6 and B12).

Why these vitamins? They metabolize homocysteine, an amino acid produced by the body when it processes protein-rich foods like meat. Elevated homocysteine levels in the blood, caused by genetics or diet, are associated with narrowing and hardening of the arteries, as well as increased risk of heart attack, stroke, and possibly Alzheimer's disease. But this association was merely observational—no clinical study had looked at the link between high homocysteine levels and heart attack and stroke risk.

VISP followed 3,680 patients (the average age was 66) in 45 centers in the United States, 10 in Canada, and one in Scotland. The UK Stroke Program was the highest enrolling U.S. center, with 124 patients. “We committed an immense amount of time and effort to participate in this study,” says Pettigrew, who was a co-author on the resulting article in the Journal of the American Medical Association in February 2004.

But the study didn't yield what researchers expected. The high-dose vitamins did do a better job of lowering homocysteine levels, but about 8 percent of the patients in both the high-dose and low-dose groups had another stroke during the two years that they were studied. “Despite the fact that these vitamins and the dosages were chosen by a panel of world authorities, and despite the fact that the vitamins had an immediate and sustainable effect on homocysteine, it wasn't sufficient to alter the likelihood of recurrent stroke and heart disease.

“It’s still being debated whether homocysteine is a causative risk factor or whether it’s a marker, a secondary risk factor,” Pettigrew explains. “But the VISP study established that there is a strong relationship between the level of homocysteine and the likelihood of vascular disease. I can envision the time when the American Heart Association posters will read: ‘Do you know your cholesterol and homocysteine levels?’”

It’s the look in your eyes, the inflection in your voice, the words you choose, and how you string them together that expresses your ideas. And for Lee Blonder expression is everything. Her day-to-day work involves evaluating conversations of stroke patients, with the goal of improving their ability to relate to other people.

“If you boil it all down, I’m interested in how deficits caused by damage in the brain affect natural communication,” she says, pointing out that her approach is a little different from other scientists’. “I come from a different background than the speech pathologists and neuropsychologists. I’m an anthropologist.

“Anthropology has always emphasized community and the cultural context within which people interact. And anthropological linguistics is interested in looking at language use in context, not just language structure,” says Blonder, a behavioral sciences professor, who joined the UK Stroke Program in 1989.

Blonder pauses to quickly describe two types of stroke-related language disorders. First, there’s aphasia, caused by damage to the language center in the brain’s left-hemisphere. Aphasia is a total or partial loss of the ability to use words. People with this disorder can have a range of problems, from trouble finding the right words to being unable to speak.

Then there’s apraxia, the absence of normal variations of pitch, rhythm and stress in speech. “These are right-hemisphere stroke patients who have this sort of ‘flat affect’—little facial expression and very restricted intonation. They also have problems perceiving facial expression and intonation in others,” she says.

Five years ago the University of Florida sought Blonder’s help. “They were putting together a clinical center with several different projects to treat people with communication disorders. But they wanted not just to measure improvement on a scale, they wanted to measure improvement in natural conversation, so they contacted me because they knew I’d done a lot of this kind of work.”

Blonder became a subcontractor. Patients in this study
were screened for and ruled ineligible if they had dementia or psychiatric disorders and had to have had a unilateral stroke (affecting only one side of the brain). After patients at the treatment sites (University of Florida, Old Dominion University and Baylor College of Medicine) go through therapy to treat their verbal or nonverbal problems, videotaped conversations with each patient are shipped to UK. “There are between 90 and 100 patients in this study, and they’ve each been assessed three to four times, so that’s a lot of videotape.”

Blonder’s team includes Jane Meara, a full-time research assistant who transcribes the videotapes, putting in codes that allow software programs to “read” them “and count the number of emotion words, count words per turn, that sort of thing,” Blonder explains. “Then Jane edits the tapes down to 60, 10-second clips and turns them over to our raters.”

The raters, two student research assistants, watch each clip and rate facial expressivity “on a five-point scale and count smiling, laughing, eye contact, crying, these kinds of behaviors, to see if the deficits that clinicians have noted at the bedside can be quantified in research.

“We’ve also developed a functional outcome questionnaire that we have caregivers fill out to find out about a patient. And we’ve discovered that caregivers rate people higher in communicative function when they have good eye contact—as determined by videotape analysis,” Blonder says.

Another part of this project involves zeroing in on intonation. “We’ve edited sentences the patient said before treatment and after treatment, scrambled the order, and the raters will be listening to the sentences and rating how expressive the tone of voice or inflection is.”

Her team has yet to analyze the post-treatment videotapes, but so far she’s found that aphasic patients say fewer words “per turn,” use shorter sentences, give more one-word answers, and more yes/no responses, but smile, laugh and have more facial expression than aprosodia patients. “Patients with aprosodia produce longer sentences, but much less facial expressivity and intonation.

“The whole goal of this research is to see if these treatments—like teaching aprosodia patients to express emotion through word choice and treating semantics and grammar in aphasia patients—work,” Blonder says. “I’m interested in understanding more about these communication disorders and how they affect natural behavior. Ultimately, I’d like to use this information to develop personalized behavioral treatments to improve the interaction between stroke patients and their families. That would be my reward.”

Why do her colleagues in the UK Stroke Program do this work?

“One reason is the very personal experience of actually being able to stop a stroke from happening. That’s rare, but when it occurs, it’s very dramatic,” Pettigrew says.

Vaishnav agrees: “For me, that’s the reason I became a doctor. We now have acute treatments, and it gives me immense satisfaction to see a dramatic change in patients. But the second part, which I also personally enjoy, is being a student about what’s next in stroke treatment. In doing clinical work, you see there are still more things to learn, and that’s probably what fascinates me most.”

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