CUT OFF

A BEREFT NERVOUS SYSTEM MAY EAT AWAY AT THE WILL TO LIVE

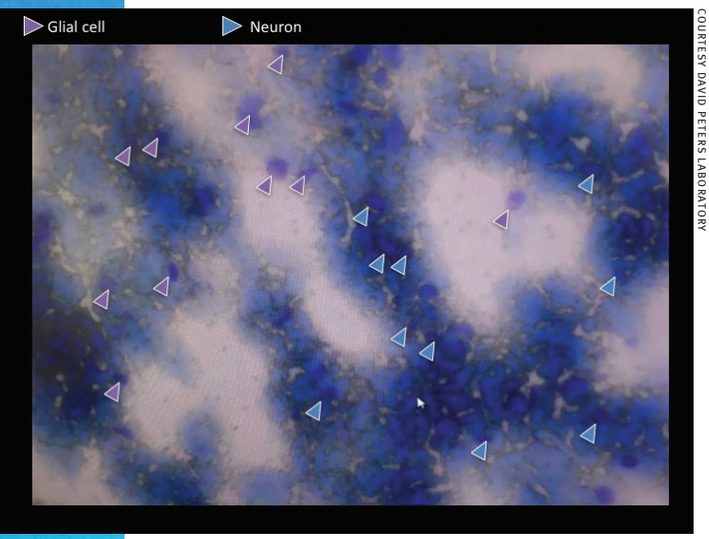
BY ELAINE VITONE

Eve was 12 when she first started thinking about suicide. By the time she was a senior in high school, she'd tried several times. Then one morning, alone at home, she downed a lethal dose of pills. The only reason Eve lived to graduation day was that her parents unexpectedly doubled back that morning. She wound up in the ICU and barely survived.

As her classmates were moving on to start college, pick roommates and majors, and fall in and out of love, Eve (not the patient's real name) and her medical team were trying everything under the sun for her severe and unrelenting depression: SSRIs, mood stabilizers, antipsychotics, even experimental medications typically prescribed to ALS patients. She had dozens of electroconvulsive therapy treatments, and for a few days she seemed to improve. Then she crashed again, suddenly and horribly. At this point, Eve was hospitalized and on 17 medicines, and she was still trying to end her life.

Certain vitamins and other supplements have turned around severe, previously intractable depression in some adolescents.

ILLUSTRATIONS | JESSE LENZ



COURTESY DAVID PETERS LABORATORY

David Peters is examining post-mortem neurons like these from individuals diagnosed with treatment-refractory major depression to identify novel biomarkers. Earlier identification of such individuals may provide alternative treatment plans and thus relieve the depressive symptoms sooner.

"I went up to see her," recalls her doctor, Lisa Pan, years later, "and there was *nothing*. No side effects. No response. *Nothing*. … And I thought, *I have never seen anything like this. What* is *this*?"

The University of Pittsburgh's Pan (Res '03, Res '05, Fel '08) began her research career studying neuroimaging markers of suicide risk in young people. In the clinic, she trained under the wing of David Brent (Res '82, Fel '85), a professor of psychiatry and pediatrics who holds Pitt's Endowed Chair in Suicide Studies and is arguably among the world's foremost experts on treatment-resistant depression (also called treatment-refractory depression) and suicidal behavior in teens. Thirty years ago, Brent envisioned and cofounded Services for Teens at Risk, or STAR, at Western Psychiatric Institute and Clinic. STAR remains one of only a handful of clinics in the country that specialize in this population. Over the years, the crosstalk between research and care at STAR has helped to elucidate suicide epidemiology, risk factors, and treatments, and to establish national guidelines for the management of adolescent depression and suicidal behavior. Brent is a member of the National Academy of Medicine (formerly the Institute of Medicine).

It was on this fertile ground for discovery that Pan, an up-and-coming physician-scientist, found the inspiration to take a way-out-of-the-box approach, with Brent's support.

Pan went to another mentor, David Finegold, a professor of human genetics in Pitt's Graduate School of Public Health. She asked what he thought of examining a lumbar-puncture test (a sampling of cerebrospinal fluid, or CSF) for clues of what was circulating in Eve's central nervous system. Could they check her neurotransmitters, look for any new leads at all? Finegold's answer: Absolutely. In fact, why not do a bigger workup, the kind that is standard when a child presents with signs of a neurological disorder?

As it turned out, Eve's CSF level of biopterin, a chemical the body uses to synthesize several neurotransmitters, was through the floor. Pan and Brent started her on a replacement-therapy regimen, and over the next few months, the team observed the gradual return of this long-absent chemical so crucial to the production of serotonin, dopamine, norepinephrine, pain modulators, and melatonin. And it had a profound effect on Eve.

Within the first week, her affect changed dramatically. She landscaped the family's entire yard in a day. At week three, she became more emotional. Suddenly she was crying over TV commercials and falling in love with the stranger on the line when she phoned in her order for a pizza.

And then, on day 31, a calm after the storm.

Her mood was low at first, but it gradually improved. She had bouts of shaking, insomnia, and trouble finding the right words, but as Pan adjusted Eve's medication dosage and frequency, the side effects subsided. Ten weeks in, she was feeling what psychiatrists call euthymia—medicalspeak for normal.

Six years later, with continued treatment for her biochemical disorder, Eve has a college degree and a job, says Pan, who, with Eve's permission, published her case in the *British Medical Journal* in 2011 and has discussed it at several well-received talks. Eve herself declines interviews about those lightless days. She's more interested in moving on, at last feeling like other young people—and finally having an adulthood and a tomorrow to plan for.

Pan and her team were skeptical at first. This must be a fluke, the scientists told themselves, an incredibly lucky break. Then they tried the same screening on three more patients suffering from treatment-resistant depression, figuring they were long shots, as well.

But all three turned out to have similar metabolic disorders, all of which improved once their systems were regularly "fed" with pills, powders, or IVs—special, highly absorbable forms of what were essentially vitamins.

In most of these patients, the trouble was folate metabolism.

Psychiatrists routinely order blood tests for this vitamin because its depletion is known to affect mood. But these patients' blood levels checked out fine. "So either something was happening with the body's ability to break down the folate enough to have it cross the blood-brain barrier or [with] the body's ability to move it across the blood-brain barrier," Pan says.

The scientists' disbelief sharpened to questions: How did these biochemical anomalies happen to these young people in the first place? Could there be others who are one lumbar-puncture test away from finding their own paths to recovery? And what if the team could do one better—build a cheaper and easier test? Could even more patients be spared years of suffering, or even death?

Practically overnight, these investigations became the new focus of Pan's career. Their first phase culminated this past August in a study in the *American Journal of Psychiatry*, and that was one of the most lauded psychiatry papers of 2016. Though the study was small—just 33 patients—the results were striking. Of these young people with treatment-resistant depression, 64 percent had some form of metabolic deficiency of the central nervous system; controls had

absolutely none. And once the patients' deficiencies were treated, the majority of their symptoms improved. For two of them, depression vanished altogether.

With each press hit, public interest in the work has surged. For Pan's team, it's been like drinking from a fire hose, e-mails and calls from all over the country continuing to flood in: *Can you see my son? Where can I get tested?*

"We spoke with 42 people yesterday," Pan told me the day after the story made *Forbes* last summer. Pan, a professor of psychiatry and of clinical and translational science, practically bubbles over with enthusiasm when she talks about this work. She talks *fast* ("I'm from Philadelphia," she says, by way of explanation), is extremely attached to her phone, and knows scores of patients' phone numbers by heart.

Pan now divides her time between seeing patients at STAR, many of whom travel from out of state; overseeing a small yet mighty testing-referral and care-coordination service for those calling and writing in from around the country; and conducting her research with an ever-expanding list of collaborators both inside and outside the University of Pittsburgh.

ity. But almost all of the patients who enrolled had at least thought about ending their lives.

For all we know about risk factors, says Pan, the problem is that we still can't tell which young adults with depression will die of suicide. Solving this puzzle is her life's work.

Soon after making their discovery about Eve, the team contacted Jerry Vockley for guidance.

An MD/PhD and chief of medical genetics at Children's Hospital of Pittsburgh of UPMC and professor of pediatrics at Pitt, Vockley directs a research program on inherited disorders of energy and protein metabolism. In recent years, he has identified the molecular basis of three.

JOSHUA FRANZOS

Lisa Pan

Vockley explains that the body is a highly efficient factory, churning away ceaselessly in chemical reactions that beget chemical reactions to turn one thing into another into another. This factory's products are our very life, growth, and health. But a flaw in the DNA that is foreman to the entire factory floor can gum up the works in curious ways.

And the same may be true for depression.

With Vockley, the team developed a panel of neurometabolic tests to aid in their search for other known disorders that might be underlying cases of life-threatening depression.

In 2014, Pan's team won a Pitt Innovation Challenge Award from the Clinical and Translational Science Institute to launch their

Once, someone told Eve her trouble was that she just wasn't working hard enough in therapy. Then her doctor learned that she may not be able to make neurotransmitters.

Once, someone told Eve her trouble was that she just wasn't working hard enough in therapy. "And then, you find out she may not be able to make neurotransmitters," says Pan.

In psychiatry, she says, "we're not so far along yet that we know exactly what we're treating. . . . When we approach mental illness, we need to keep an open mind about what might be occurring that we don't understand."

Of the 15 million American adults with major depression, 15 percent do not respond to any available treatments. When Pan first launched her studies, this was the main criterion—treatment-resistant depression, not suicidal-

At that point, it's like a clogged pipe, says Vockley. You'll have one of two problems: either a deficit—no water coming out of the faucet—"or you have a backup of things that shouldn't be there going to places they shouldn't be, like a flood in your basement. That can be toxic to the body. So the body is literally poisoning itself."

Medical genetics is a specialty of last resort, the place patients and their families turn to when their doctors diagnose them with mysterious and troubling conditions like "failure to thrive." But these are symptoms—basement floods, water outages—not diseases. The disease is the cause. For a symptom like intellectual disability, for example, there are literally hundreds of genetic causes to consider.

headlining study. (More funding followed from the American Foundation for Suicide Prevention, the Brain and Behavior Research Foundation, two anonymous donors of Children's Hospital of Pittsburgh Foundation, Joe and Louise Lohman, and The Fine Foundation.) The support allowed Vockley to develop a new panel casting a wider net in the search for patient subsets.

Though Vockley was intrigued by the possibilities, even he had his doubts as the first several patients began to recover.

"I'm no longer skeptical," he says, recalling, among many young people with similar stories, a woman who tried to hide in a corner on the floor. "She couldn't even face me. I examined her under the exam table.

"I couldn't believe she was still alive. This had been going on for years." But the team identified a metabolic deficiency in this young woman's nervous system and treated it. The patient continues to struggle but is no longer suicidal.

The team is hard at work on a multifront research effort: validating their findings in a larger patient sample; examining possible genetic and environmental factors in these deficiencies; widening their scope to include more metabolites; and developing a bigger, better test.

This is not a treatment study, Pan is careful to note. And it's certainly not a double-blind comparison of an experimental treatment versus placebo. It is an effort to understand some of the molecular mechanics of treatment-resistant depression and suicidal behavior, to begin to characterize the biological bases of the many diseases we now lump together under the same umbrella.

"And *then*, moving forward, potentially with help, we may later consider treatment studies," Pan says. (Colleagues at Harvard, Northwestern, and McGill are already lining up to collaborate.)

At STAR, counselors on Pan's team, who are trained in suicide risk assessment, evaluate and enroll study participants. Patients' CSF and blood samples are collected and tested, and if a CSF test reveals a metabolic disorder, Pan's team refers the patient to biochemical genetics for treatment.

The patient returns to STAR six months later for follow-up.

"The lab result actually directly informs the treatment," says Brent. "It's much closer to precision medicine than many things we're doing in psychiatry."

Meanwhile, Robert Naviaux, a colleague in the genetics division at UC San Diego, runs a broad-spectrum analysis on the plasma samples, examining some 600 different metabolites for potential new markers of the disorders the team is finding. And in Pittsburgh, postdoctoral fellow Lora McClain mines the patients' genetic data for variants that might be culprits. This enormous task, at 150,000 data points per study participant, is her sole focus.

Mental illness has always been a difficult challenge from a geneticist's standpoint because there are still woefully few biological measures for psychiatric diagnoses. So even zeroing in on the right patient population to study—the phenotype, as this is called—has been a problem. "But what Lisa has done is filtered it down to depression in the most extreme phenotype," says Finegold.

From the original 33 participants, the study has quickly expanded to 140. And at last count, the finding was still holding up: 57 percent of those tested have a metabolic disorder of the nervous system, all of which are treatable.

Thus far, the team has identified five distinct metabolic deficiencies. (Cerebral-folate deficiency accounts for the lion's share, affecting about a third of the patients enrolled in the study overall.) And for each deficiency, the team is beginning to identify multiple gene variants that are likely implicated.

Interestingly, the study is not just illuminating depression; it's also adding new wrinkles to the science of several other neurological diseases.

Cerebral-folate deficiency, for example, has long been known to cause neurological disorders, sometimes with mood changes as well. But the folate-deficient patients in Pan's study, who present with depression as their only symptom, are believed to be the first of their kind ever documented. And for another metabolic deficiency the team has found in this patient population, an extremely rare disease called lamin B1 deficiency, depression had not been known to be a presenting symptom. Yet another patient subgroup appears to have a mitochondrial disorder—cellular-energy metabolism gone awry—which Pitt postdoc Kaitlyn Bloom is working to get to the bottom of.

The human brain doesn't exactly lend itself to biopsy, notes David Peters, a collaborator with the team for going on two years now. The next best thing, cerebrospinal fluid testing, is kind of like tapping a sewer line.

"It likely reflects the molecular physiological nature of the entire brain," says Peters. So, how do you take this mixed sample, sift through it, and figure out what it's telling you? And how does that translate to an even more distant cousin, the blood?

Peters, an associate professor of obstetrics, gynecology, and reproductive sciences, has in the works a new technology that may help. Funded by the Children's Hospital of Pittsburgh Foundation, a "stethoscope for the brain" will aid the scientists as they comb through samples for clues.

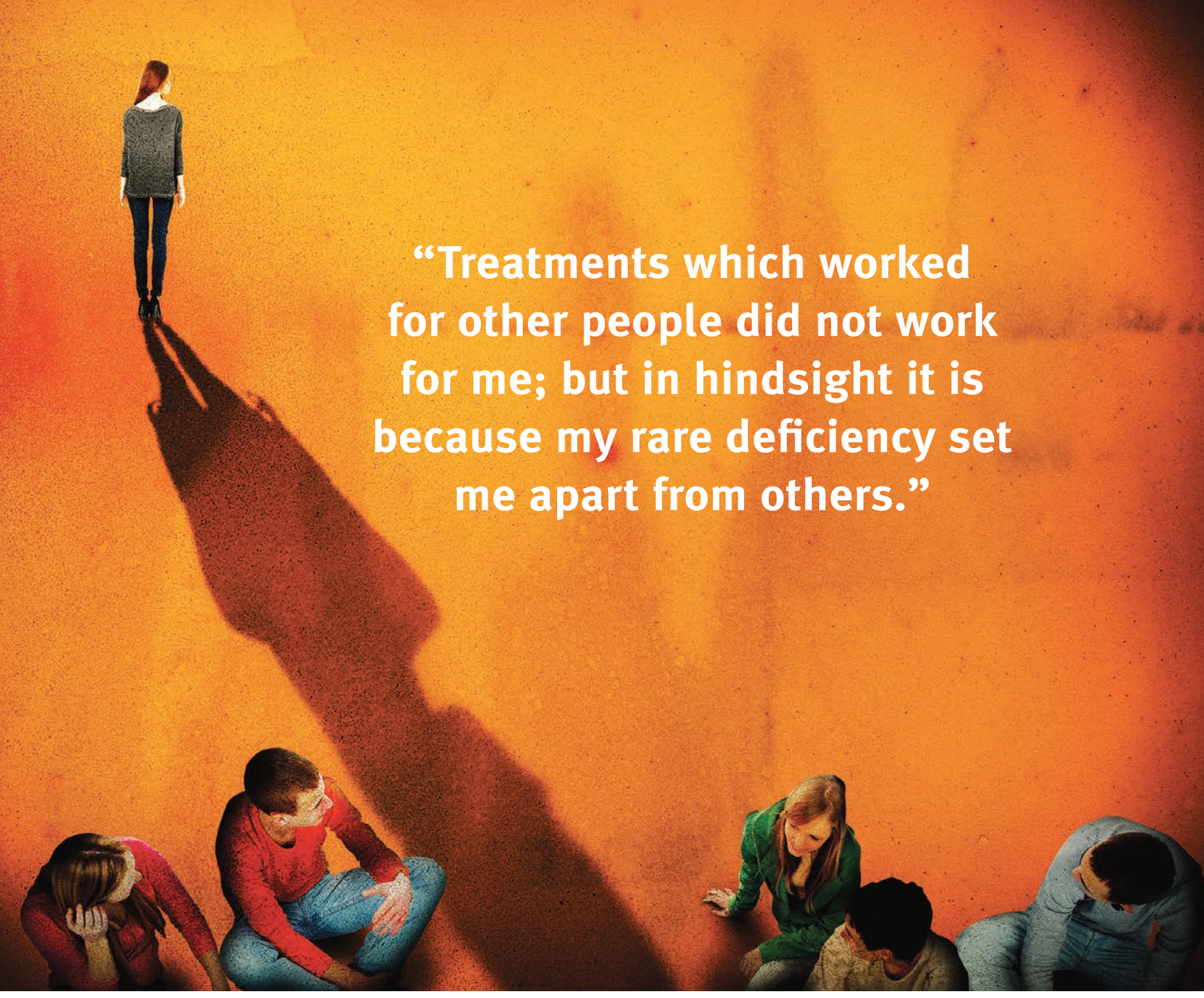
Another investigation led by Peters draws from Pan's expertise in imaging-based markers of suicidality. Previously, using functional neuroimaging, she identified areas in the brain that are associated with a past suicide attempt. Now the team is examining brains donated by people who've died of suicide, with particular focus on these areas.

Finegold, who can't say enough glowing things about Pan ("She understands genetics really well; I'm essentially superfluous"), is optimistic that Pan's findings are not only the tip of the iceberg in treatment-resistant depression, but also a possible starting point for much more. For example, how much of this metabolic-disease framework would transfer over to schizophrenia? If you can develop a new paradigm, he says, sometimes it will work elsewhere, and you can expand it, and sometimes it won't. "But if it doesn't fit, you learn a lot about *why* it doesn't fit."

Pan notes that for many patients, depression and suicidal behavior begin in times of physiologic stress. Which makes her wonder if there are parallels in postpartum depression. A possible multi-institutional collaboration along these lines is in its early stages. "Are these maybe people who have some of these metabolic disorders, and there's been a physiologic change that sets it off?"

Brent, famously rigorous in his approaches, notes that causality is something the team must continue to question. By the time patients walk through STAR's door, they've been suffering from their symptoms for more than a decade. "We don't know whether these [metabolic disorders] cause depression, or whether they emerge secondary to depression," says Brent.

Hence, Pan plans to also study patients who have less severe cases of depression that *do* respond to treatment, in hopes of discovering what sets them apart.



Pan has “a frighteningly good memory,” says Peters, just after one of the team’s Skype meetings that connect the investigators from their offices across Oakland and Lawrenceville several times a week. As they discuss what the data are telling them, Pan computes it all in her head and churns out lists on the spot. *Oh no, absolutely, this is patient X, patient Y, and patient Z,* she says, describing their cases with clarity and detail that are downright “scary,” Peters notes, laughing.

And as the team sketches out the blueprints for what they will build next, these kids are never far from her mind. Pan doesn’t necessarily want the study design that will ensure the quickest way to a grant proposal, says Peters. “She’ll say, ‘I just want to do this because I want to know why such and such is happening.’”

“She’s not distracted by the beauty of the science. It’s: How do we help these poor souls?” he adds.

A growing number of young people are getting their lives back, and that’s happening in a place where care informs science and science informs care.

Recently, the first of them, the archetypal Eve for this potential new paradigm in psychiatry, wrote as much in an e-mail to her former doctor (who still recalls Eve’s phone number six years later):

I owe my life to the successful diagnosis of my biopterin deficiency. Trial after medical trial, there came a point when living what I thought to be a normal life was unfathomable. Treatments which worked for other people did not work for me; but in hindsight it is because my rare deficiency set me apart from others. Were it not for the identification and treatment of this illness, my current success as both a double major and dean’s list student would not be possible. Diagnosis of this medical illness undoubtedly gave me the opportunity to live a life of my own: one with a future. ■