S T A N F O R D

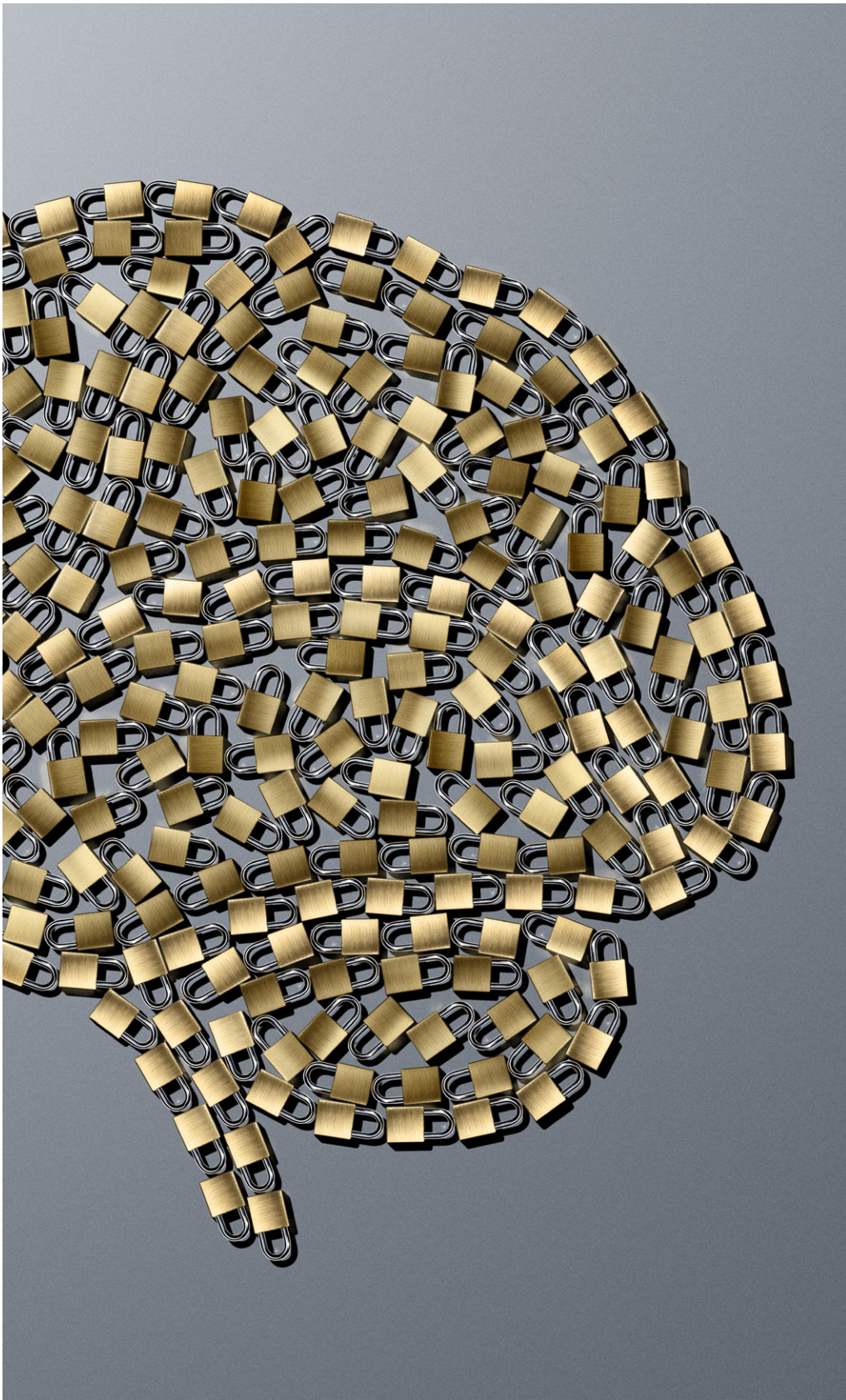
M E D I C I N E

Issue 2 / 2021

special report

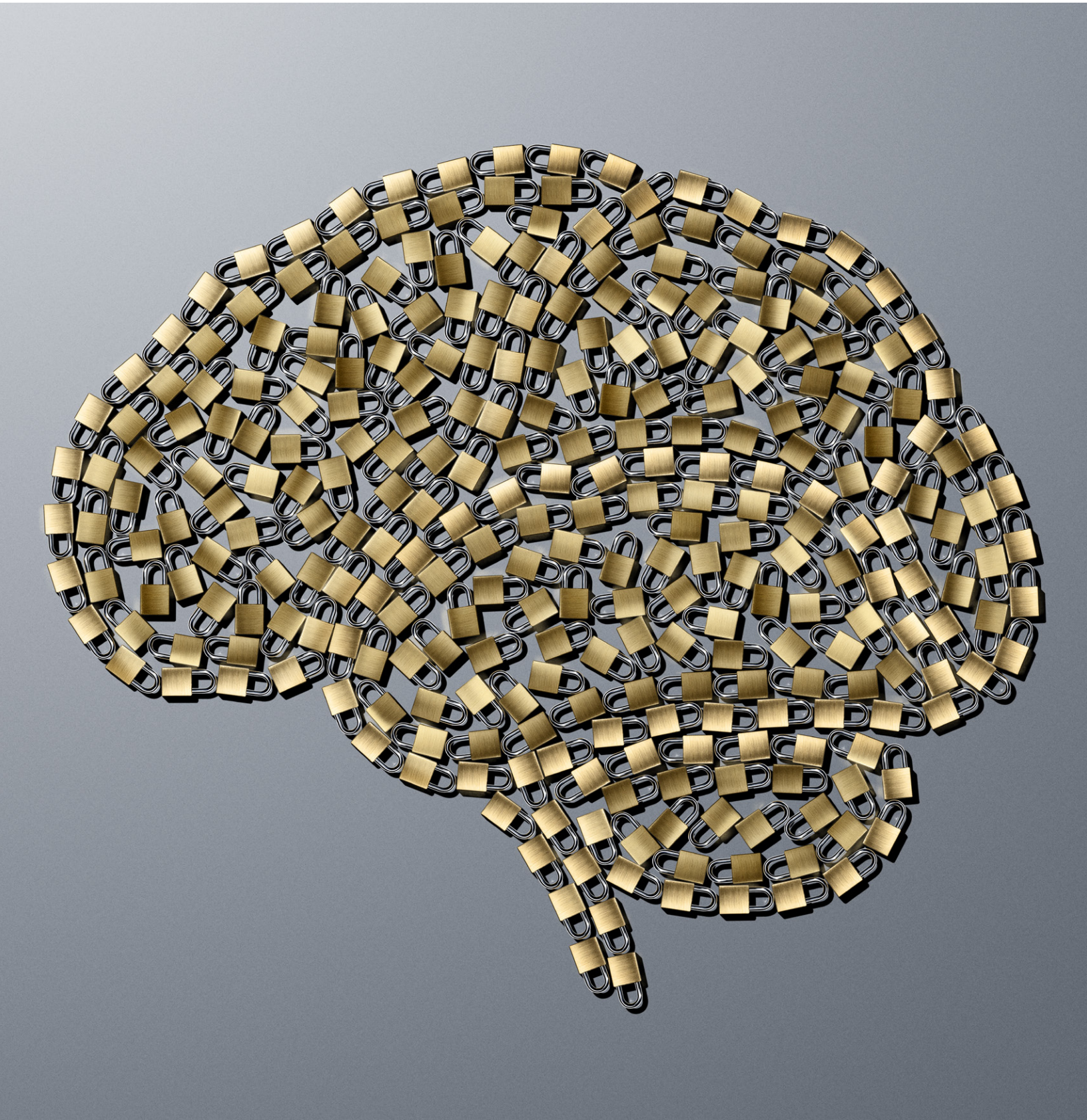
THE MOST MYSTERIOUS ORGAN

Unlocking the secrets of the brain



STANFORD MEDICINE

Issue 2 / 2021



THE CASE OF THE VANISHING BRAIN TUMOR

THE BRAIN IS A NEW FRONTIER FOR CANCER IMMUNOTHERAPY

It was around 2010 and neurosurgeon Michael Lim, MD, was taking a patient to the operating room to remove a brain tumor. Prior to the surgery, the patient received an experimental drug to stimulate his immune system to attack his cancer, which had begun as kidney cancer and metastasized.

"I remember taking him to the OR and thinking this was going to be a routine case," recalled Lim, now chair of the Stanford University School of Medicine's Department of Neurosurgery. "I took his tumor out. But when the pathology report came back, it indicated the mass was just inflammatory cells and no active cancer. And over the next months, the tumors in his body started to melt away. My interest was piqued by that finding and I became very interested in that drug."

The drug, which became known as Opdivo, belongs to a new class of medications called checkpoint inhibitors. Although our immune systems are honed to recognize and kill developing tumors, the tumors can evade them by exploiting biological safety valves called checkpoints, which normally tamp down any overactive immune responses that could lead to autoimmune disorders or inflammation.

Lim, who trained at Stanford Medicine but was working at Johns Hopkins University School of Medicine at the time, wondered if checkpoint inhibitors might also be effective against tumors that start in the brain, like glioblastomas. Although subsequent experiments in mice and clinical trials in patients uncovered some significant stumbling blocks, Lim said he is excited to see a way forward for patients with the devastating cancer.

"It's clear that brain cancers are different from other types of cancers," Lim said. "For example, we've found that, although all tumors suppress the immune response in the microenvironment, tumors that originate in the brain cause a global immune suppression that affects the whole body. This makes it very hard to induce an immune response to the tumor."

Targeting the culprits behind the immune suppression — a class of cells called myeloid cells — could reverse this phenomenon, researchers believe. Another approach focuses on reviving a kind of immune cell called a T cell that leads the charge against cancers but can become exhausted and ineffective over time. A series of experiments in Lim's lab suggested that combining a checkpoint inhibitor with a molecule to combat T cell exhaustion is safe. A study of the combo's effect on patients confirmed the treatment's safety and found it resulted in longer survival times for some of the participants.

"Now we're going back to the lab bench to try to learn why some patients responded to the combination treatment and some didn't," Lim said. "We hope to go on to a larger clinical trial. There's so much amazing science here at Stanford — we're able to go from the bench to bedside and back to the bench to solve these problems."

Lim and his colleagues hope to one day see outcomes for glioblastoma patients that are similar to those experienced by patients with metastatic brain cancer.

"Glioblastoma is such a malignant disease. I've treated hundreds of these patients, and every conversation I've had with them fueled me to try to do better for them. Each one gives me a new sense of urgency," he said.

"Right now, we are understanding cancer at a level we've never achieved before. As we learn how to assess a patient's tumor, we can become more and more precise with the therapies we can offer. We're not just wielding blunt tools anymore. I'm optimistic and excited about the future for these patients." — KRISTA CONGER

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letter from the dean

It was a eureka moment that shaped my early career. I was in an undergraduate bioengineering course, and the professor was using mathematical and bioengineering models to help us explore the vestibular system.

I was fascinated by the complex yet elegant sensory system that is responsible for our sense of balance and spatial orientation. Its neural pathways stabilize our gaze when outside forces jostle us, enabling us to see while out on a morning jog or read a GPS while driving on a bumpy road. I came away from the experience with a passion to more fully understand vestibular neurophysiology.

The human brain and nervous system form an astonishingly intricate network of billions of cells. It is also the original black box. For centuries, even as science revealed the workings of the rest of the human body, the brain remained stubbornly mysterious.

In the process, the brain has captured our imaginations, evolving from what Aristotle considered simply the body's radiator to how we see it today: the matter that makes us individuals, containing the seat of intellect and reason, memories and personality, emotions and senses, our very consciousness.

More recently, imaging technologies and innovative research are shedding new light on how the brain works, letting us peer inside and reveal its secrets. The more we see, the more we realize how much more there is to learn. The brain's abilities might be even more impressive than we imagined.

One of our most fascinating discoveries is that the brain isn't as fixed and fragile as we once believed. The organ we thought was set in its ways by our late 20s is much more active — and resilient — for our entire lives.

This new understanding has led to transformative changes in how we treat diseases and problems of the brain. For example, decades of Stanford research drove a radical change in standards of care for stroke in 2018, opening treatment to tens of thousands of people who would otherwise have been told it was too late.

Years ago, the intersection of research, technological innovation and luck translated into my development of a new treatment. In a span of weeks, two of my patients complained of mysterious and often bizarre symptoms — like hearing their eyeballs move in their sockets or seeing objects dance when they sang in the shower. I hypothesized that those seemingly unrelated issues might have the same source: the vestibular system.

Thanks in part to our earlier research and access to leading-edge imaging and digital technologies, my colleagues and I identified the problem: a hole in the inner ear canal. By defining the condition, superior canal dehiscence syndrome, and developing a surgical solution, we have helped thousands of people resume normal lives.

As a leader of Stanford Medicine, I am awed by how our health system drives neuroscience and biomedical research through robust, multidisciplinary efforts. Physicians and scientists make discoveries every day that increase our understanding of biological systems and lead to new surgical techniques, digital technologies and innovative therapies to restore function, fight disease and improve quality of life.

With each advance, we better understand the remarkable organ that is both mind and matter — and slowly open up the black box of ourselves.

Sincerely,
Lloyd Minor, MD
Carl and Elizabeth Naumann Dean of the School of Medicine
Professor of Otolaryngology – Head & Neck Surgery

GLENN MATSUMURA

upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD MEDICINE

Mighty mouse

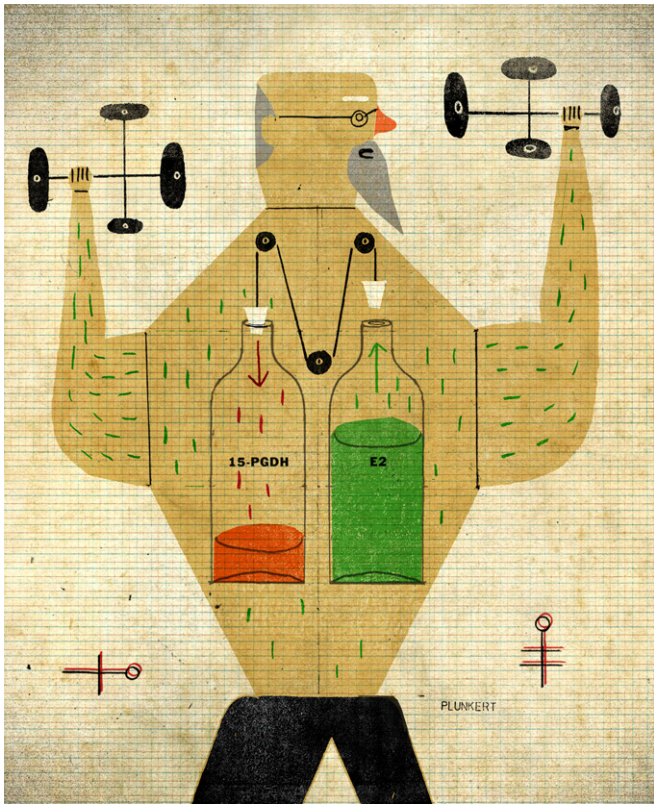
WITH AGE COMES WISDOM, they say. But as we grow more wise, our bodies often falter. In particular, our muscles shrink and lose strength as the years march on. What if there were a way to restore strength and mass to aging muscle?

New research in the laboratory of Helen Blau, PhD, professor of microbiology and immunology, suggests that conjecture could come true. She and senior scientist Adelaida Palla, PhD, found that blocking the activity of a protein called 15-PGDH in elderly laboratory mice revitalized the animals — strengthening their muscles and allowing them to trot longer on a treadmill than their untreated peers.

"The improvement is really quite dramatic," Blau said. "The old mice are about 15% to 20% stronger after one month of treatment, and their muscle fibers look like young muscle. Considering that humans lose about 10% of muscle strength per decade after about age 50, this is quite remarkable."

Conversely, increasing the expression of the protein in young mice caused their muscles to atrophy and weaken.

They published their findings online December 2020 in *Science*.



DAVID PLUNKERT

The protein hadn't previously been implicated in aging. But earlier work in Blau's lab showed that another molecule, prostaglandin E2, can activate stem cells in the muscle that spring into action to repair damaged muscle fibers. 15-PGDH, which is more plentiful in muscles of older animals, blocks this strengthening effect by breaking down prostaglandin E2.

"We're hopeful that these findings may lead to new ways to improve human health and impact the quality of life for many people," Blau said.

In response to COVID-19, Stanford Health Care increased its donations to community health programs in fiscal year 2020 to **$861 million**— 79% more than the previous year. Read more at stan.md/community

Disease blueprints

A NEW STANFORD service enables patients to look within themselves — all the way down to their genomes — to help determine underlying reasons for certain medical conditions.

The idea is to parse a person's complete genetic code to identify possible roots of disease, and even tailor treatments to the individual.

The service, led by Euan Ashley, MD, PhD, professor of medicine, of genetics and of biomedical data science, is available for Stanford Health Care patients with inherited cardiology disease. It is among the first of its kind to be offered by a hospital. Ashley plans to expand it into other specialties, such as cancer care.

upfront

Herniated disc relief

THE EXCRUCIATING pain first started for Andrea Hogue in October 2019, with numbness that shot down her leg. For the next year, Hogue, a middle school teacher in Merced, California, tried everything to find relief.

"It hurt to sit down," Hogue said. "It hurt to stand up. It felt like my whole left leg was in a permanent cramp."

Finally, an MRI revealed she had a herniated disc, which occurs when a bulge pushes through a hole in the cushioning discs between vertebrae and presses on a nerve. She underwent a discectomy, a common spinal surgery to remove the herniated portion of the disc, at Stanford Health Care - ValleyCare.

That worked, but the disc reherniated and the pain returned. Her surgeon, John Kleimeyer, MD, recommended a second discectomy but with something new — a tiny device, Barricaid, implanted in an adjacent vertebra to block the hole.

The device, which is designed to prevent reherniations, was developed by Eugene Carragee, MD, a professor of orthopaedic surgery at Stanford Medicine, after years of research.

Hogue agreed to the second procedure and was the first in California to get the device after the FDA approved it in 2019. That surgery was a success.

"I didn't know what a fog I was living in," Hogue said. "I've been taking walks with my dog, and that has been wonderful."

Scar-free healing

A TEAM OF STANFORD MEDICINE RESEARCHERS looking to figure out why we scar recently identified a drug that can prevent scarring altogether. They published the research April 23 in *Science*.

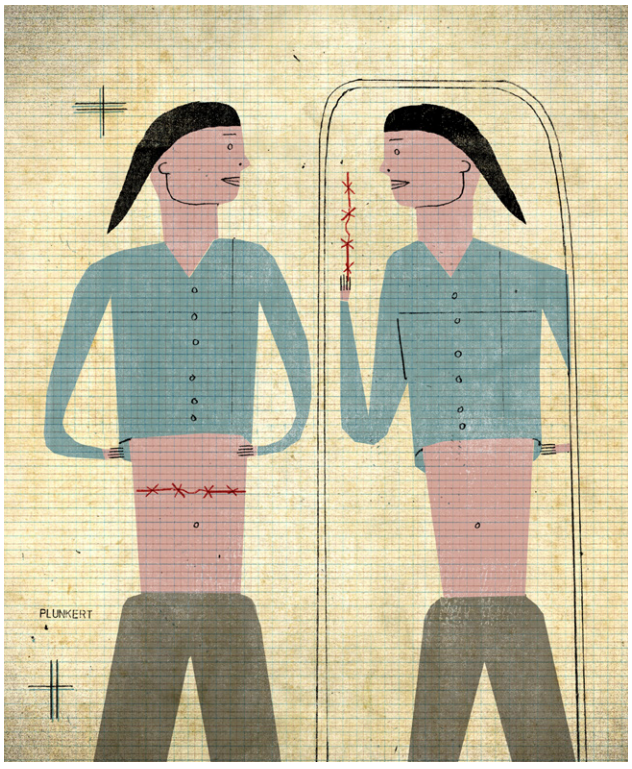
Scars form because they seal an opening in the skin more quickly than normal skin can grow. "A scar is a spot weld — it covers the wound quickly," said Michael Longaker, MD, a senior author of the study and the Deane P. and Louise Mitchell Professor in the School of Medicine.

But the result can be problematic: Scars lack hair follicles and oil glands and are weaker, thicker and less flexible than other skin.

The study started with exploring the role our skin's tightness plays in scarring — a clue borne from the scientists' observations that children and adults scar, but fetal tissue doesn't, and that the loose skin of older people has minimal scarring.

Their research found that a gene called engrailed signals fibroblasts — a skin cell type that drives scarring — to form scar tissue, but only when skin is stressed. The study's lead author, graduate student Shamik Mascharak, identified an eye-disease drug called verteporfin that, when applied to surgical wounds in mice, blocked engrailed from signaling scar formation. "It's estimated that 45% of Americans die from a disease that involves scarring in some form," Longaker said. "So there are potentially many more applications."

Geoffrey Gurtner, MD, the Johnson & Johnson Distinguished Professor in Surgery II, shared senior authorship with Longaker.



DAVID PLUNKERT

Nitrate risk in pregnancy

PREGNANT WOMEN EXPOSED to too much nitrate in their drinking water are at greater risk of giving birth prematurely, according to a study of more than 1.4 million births in California.

Most affected were women whose tap water exceeded the federal nitrate limit of 10 milligrams per liter, double the effect of levels of less than 5 milligrams. But effects were also seen at levels between 5 and 10 milligrams.

"That was surprising," said lead author Allison Sherris, a graduate student in the Emmett Interdisciplinary Program in Environment and Resources at Stanford. The senior author was Gary Shaw, DrPH, professor of pediatrics.

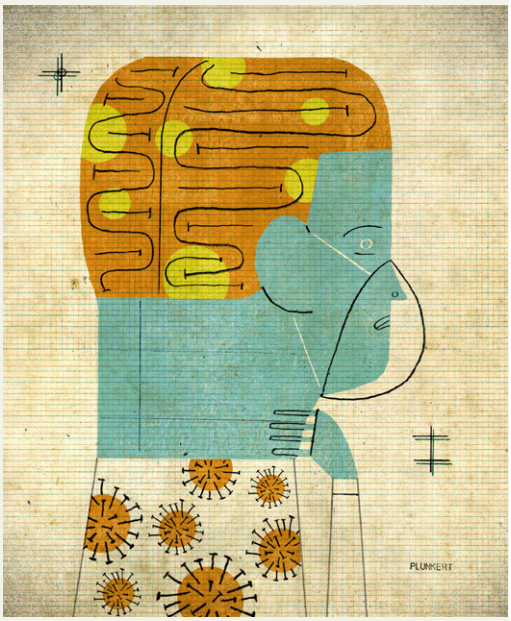
The largest impact occurred in farming regions, where agricultural runoff leads to higher levels of nitrate in groundwater.

The research was published online May 5 in *Environmental Health Perspectives*.

COVID FOCUS

A QUICK LOOK AT PANDEMIC-RELATED NEWS

COVID-brain clues



INVESTIGATORS AT STANFORD MEDICINE and Saarland University in Germany report, in a study published in *Nature*, that autopsied brains of COVID-19 patients displayed extensive inflammation and neurodegeneration, though no sign of the virus that causes the disease.

The findings may help explain why many COVID-19 patients report neurological problems. About a third of those hospitalized for COVID-19 have symptoms of fuzzy thinking, forgetfulness, difficulty concentrating and depression, said Tony Wyss-Coray, PhD, professor of neurology and neurological sciences at Stanford and a senior author of the paper.

'Our findings may help explain the brain fog, fatigue, and other neurological and psychiatric symptoms of long COVID.' — TONY WYSS-CORAY

The researchers obtained brain tissue from eight people who died of the disease. Brain samples from 14 people who died of other causes were used as controls. Researchers logged the activation levels of thousands of genes in each of 65,309 individual cells taken from brain-tissue samples from both groups of people.

In all major cell types in the COVID-19 patients' brains, activation levels of hundreds of genes — many associated with inflammatory processes — were higher compared with levels in the brains of people in the control group. There also were signs of distress in neurons in the cerebral cortex, the brain region crucial to decision-making, memory and mathematical reasoning.

"Our findings may help explain the brain fog, fatigue, and other neurological and psychiatric symptoms of long COVID," said Wyss-Coray, who is the D. H. Chen Professor II.

Children's vaccine trials

STANFORD MEDICINE is participating in clinical trials to evaluate the response of children under 12 to the Pfizer-BioNTech COVID-19 vaccine. Since May, researchers have tested whether the vaccine produces an immune response and prevents COVID-19 in children 5 through 11 years old. The Stanford study site is also evaluating vaccine dosages for children 6 months through 4 years old. Final results for the older age group are expected later this year.

"Children under 18 make up about a quarter of the U.S. population, so if we want to get the virus under control, we really need to include them," said Yvonne Maldonado, MD, who is running the trials' Stanford site. Maldonado is the Taube Professor in Global Health and Infectious Diseases at Stanford.

Pandemic hits Latinos hard

MORE LATINOS IN CALIFORNIA have had COVID-19 exposure and become sick or died from the disease than have non-Hispanic white people in the state, a Stanford-led study shows.

Researchers analyzed testing and case rates from March 22 to Oct. 3, 2020. The data included 15.4 million tests and confirmed cases of more than 800,000. The exposure risk estimates were based on the proportion of people living in households with an essential worker and on the number of homes with fewer rooms than household members — a measure of ability to isolate at home if exposed.

Latinos in the state are 8.1 times more likely to live in high-risk households and three times more likely to get COVID-19 than white people. The death rate for Latinos was 1.5 times higher.

"The fact that Latinos in California are the majority racial or ethnic group yet have the worst COVID rates highlights that this is not just a small-population issue," said Marissa Reitsma, a PhD student at Stanford Health Policy and a co-lead author of the study, published May 12 in *Health Affairs*.

Scientists long believed the brain was immutable, unable to recover functions lost to injury or disease. But in the past few decades, researchers have devised methods to manipulate the brain and central nervous system to help the paralyzed move and enable the blind to see, and they're moving closer to restoring lost cognitive abilities.

"We are at an inflection point where we are starting to give functions back to people," said Michael Lim, MD, professor and chair of neurosurgery.

Technological advances are driving the field's progress. Using new imaging methods, scientists can view cells in the brain in exquisite detail and monitor their activities in real time. Powerful data science allows them to track the sequence of brain processes involved in human thought and quickly analyze the resulting terabytes of data. With advances in stem cell technology, they can also regenerate tissues to help people with severe brain injuries return to everyday activities like walking and talking.

At Stanford Medicine, these advances — plus a tradition that values collaboration and out-of-the-box thinking — are empowering innovations that were the stuff of science fiction just a few years ago.

making a comeback

NEW WAYS TO PREVENT –
OR EVEN REVERSE –
DEMENTIA, PARALYSIS AND BLINDNESS

BY RUTHANN RICHTER

ILLUSTRATIONS BY HARRY CAMPBELL

PHOTOGRAPHS BY LESLIE WILLIAMSON

"You need a critical mass of bright people," Lim said. "Stanford has the right formula — the many departments coming together and the culture that values innovation and pushing the field forward. We have the infrastructure and everything from the hardware to the software to process information. We are in a unique situation."

Stanford's outstanding fundamental sciences research and advanced core technologies have helped fuel progress in the field, said Frank Longo, MD, PhD, the chair of neurology and neurological sciences and the George E. and Lucy Becker Professor of Medicine.

"We have strong basic science, a deep culture of interdisciplinary collaborations and the availability of resources, like great imaging capabilities, that allow us to do experiments more efficiently," Longo said.

MIchael Lim, MD, chair of Neurosurgery

Here are just a few of the many projects in which Stanford Medicine scientists are restoring abilities that are crucial for patients' daily living — and in some cases striving to prevent their loss in the first place.

Overcoming cognitive loss

TAKING A DIFFERENT APPROACH ON ALZHEIMER'S

Much of the effort to treat Alzheimer's disease has focused on the protein known as amyloid, which forms sticky plaques that clog the brain and contribute to neurodegeneration.

But Longo has taken a different tack.

"I think that with Alzheimer's and some of these other degenerative diseases, there are multiple forces that promote degeneration," with amyloid being just one of them, he said. "We wanted to create a therapy that could address multiple mechanisms at one time."

Normally, neurons respond to signals to maintain or shut down their synaptic connections, an essential part of the brain's communication system. Some of these connections are lost naturally as we age, but in Alzheimer's, the signal to kill these connections becomes overly active, Longo said. That leads to memory loss and other cognitive impairments.

Early in their Alzheimer's research, Longo and his colleagues zeroed in on a molecule on the surface of neurons that regulates the network signals involved in this degenerative process. They then developed a synthetic molecule that binds to it to block the destructive process and promote regeneration. That molecule was C-31.

In studies with mice, they found that C-31 made the neurons resistant to the effects of amyloid, prevented the formation of the toxic tau proteins that occur in the brain in the later stages of Alzheimer's, decreased inflammation and reversed some of the effects of aging on the cells, like the shrinkage of neurons, he said.

"Our hope was that doing all of these four things might have a more powerful effect than just removing amyloid," Longo said. "One of the great mysteries in our field now is that we see people — even at advanced ages — with a brain full of amyloid but with memory and other cognitive function intact. While we do not understand this phenomenon and why it occurs in only a minority of people, we think we have created a compound that confers a therapeutic version of amyloid resilience."

In mouse studies, the compound not only prevented damage to the synapses but also restored one of their most delicate structures — the dendritic spine, a protrusion in nerve cells that helps them communicate.

"We can apply it in a late state in the disease, when the dendritic spine is lost. The animal recovers to the levels of a young mouse," he said. "It's truly a regenerative effect."

The beauty of the compound is that it can cross the blood-brain barrier, so it can be taken in pill form, making it easy and inexpensive to administer, Longo said.

Researchers in Europe recently completed a clinical trial to evaluate the molecule's safety and explore ways to mea-

sure reductions in brain degeneration. The trial included 242 patients with mild or moderate Alzheimer's disease and was conducted by a company that Longo founded. Analysis of the trial is underway and, if indications are positive, the next step is a much larger trial to test for efficacy.

Longo and his research team are exploring how this experimental drug works and are finding additional conditions, such as Parkinson's and Huntington's disease, for which it might be useful. They have also found that C-31 may be able to counter nerve damage caused by the common cancer chemotherapy drug cisplatin.

Frank Longo, MD, PhD, chair of Neurology and Neurological Sciences

"It gives us another entry point to better understand the mechanisms underlying these diseases, and in an exciting way, to gain insight into the emerging topic of brain resilience. This knowledge will help us develop additional, entirely new approaches," he said.

More information on active Alzheimer's disease trials available at Stanford is on the website of the Iqbal Farrukh and Asad Jamal Alzheimer's Disease Research Center, which was renamed in 2021 in recognition of a donation made by the Good Planet Foundation: med.stanford.edu/adrc.html.

LOOKING FOR NEW ALZHEIMER'S CLUES IN THE GENES

NEUROLOGIST MICHAEL GREICIUS, MD, began his latest quest for a new Alzheimer's drug in 2014, when he met a 57-year-old woman in the throes of advanced disease. She came to the clinic with her parents, both in their 70s.

Genetic tests showed that the patient had one copy of the gene for APOE4, a protein involved in cholesterol metabolism that is also thought to affect brain function. People with the gene are at greater risk of Alzheimer's, but those with two copies carry a risk that is extremely high. Remarkably, the patient's mother had two copies of the APOE4 gene, yet she was in excellent health.

"That is when I scratched my head," said Greicius, the Iqbal Farrukh and Asad Jamal Professor. "She had a double risk. She's perfectly healthy and yet her daughter, with only one APOE4 gene, is already affected. Something is protecting the mother. I pretty strongly suspect it's a gene."

He resolved to look for rare genetic variations that could be protective — something the mother had but her daughter hadn't inherited.

"The idea would be to try to find drug targets in those molecular pathways — mimic what these people have in their natural genomes," said Greicius, who directs the Stanford Center for Memory Disorders.

Greicius is four years into the NIH-funded study for which he and his colleagues have amassed a collection of sequenced genomes from more than 500 people with and without Alzheimer's. About half of these people are "protected" APOE4 carriers like the patient's mother. The researchers have obtained extensive biologic data for some participants through clinical exams, spinal taps, brain imaging, immunologic testing and skin biopsies. Greicius is screening the material from these individuals, looking for genes that might have a protective effect.

He's also examining patients at the opposite end of the spectrum — those who don't have the high-risk APOE4 gene but who develop Alzheimer's at an earlier age, before they reach 65. This could point to previously unknown variants that could be implicated in the disease, he said.

Once these genes are identified, researchers can pinpoint the proteins they produce, then develop new drugs that may be able to block damaging proteins or enhance protective ones and, as a result, slow or stop the degenerative process.

Greicius' work has already borne fruit. He analyzed 25 independent studies and showed that a common genetic variation known as Klotho-VS, which protects against age-related cognitive decline, reduces the risk of Alzheimer's by 25% to 30% in older people who carry the risky APOE4 gene. He published papers on the work in *JAMA Neurology* in April 2020 and in *Neurobiology of Aging* in January 2021.

"That was a reassuring example that these variants are out there," he said. "Thirty percent is good. We're looking for

variants that reduce risk by 80 or 90%. But this is certainly a good start."

More information is on the website of the Iqbal Farrukh and Asad Jamal Alzheimer's Disease Research Center: med.stanford.edu/adrc.html.

FIGHTING COGNITIVE DECLINE BY TAMING INFLAMMATION

SCIENTISTS HAVE LONG focused on inflammation as a major cause of cognitive decline among patients with Alzheimer's and other neurodegenerative diseases. But they have never understood the mechanisms behind it.

Katrin Andreasson, MD, a professor of neurology and neurological sciences, recently identified a possible pathway for inflammation in the brain and found a way to inhibit it to restore cognitive function, a finding she described in a January article in the journal *Nature*.

The key, she found, lies with a group of immune cells known as myeloid cells, which are among the body's first line of defenders. In the brain, myeloid cells are known as microglia, which also help clean up debris (like the plaques in brains of people with Alzheimer's) and control inflammation levels. In the blood, these cells are the macrophages and monocytes.

In her experiments, Andreasson compared these immune cells from older people (over 65) with those from younger people (under 35) and found the cells change dramatically as we age. In older brains, microglia promote a damaging, hyper-inflammatory environment instead of maintaining calm.

Andreasson's research revealed a downward spiral of events that begins with older cells producing significantly more of the hormone prostaglandin E2, which regulates inflammation in the body. She detailed other molecular changes in which more of the hormone molecules bind to cells, ultimately depleting the cells' energy stores and leaving them in a perpetually exhausted state. The cells essentially devolve from young to old. Surprisingly, the changes occur not only in the immune cells in the brain but also in the macrophages in the blood, she said.

Most importantly, Andreasson and her colleagues tested older and younger lab mice using two compounds known to block the binding of the hormone and the molecule it attaches to on the cell — the EP2 receptor. They were able to stop the damage from occurring in the cells in the brain, as well as in the blood.

"We were able to restore cognition to a youthful level," she said, as the older mice were able to navigate a maze just as well as young ones. "What was a real shock was when we tested it in the circulating blood (outside the brain). ... We found if you block an EP2 receptor in a macrophage, you could restore youthful metabolism."

That means it may be possible to devise a drug that preserves cognitive function but doesn't have to reach the brain. "That's good news," she said, "because every time you put something into the brain, there is potential for side effects."

Scientists haven't tested either compound in humans, so the drugs' toxicities aren't known, Andreasson said. But it's a promising avenue for scientists to pursue in preventing cognitive decline.

"If we could somehow change our microglia so they are behaving in a healthier way, that might go a long way toward slowing

In her experiments, Andreasson compared these immune cells from older people (over 65) with those from younger people (under 35) and found the cells change dramatically as we age.

down the process of Alzheimer's disease," she said.

More information about Alzheimer's disease research and treatment is on the National Institutes of Health website: nia.nih.gov/health/alzheimers.

Getting moving again

RESTORING HAND FUNCTION THROUGH NERVE TRANSFER

People who have lost use of a hand because of spinal cord injuries or stroke now have an option for regaining movement: It's called nerve transfer, a microsurgical technique that has emerged in the past five to 10 years, said Thomas J. Wilson, MD, clinical associate professor of neurosurgery.

In nerve transfer surgery, surgeons steal a functioning nerve with a less critical role and stitch it to a damaged nerve. The functioning nerve then regenerates through the damaged nerve to reestablish nerve supply to the target muscles and restore function. It can take as long as two years for patients to regain movement because the nerve grows very slowly and has to work its way into the muscle, he said.

"It's a rob-Peter-to-pay-Paul phenomenon," Wilson said. "You can steal something less important and give it to a more important movement."

He has had good results using this technique in patients with spinal cord injuries. These patients report valuing hand function even more than walking, he said, because use of their hand increases their independence, allowing them to feed and dress themselves and to manually operate a wheelchair.

For the past year, Wilson has participated in a national clinical trial, sponsored by the U.S. Department of Defense, to track 70 spinal cord injury patients who are undergoing nerve transfer. The goal is to better predict which patients will do well after the surgery and to characterize the results they experience.

Wilson is also among a handful of neurosurgeons in the country using nerve transfer surgery to restore arm use in stroke patients. This procedure is more complex because the disabled limb is not a useful source of functioning nerves: The original injury is in the brain and broadly impacts nerves in that limb.

Instead, he swipes a nerve from the opposite limb. For instance, in someone with left-sided weakness, he cuts a segment of the cervical 7 (C7) nerve on the right side of the body, brings the nerve across the neck, and connects the right C7 nerve to the left C7 nerve to restore left-arm function. The C7 nerve's function overlaps with that of other nerves, so it can be sacrificed in the unaffected limb without significantly compromising its use.

Normally, the body's left side is controlled by the right side of the brain, and vice versa. But in this case, the hope is that the brain will adapt to allow the left side to assume control over the left limb.

"It turns out it actually does work," Wilson said. A functional MRI, which maps the area of the brain being activated, shows that after a successful nerve transfer to the left side, the left region of the brain lights up, he said.

Wilson has treated three stroke patients with the surgery, two of whom are far enough into recovery to show improvement in arm function. These patients are able to dress, bathe and feed themselves using their once-paralyzed limb.

He said other neurosurgeons have used nerve transfer surgery in people with traumatic brain injuries, as well as those with cerebral palsy, to restore or improve hand and arm function.

"Traditionally, nerve transfer surgery has been used for nerve injuries, but we are starting to think outside of the box, and we are applying this technique to other patients, including patients with spinal cord injury, stroke and traumatic brain injury. The results have been very promising, but there is still a lot to learn in order to optimize our patient selection and outcomes," he said.

"The next major hurdle is re-educating the medical community and making them aware that these techniques are available. I think there are probably a lot more people we could help if more clinicians were aware of what we have to offer."

More about the procedure is on the Stanford Center for Peripheral Nerve Surgery website: stan.md/nervesurgery.

IMPROVING BRAIN IMPLANTS TO TREAT PARKINSON'S DISEASE

THE BRAIN may look like a big scoop of spaghetti. But it's really an immensely complex electrical device whose component nerve cells, or neurons, are analogous to insulated, current-carrying wires.

Helen Bronte-Stewart, MD, the John E. Cahill Family Professor in the department of neurology and neurological sciences and chief of that department's movement disorders division, is spearheading an effort to boost the ability of elec-

trodes implanted in the brain to treat Parkinson's disease.

Parkinson's, the second most common neurodegenerative disease, affects 10 million people worldwide, according to Bronte-Stewart, the director of the Stanford Comprehensive Movement Disorders Center.

The motor-impairment aspect of the disease stems from the mysterious die-off of a set of neurons in the midbrain that form part of the sensorimotor network. One of the consequences of the die-off is that neurons in this network acquire an overly pronounced tendency to fire in sync at specific frequencies, akin to a brain arrhythmia. They begin transmitting prolonged spontaneous rhythmic bursts of movement-impairing signals instead of movement-shaping ones.

Medications can mitigate Parkinson's symptoms — including visible tremor, faulty gait, limb rigidity, difficulty in initiating movements, slurred speech and, sometimes, impaired cognition. But they can also cause side effects and, as the disease worsens, fail to control symptoms, Bronte-Stewart said.

When medications fail, patients can benefit from an increasingly popular treatment called deep brain stimulation, or DBS, which restores control by disrupting the brain's unwanted rhythmic firing.

Approved in 1997 for Parkinson's disease, deep brain stimulation involves embedding electrical leads in the brain (most often the subthalamic nucleus) to act as a kind of anti-noise system. Driven by a battery-operated pulse generator implanted in the chest, the leads fire their own trains of electrical pulses in the appropriate spot, countering the errant outbursts that cause Parkinson's symptoms.

With standard DBS, the stimulator-driven pulse train flows steadily, changing only when the physician adjusts the patterns, on a trial-and-error basis, to maximize tremor inhibition and gait improvement without triggering side effects such as slurred speech, sensory disturbances, involuntary muscle contractions or balance problems.

In 2013, the FDA approved, for experimental purposes, a version of the implanted pulse generator that not only sends electrical bursts to the brain but also can record how the brain neurons are firing. Researchers could now accumulate data on brain-signaling patterns in the vicinity of the implanted electrodes while the patient was walking, speaking, sitting, sleeping or engaging in other activities.

In June 2020, the FDA approved the commercial implantation of this "listening" device, making it much easier for physicians to make therapeutically useful setting adjustments because they can read brain signals from the device instead of inferring them from a patient's motion, posture and comments.

Bronte-Stewart intends to further optimize and personalize this feedback. She is the principal investigator on a global trial of an advanced version of DBS called adaptive DBS. The goal is to transmute the accumulated data of years of research into an algorithm that lets the pulse generator do the reading in real time and, in response to what the brain is doing, directly alter its signaling pattern.

DBS was first approved in 1991 for essential tremor, a movement disorder that's more common than Parkinson's disease. It's also approved for some types of dystonia, a movement disorder in which a person's muscles contract uncontrollably; for epilepsy; and, in certain cases, for obsessive-compulsive disorder.

DBS is also being tested in a clinical trial led by Jaimie Henderson, MD, professor of neurosur-

Researchers could now accumulate data on brain-signaling patterns in the vicinity of the implanted electrodes while the patient was walking, speaking, sitting, sleeping or engaging in other activities.'

gery, to treat reduced consciousness induced by brain trauma.

DBS device implantations have been performed on about 200,000 patients worldwide, close to 1,500 of them at Stanford.

For more information on deep brain stimulation to treat Parkinson's disease, see stan.md/DBS.

RESTORING MOVEMENT FOR STROKE PATIENTS THROUGH STEM CELL TRANSPLANT

NEUROSURGERIES WITH stem cells have demonstrated just how resilient and adaptable the brain can be. In multiple studies, Gary Steinberg, MD, PhD, has used stem cells in stroke and traumatic brain injury patients to restore their ability to walk, speak and return to some of their normal activities.

Steinberg published results from a landmark trial in 2016 in the journal *Stroke* in which he injected bone marrow-derived stem cells into an injured area of the brains of 18 patients. Three-quarters of the patients had clinically meaningful recoveries, meaning their daily lives were changed for the better. The others had slightly less improvement or remained the same. The recovery of some of the patients was dramatic — they were able to run and speak again after having been trapped in their injured bodies.

"Those circuits that we thought were dead in stroke patients were not irreversibly damaged," said Steinberg, the Bernard and Ronni Lacroute-William Randolph Hearst Professor in Neurosurgery and Neurosciences. "They were repressed and could be resurrected."

Steinberg has since been examining the underlying mechanisms of these recoveries. In MRI images of patients taken after the procedures, he observed a transient signal near the injured area — a bright spot — that correlated with how well the patients fared over the longer term. He speculated that this signal might indicate a beneficial inflammatory response, which his recent lab studies have borne out.

He found that the stem cells were not creating new neurons, as he initially thought, but were releasing dozens, if not hundreds, of different healing molecules. These molecules include growth factors that build new nerve fibers and proteins that help create blood vessels, as well as a number of immune system cells that can enhance brain repair.

"It turns out that the beneficial inflammatory response is present not just where the lesion is but is more widespread throughout the brain," he said. "It probably stimulates circuits very widely throughout the brain."

Steinberg has tested the same stem cells as part of a multicenter trial involving patients who suffered traumatic brain injuries at least a year before the treatment. As in the stroke study, after six months, the treated patients showed significant improvement in their ability to move and walk, compared with control patients. The researchers reported the results in the journal *Neurology* in January 2021. The most common side effect was headaches, likely related to the surgical procedure, the scientists reported.

Steinberg is embarking on a study of a different kind of stem cell — neural stem cells derived from human embryonic tissue, known as NR1 cells. These stem cells, which he developed 20 years ago, have advantages: They are easier to grow than bone marrow-derived cells, can be manufactured in large quantities and are not genetically altered.

He plans to begin testing them this year in a Stanford-sponsored, first human trial in about 20 chronic stroke patients with partial paralysis. The procedure involves transplanting the cells directly into the brain near the area of the injury. Steinberg is the only investigator in North America using direct brain transplantation of stem cells for stroke.

"We expect that if this strategy works, we will be extending it to other indications like traumatic brain injury, spinal cord injury and, hopefully, even neurodegenerative diseases like Parkinson's, ALS or, ultimately, Alzheimer's, though that's quite a bit in the future," he said.

For more information on participating in the trial, email stemcellstudy@stanford.edu.

A HIGH-TECH GLOVE COULD ENABLE STROKE PATIENTS TO REHAB AT HOME

ANOTHER NEW APPROACH TO TREATING PATIENTS who've suffered strokes could come from the wearable technology field.

By 2030, nearly 4% of American adults will have had a stroke, according to the American Heart Association, and as many as 80% of those who survive will end up with weakness and loss of sensation in their arms and hands.

"Having the use of two hands is absolutely essential for normal functioning. But currently there aren't many effective interventions that can help people get that function back following a stroke," said Caitlyn Seim, PhD, a research fellow at the Wu Tsai Neurosciences Institute at Stanford.

Most health insurers cover a limited amount of exercise-based stroke rehabilitation, and half of stroke survivors don't have the mobility to even access these programs. To close this gap, Seim engineered a high-tech glove that she and her collaborators hope will one day let stroke survivors recover lost function in the comfort of their homes.

The gloves use haptic technology — originally developed for the video game industry to simulate interacting with objects and other sensory experiences — to stimulate patients' hands with programmed patterns of vibration.

Researchers have hypothesized that applying vibration to specific muscle and sensory receptors in the hands could trigger a long-term rewiring of the brain, allowing people to regain control of their weakened limbs. More immediately, the vibrations could also help relieve involuntary muscle contractions which distort patients' limbs and constrict movement.

This idea has not been tested outside of limited laboratory studies, but that will change with Seim's new wearable technology, which she is designing for real-world use in collaboration with Stanford Medicine stroke expert Maarten Lansberg, MD, PhD, a professor of neurology, and haptics expert Allison Okamura, PhD, a professor of mechanical engineering.

"A vibrating glove that improves hand function after stroke would be a breakthrough in the field of stroke rehabilitation," said Lansberg. "Dr. Okamura and I are very excited about this technology, which can be easily used by people in almost any environment."

The research team has designed the gloves to be easy to use in a home setting by patients who suffer a wide variety of stroke-related symptoms. "Patients need to be able to put them on themselves and wear them comfortably at home, whether they have really tight fingers or really weak fingers," said Seim, whose work is supported by grants from the Wu Tsai Neurosciences Institute and the National Center for Medical Rehabilitation Research.

The team has enrolled 20 patients in a clinical trial to test how well the gloves work in a home setting. Patients will use the gloves for two months, then researchers will monitor hand function for up to six months. A second trial is underway to determine how haptic stimulation affects communication between hand and brain.

"So far, everyone who's finished with the device says they miss it, they want it back, they love it," Seim said. "And this is after we made them wear the glove for 160 hours. So I think that's a promising sign."

Lansberg and neurology and neurosurgery professor Marion Buckwalter, MD, PhD, who direct the Stanford Stroke Recovery Program, are also adapting gaming technology to help patients recover hand function. A study published in March in the rehab-focused journal *PM&R* found that patients who used a virtual reality rehabilitation gaming device for eight weeks at home showed marked improvement of hand function and were highly satisfied with the device. The team is testing this approach in a larger, randomized controlled clinical trial.

More about efforts to improve mobility and other functions after stroke is on the Stanford Stroke Recovery Program website at stan.md/strokerehab.

New ways to see

RESTORING SIGHT TO THE BLIND WITH A RETINAL IMPLANT

After more than 15 years of research, Daniel Palanker, PhD, and his collaborators have produced and successfully tested a first-generation retinal implant that can restore vision in people with age-related macular degeneration.

The eye disease leads to a gradual loss of sight in the center of the visual field because of damage to light-sensing nerve cells in the retina, called photoreceptors. Palanker's lab has developed a technology that does the job of photoreceptors — a photovoltaic implant that converts incident light into electric current and transmits the visual information to the remaining, intact inner retinal cells.

"We are just replacing one layer of cells that has been lost with photovoltaic pixels," said Palanker, a professor of ophthalmology. "We use the rest of the retina to process the electronic visual input and thereby help restore sight."

A company that has licensed his technology from Stanford tested the first generation of the device (called PRIMA) with 100-micron pixels in five patients in France. Four of them achieved visual acuity close to the 20/420 limit set by this pixel size, he said. With electronic zoom, they were able to read letters four times smaller (20/100) on a vision chart. Moreover, they could simultaneously use the prosthetic for central vision along with their remaining natural peripheral vision. Palanker and his colleagues published the findings in March 2020 in the journal *Ophthalmology*.

"It's a very exciting confirmation of many assumptions we have made at the beginning of a very long journey," Palanker said. Researchers will now begin a larger clinical trial of the implant in 38 patients in Europe and in the United States, including Stanford.

Macular degeneration is the most common cause of untreatable blindness in the United States among people 50 and older. Drug injections in the eye can minimize vision loss in some forms of the disease, but it goes only so far in preventing blindness.

Palanker's device consists of a 2-millimeter chip that is surgically implanted under the retina. The procedure takes about two hours, often under general anesthesia to minimize a patient's movement. With the chip in place, patients don augmented-reality glasses with a small video camera on the rim. The camera captures images, and the glasses project them onto the chip implanted under the retina using invisible near-infrared light. Each pixel in the chip converts the incoming light energy into an electric current, much the way a solar panel converts sunlight to electricity, Palanker said. The electric current flowing through the tissue stimulates the nearby neurons, which relay these signals to the rest of the retina and ultimately to the brain, which decodes the image so the patient can see.

In a recent preclinical study, submitted to a Nature Portfolio journal, Palanker's group demonstrated much higher resolution in rodents by making the pixels as small as 20 microns. If these implants work well in human patients, they could achieve 20/80 vision; with double magnification, they could see well enough to drive, he said.

"I think these implants will be affordable because the fabrication technology is scalable to large numbers, as with any silicon chip," he said.

Palanker is a consultant for the company that licensed the technology and an inventor of the Stanford-licensed patents.

For more information on the retinal implant, see stan.md/retinaimplant.

BUILDING AN ARTIFICIAL RETINA

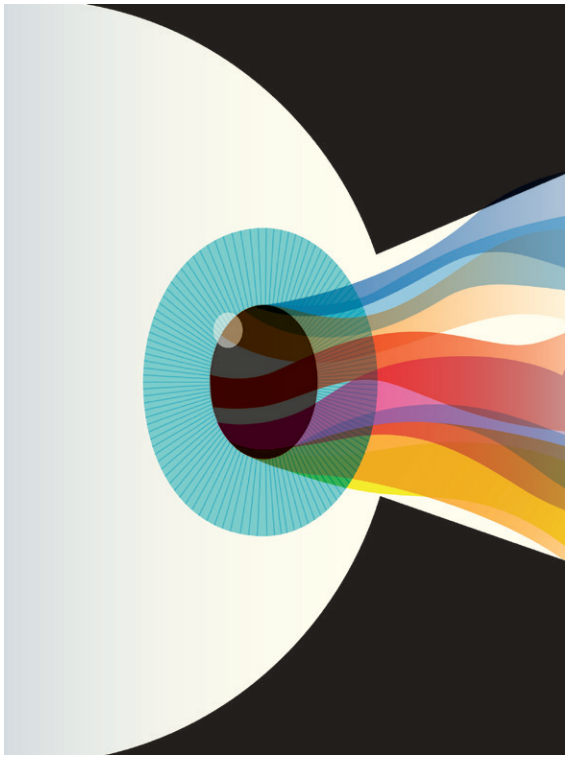
NEUROSCIENTIST E.J. CHICHILNISKY, PHD, is also developing a device to help restore vision for people with retinal disease, but his approach is different. His group is designing an artificial retina — an electronic implant that replicates the complex process by which key nerve cells, known as the retinal ganglion cells, convey visual information to the brain.

The advantage of this approach, compared with Palanker's device, is that it bypasses the photoreceptors and targets the underlying retinal cells that have a direct communication line to the brain.

There are more than a million of these cells in the inner layer of the retina but, unlike photoreceptors, they are not uniform.

There are some 20 types of retinal ganglion cells, each with a different role in conveying visual stimuli to specific areas of the brain. The researchers have to learn the language of each of these cells and how each communicates with the brain.

"What we are doing is developing a smart device that records the activities of these cells, uses that information to figure out who is who, and figure out how to target each of these cells individually with customized information so they can send the right signals to the brain," said Chichilnisky, the John R. Adler Professor of neurosurgery and of ophthalmology. "It's a high-end kind of interface."



In other words, the scientists have to faithfully reproduce the way the cells encode visual stimuli so the brain responds with an accurate visual image.

The device could help the millions of patients who have macular degeneration or retinitis pigmentosa, conditions caused by lost or damaged photoreceptor cells. The retinal implant would bypass these cells to restore vision.

As part of the Stanford Artificial Retina Project, Chichilnisky is collaborating with Palanker and about 20 other scientists, including experts in electrical engineering, retinal surgery,

If these implants work well in human patients, they could achieve 20/80 vision; with double magnification, they could see well enough to drive.

Brains on brains

WU TSAI NEUROSCIENCES INSTITUTE DRAWS RESEARCHERS TOGETHER TO EXPLORE THE MIND

BY NICHOLAS WEILER

At the founding of the Wu Tsai Neurosciences Institute in 2013, director Bill Newsome, PhD, invited faculty members from across Stanford to a series of dinners where he would pose the same question: "What can we do together to solve fundamental questions in brain science that are too big to tackle alone? Assume funding is no object."

After only a moment's hesitation, the gathered scientists, clinicians, engineers, educators and ethicists began talking all at once, in conversations that set the tone for priorities for the institute that stand to this day.

"Understanding how the 3 pounds of matter in our skulls generates our mental life and behavior is among humanity's biggest questions, and developing new treatments for brain diseases is one of society's most urgent priorities," said Newsome, the Vincent V.C. Woo Director of the institute and Harman Family Provostial Professor of neurobiology.

"These are questions we can solve only by coming together as one neuroscience community to share ideas and technologies that will reveal the workings of the brain in health and disease."

The Stanford Neurosciences Building opened in 2020. It houses labs and resources for neuroscience researchers throughout campus.

The institute — renamed in 2018 after donors Clara Wu Tsai and Joe Tsai — promotes collaborative, interdisciplinary research with three broad goals: discovering fundamental principles of brain function, engineering new tools to probe and connect with brain circuits, and advancing brain health by translating neuroscience discoveries into treatments.

The institute has grown to encompass more than 400 Stanford faculty with backgrounds in neuroscience, medicine, engineering, psychology, education, law and other fields, including six scholars the institute has hired whose work transcends traditional disciplinary boundaries.

The institute has committed more than $26 million in targeted grants to support cross-disciplinary teams advancing new ideas and technologies in brain science, including its ambitious Big Ideas in Neuroscience initiatives, which are aimed at fundamentally transforming the field.

The institute also supports the next generation of neuroscience leaders through interdisciplinary fellowships for graduate students and postdoctoral scholars as well as summer research opportunities for undergraduates. It is dedicated to diversity, inclusion and equity as essential to the advancement of science and the development of a vibrant intellectual community.

In February 2020, the institute moved into the new Stanford Neurosciences Building. Designed to maximize collaborative research between experimentalists, engineers and theorists, the building houses 24 neuroscience labs, a theory center dedicated to computational neuroscience, and community laboratories where researchers from different disciplines can share access to technologies and expertise.

"The collaborative community we've nurtured over the years has been incredibly fruitful in advancing our knowledge," said Newsome. "In the next decade, I'd love to see us expand our impact — not only in the realm of brain health, but also in education, economics, health policy and all the realms where unraveling the mysteries of human behavior could help lead us to a more just and equitable world."

neurophysiology, computational neuroscience and visual behavior. The project kicked off six years ago, when the group received a Big Ideas in Neuroscience grant from the Wu Tsai Neurosciences Institute.

The researchers have developed a prototype chip and a series of advanced algorithms that they have been testing in animal models and in donated human retinas. They are refining the technology and hope to have a 2-millimeter implant in two to three years so they can begin human trials.

"We do want to restore vision to the blind, but we also believe this technology could have implications for other areas of the brain while producing a spectacular instrument to understand the visual pathways," Chichilnisky said.

In the near term, he said, the research could benefit patients such as those with Parkinson's disease by improving techniques for deep brain stimulation. Surgeons implant an electrode that activates neurons in a specific area of the brain, but how the method works is not well understood. The retinal project could shed light on the natural patterns of the underlying brain circuits and how to interface with them, and thus help make deep brain stimulation more targeted and effective. It also might contribute to other brain interfaces to help people with memory loss, paralysis or other disorders tied to the brain.

For more details on the Stanford Artificial Retina Project, go to: artificial-retina.stanford.edu.

USING DRUGS TO TACKLE GLAUCOMA AT ITS SOURCE

OPHTHALMOLOGISTS TYPICALLY manage glaucoma — the world's leading cause of blindness — through various methods to lower the fluid pressure within the eye. Over time, elevated pressure damages retinal ganglion cells and their long projections, known as axons, that form the optic nerve. This degenerative process kills the optic nerve and results in blindness.

Jeffrey Goldberg, MD, PhD, professor and chair of ophthalmology, believes it will not be enough to focus exclusively on managing internal eye pressure. Rather, he sees the future of glaucoma care in new therapies that preserve and protect the retinal ganglion cells and their axons and, possibly, regenerate those that are lost.

"For many years, it was thought that vision restoration trials weren't possible — that you needed too many patients, that the disease was slow and variable so it would take too many years and be too expensive," said Goldberg, the Blumenkranz Smead Professor and director of the Spencer Center for Vision Research. But his recent experience has shown it is possible to conduct short-term trials and generate encouraging results.

One study involves a molecule called C1q, discovered by the late Ben Barres, MD, PhD, former chair of neurobiology. C1q is believed to underlie many neurodegenerative processes, including the destruction of retinal ganglion cells. A South San Francisco, California, company co-founded by Barres, has developed a monoclonal antibody that binds to C1q and inhibits its activity. In a Phase 1 trial, Goldberg and his colleagues tested the antibody in the first human trial by injecting it into the eyes of glaucoma patients.

"We did a molecular characterization and showed that the antibody drug was indeed mopping up all the free C1q from inside the eye," he said. The next step is to see if it can improve vision.

In other trials, Goldberg and his colleagues have tested different nerve growth factors that nourish and maintain nerve cells. In one study, they have experimented with an implant filled with cells genetically engineered to make ciliary neurotrophic factor, a naturally occurring molecule shown in animal studies to protect and regenerate axons in the optic nerve.

The scientists implanted a 1-by-5-millimeter capsule into the middle of the eye, where it released a steady flow of the growth factor onto the retina and optic nerve. The results showed a thickening of the nerve fibers, which is encouraging, as these fibers typically thin out as glaucoma progresses, Goldberg said. The scientists are testing the use of two implants, instead of one, and treated their first two patients this spring and early summer.

"The implants look great, but it will take some time to measure their effects," Goldberg said.

In a separate trial, researchers tested eyedrops containing high doses of human nerve growth factor, a naturally occurring protein that similarly supports nerve cells. They enrolled 60 glaucoma patients at Stanford over the course of a few months in a randomized trial designed to gauge safety. These results were also encouraging, with some signs of nerve fiber thickening and a great safety profile. "The ideal next step is to test the eyedrops for a full year to see if they help improve the patients' vision," Goldberg said.

Whether these or other candidate therapies in clinical trials for glaucoma could prove effective, pushing the field to complete such trials is showing a positive effect, he said. "What we've learned through all these trials is that we can do them in a reasonable fashion and time frame and start to address this big unmet need of vision loss in glaucoma." SM

For more on these trials, visit: stan.md/glaucomadrops.

BRUCE GOLDMAN AND NICHOLAS WEILER contributed to this article.

— Contact the authors at medmag@stanford.edu

SAME INJURY, DIFFERENT BRAIN

EXPLORING HOW WOMEN'S TRAUMA RECOVERY DIFFERS FROM MEN'S

By Hanae Armitage

ILLUSTRATION BY HARRY CAMPBELL

Five years ago, Odette Harris, MD, professor of neurosurgery and a brain trauma expert, began to weave an age-old question into her research: What are the differences between men and women?

Harris had not intended to bring sex differences into her work, but while analyzing brain trauma data from the Department of Veterans Affairs, she realized there's a big gender difference in the aftermath of traumatic brain injuries, and no one was talking about it.

In fact, in her analysis, Harris, director of the Traumatic Brain Injury Center of Excellence at the VA Palo Alto Health Care System, found several unexpected trends: Women with brain injury trauma and other severe injuries typically saw higher rates of depression, substance abuse, memory problems and homelessness, among other troubles, than men with brain trauma.

Initially, Harris was wary of widely sharing her findings. "I was concerned that this information could be weaponized or misconstrued. We're not saying women don't do as well as men, or women aren't as strong as men. That's not it at all," she said. "We're saying that women and men experience brain injuries differently, and we need to treat them as such. This is a challenge in our field that deserves attention."

STUDIES BY NEUROSCIENTISTS ODETTE HARRIS, LEFT, AND MAHEEN ADAMSON REVEAL KEY DIFFERENCES IN HOW BRAIN TRAUMA AFFECTS WOMEN WHEN COMPARED WITH MEN WHO HAVE SIMILAR INJURIES. THE NEUROSURGERY PROFESSORS HOPE THEIR INSIGHTS LEAD TO BETTER TREATMENT AND RECOVERY FOR FEMALE PATIENTS.

To better understand the nature of brain trauma in women — physiologically, psychologically and socially — Harris teamed up with colleagues, including Maheen Adamson, PhD, a clinical scientific research director for Rehabilitation Services at the VA Palo Alto and a clinical associate professor of neurosurgery at Stanford School of Medicine. Using data from surveys, neuropsychological testing and brain imaging, they have conducted matched analyses comparing male and female patients, meaning that, sex aside, the comparison groups' specifics — age, severity of injury and time since the injury — were equal.

Their work has so far revealed some big differences in the brains and behavior of men and women with post-trauma injuries — insights that could guide treatment for women who have suffered debilitating injuries to the head.

Lisette Meylan is grateful for the new direction. In 2004, her daughter, Mariela, who was on duty in Kuwait, suffered severe head and other injuries when a car hit her and four other soldiers as they changed a flat on their truck. She survived the accident but ended up in a coma, receiving care in a nursing home for veterans in Washington, D.C. "Her doctors told me I needed to be prepared for my daughter to never wake up," Meylan said.

But Meylan could not give up on her daughter, so she moved her closer to home, in Livermore, California, to the VA's Livermore division. There, Meylan and her daughter's care team tried different therapies to wake her from a vegetative state. It seemed all but hopeless. Two years passed. Then, one day, Meylan saw a light blinking on her phone's message machine, indicating a new voicemail.

She played the recording: "This is Mariela, I'm your daughter, and I love you."

"Those were the first words she'd spoken in two years," said Meylan. Since then, her daughter's recovery has been challenged by physical and mental hurdles, such as learning to walk again, but she has progressed immensely.

"My biggest challenge is my memory," said Mariela Meylan. That's more common for women who have experienced multiple traumatic injuries, compared with men, according to Adamson. "My short-term memory has been affected the most. But through the support of my family and my team of practitioners, I'm able to continue to heal and show up for my life."

In 2014, she participated in a storytelling workshop run by Harris for women who've experienced traumatic brain injury to share their stories with other women who have the diagnosis and health care professionals. Through intensive physical therapy at the Livermore VA, she now regularly practices yoga, rides horses and swims. She lives with her mother, who helps her navigate other day-to-day activities, like making meals.

LESLIE WILLIAMSON

'MY BIGGEST CHALLENGE IS MY MEMORY.' THAT'S MORE COMMON FOR WOMEN WHO HAVE EXPERIENCED MULTIPLE TRAUMATIC INJURIES, COMPARED WITH MEN. 'MY SHORT-TERM MEMORY HAS BEEN AFFECTED THE MOST.'

"Patients like Mariela are the reason we do this," said Adamson. "The stories of their strength, perseverance and motivation give my research a purpose and motivate me to never stop discovering."

Surveys and analysis of health record data by the Stanford researchers and others continue to find stark differences in how men and women experience severe brain injury. But there's also a physical clue: The imaging research suggests a link between a physical trait of women's brains — a thinning of part of the cortex — and the tendency to experience a different array of post-brain injury symptoms than men do.

Their analysis will help fill in research gaps. "Females account for 15% of the traumatic brain cases we see, yet the studies investigating TBI comprise data almost exclusively from men," said Adamson.

SETTING WOMEN UP TO SUCCEED

IN HER DEEP DIVE into the Armed Forces Health Surveillance Center data from 2000 to 2010, Harris found several key differences in the aftermath of severe head trauma for men and women, including that women are four times more likely to abuse drugs, seven times more likely to be homeless and about three times more likely to be unemployed.

Women with traumatic brain injury are also 30% more likely than males to suffer from post-traumatic stress disorder. And they experience higher rates of vertigo — the feeling that the environment is moving (often spinning) around you.

Part of the research goal is to figure out how best to set women up for success after brain trauma. It's not always the same as what's best for men. "For instance, when we see unemployment in males with traumatic brain injury, our approach is to assist in education and skills training," said Harris.

"So the knee-jerk reaction is to find ways to increase education and training when we see unemployment in women with traumatic brain injury. But we found that female veterans were better educated and more likely to have a college degree than their male counterparts."

So education and skills training might not be as helpful for women as it is for men.

WEB EXTRA

Watch a video about a woman's experience with brain trauma: stan.md/neurotrauma

BRINGING IT BACK TO THE BRAIN

WHAT'S CAUSING THE differences in the impact of brain injury trauma on women and men?

In 2016, Adamson began investigating, using neuropsychological testing and brain imaging. The tests gauged general brain function and memory, among other abilities. The imaging portion of the study, which comprised 70 veterans (28 women and 42 men) used MRI to measure the thickness of the cortex, the thin outer layer of the brain's cerebrum.

"Scientists have looked at how cortical thickness changes in a variety of neurological diseases, such as schizophrenia, and we thought it made sense to start there for this research, too," said Adamson.

Under healthy conditions, women's cortex is about 6% thicker than men's. In the MRI study, injured brains of all veterans exhibited signs of cortical thinning, only for women it was significantly worse.

The brains of the women she studied had more patches of cortical thinning, especially in regions that regulate emotion and decision-making. Scientists know cortical thinning is not good, but it's too early to say how the condition impacts behavior or overall health of the brain.

Researchers are recruiting more participants to further explore how cortical thinning impacts symptoms and post-brain injury outcomes for women, said Adamson. "We're just hitting the tip of the iceberg here."

She and Harris are also considering other populations of brain trauma survivors and how their experiences differ.

"I see our research as aligning well with a shift we're seeing at the national level — incorporating gender, race, ability and other differences into science and patient health," said Harris.

"We're seeing a shift toward looking at differences between male and female traumatic brain injury more deeply, and my hope is that that trend will extend to other groups within the traumatic brain injury patient population. That's what will enable us to improve outcomes and ensure equitable care for all people, not just women."

— *Contact Hanae Armitage at harmitag@stanford.edu*

a delicate operation

removing a tumor from deep in a 2-year-old's brain

BY GORDY SLACK

PHOTOGRAPH BY GREGG SEGAL

In August 2018, 2-year-old Ari Ellman's parents took him to an emergency department near their home in San Francisco for the latest in a series of uncontrolled vomiting bouts. While awaiting an abdominal MRI, Ari had his first seizure, shifting doctors' attention from his abdomen to his head.

A brain MRI revealed a golf-ball-sized growth in the difficult-to-reach central lower part of his brain, near the base of his skull. The rare, non-cancerous but fast-growing tumor, called a craniopharyngioma, was entangling the critical brain structures in the skull base. Unless the growth was removed, it would endanger all those structures and ultimately Ari's life.

The Ellmans' world turned on its head that day. "I barely had time to feel sorry for myself, though," remembered Ari's father, Jonathan. "A friend said, 'There's no time for self-pity, or anything else really … except focused action.'"

The Ellmans seized the reins of Ari's care and didn't let go. "The night after the diagnosis, my heart was all over the floor," said Ari's mother, Na'ama. "But Jonathan turned his computer toward me and said, 'These are the top hospitals and craniopharyngioma surgeons we need to speak with. *Tomorrow*!'"

ARI ELLMAN WAS 2 WHEN SURGEONS REMOVED A GROWTH AT THE BASE OF HIS SKULL BY ENTERING THROUGH HIS NOSE, AN UNPRECEDENTED APPROACH FOR A CHILD SO SMALL.

A DARING APPROACH

MILLIONS OF YEARS of evolution buried such essential brain structures as the pituitary gland and hypothalamus in the bottom middle of the human head where they would be well-protected from a world full of sharp and heavy dangers. So, it is no accident that the same important part of the brain, known as the skull base area, is notoriously difficult for surgeons to reach. For the first century of modern brain surgery, the only way to get there was by opening the top of the head, spreading the brain's hemispheres apart, and tunneling down between them to the core.

Because the optic nerves, which connect the vision-processing part of the brain to the eyes, stand between the skull base area and that cranial opening, surgeons often had to work around those delicate and vulnerable structures, too. Collateral damage to essential brain tissue on the way down could be devastating, and further damage could be imposed when surgeons were pulling a tumor up and out.

In the past decade, though, advances in imaging, surgical anatomy and surgical tools have enabled surgeons to use a less destructive approach. Instead of entering the skull from above, they enter through the nose and sinus area, just below the hardest-to-reach skull base structures. This method, known as transnasal endoscopic skull base surgery, has become the preferred method for removing tumors in this part of the brain — but only in adults. Children have much smaller sinus cavities, and at the time Ari became ill, surgeons still approached pediatric skull base tumors the old-fashioned way — open surgery from above.

However, as the Ellmans would soon discover, an extraordinary team of Stanford neurosurgeons and rhinologists believed a transnasal approach would be feasible even in small children. They just needed the right case to prove it.

If successful, they would not only have an opportunity to save the life of a dangerously ill patient but also to provide pediatric neurosurgeons with a technique for skull base surgeries in small children for generations to come. Their method would give them direct access to essential parts of the young brain that have been excruciatingly hard to reach. A failure would make that path much more difficult for future surgeons to take — or even consider.

In the first week after learning Ari's diagnosis, his parents sent his case to tumor boards — multidisciplinary groups of specialists — at 15 leading medical centers. Some suggested old-school open-brain surgery, which, in addition to the obstacles described above, often fails to remove the entire tumor, partly because the roots of craniopharyngiomas, at the bottom of the brain, may be inaccessible from above.

Other surgical groups suggested radiation, but that can cause devastating and lasting side effects in a young child. It was the third and rarest option suggested, transnasal endoscopic skull base surgery, that really caught the family's attention. For this method, surgeons slide endoscopes — thin tubes with a light and camera, through which surgical tools can pass — into the brain via the patient's nose. Unfortunately, only a handful of endoscopic skull base craniopharyngioma surgeries had been conducted on young children, and none of those children was younger than 5. Ari was only 2. It wasn't just Ari's age and size that made the surgery an extraordinary challenge, but it was also his tumor's relatively large size and specific characteristics. It consisted of multiple cysts, and portions of it were calcified.

Most surgeons the Ellmans contacted wouldn't even consider endoscopic skull base surgery for a huge craniopharyngioma in a child like Ari. It would be an unprecedented operation requiring extraordinary degrees of both expertise and technology that were available at only a few surgical centers around the world.

But not only were doctors at Lucile Packard Children's Hospital Stanford willing to try it, they also recognized it as an opportunity to advance surgical knowledge, said Juan Fernandez-Miranda, MD, a skull base surgeon who was recruited to Stanford from the University of Pittsburgh just a couple months before Ari's family approached Stanford. It was a case with the right patient, the right surgeons, the right family and the right technology, all coming together in one place. "I felt like I'd been preparing for this surgery for 15 years," said Fernandez-Miranda, professor of neurosurgery and surgical director of the Stanford Brain Tumor, Skull Base and Pituitary centers.

'This same tumor in an adult patient would still be very difficult to remove. ... Now add a 2-year-old patient to the picture and you get a truly unique case...'

The Stanford surgical team also included Gerald Grant, MD, Stanford's chief of pediatric neurosurgery, and Peter Hwang, MD, professor of otolaryngology and a world-renowned endoscopic otolaryngologist who has been conducting adult and pediatric endonasal sinus surgery for over 20 years. Hwang is also division chief of rhinology and endoscopic skull base surgery.

"We have a unique combination of endonasal skull base surgery expertise and pediatric neurosurgery experience. Both are essential for a resection like Ari's," said Grant, the Botha Chan Endowed Professor.

When the Ellmans met Grant, Hwang and Fernandez-Miranda, they knew they had found their team. Their decision was reinforced by the group's record of surgical excellence, their focus on pediatrics, their attentiveness and warmth, and the advanced technology dedicated to neuroendoscopy in Lucile Packard Children's Hospital's surgical suites.

"This same tumor in an adult patient would still be very difficult to remove, even for very experienced neurosurgeons," said Fernandez-Miranda, explaining the challenges of Ari's case. "Now add a 2-year-old patient to the picture and you get a truly unique case, never done before — not just difficult, but thought by many to be impossible."

TAPPING TECHNOLOGY TO HELP PREPARE FOR SURGERY

Preparations began weeks before the surgery. A single high-resolution 3-D digital image of Ari's brain was created by combining several simpler digital images — such as MRIs and CT scans — then loaded into a virtual reality tool called Surgical Theater. The tool's users wear virtual reality headsets that turn the 3-D brain image into what video game players call an "immersive environment" — a "landscape" through which users seem to be moving around and exploring at will. Except, instead of moving around inside a digitally constructed room, as they might in a game, this tool allows users to move around inside their patient's brain and to closely study the geography of that brain — its nerves, ventricles, arteries and other essential structures, as well as tumors. They can plan the trajectories their surgery could take and the effects different approaches could have on nearby brain tissue. Using the tool, Ari's surgical team carefully mapped and rehearsed the best possible path to his tumor and the best way to remove it while protecting essential brain structures.

"Clearly visualizing the brain structures surrounding the tumor in advance is key," said Fernandez-Miranda. In addition to the virtual digital modeling, a resin scale model of Ari's skull base was 3-D printed so the team could take it to the Stanford Neurosurgical Training and Innovation Center, which Fernandez-Miranda directs, to plan and practice for several hours with actual surgical tools and "to make sure we had enough space in the nasal cavity to get into the skull base safely."

"A 2-year-old's sinuses are only 20 millimeters wide or narrower. And you're removing a tumor that may be wider than the nasal passage itself," said Hwang. "It's like getting a ship out of a bottle. You have to figure out how to take it apart and bring it out through this very narrow corridor. You don't want to wait until it is game time to iterate and innovate — you really need to have your plans in place well before the day of surgery. That's why these additional technologies can play such an important role in pediatric skull base surgery in particular."

MOVING THROUGH THE BRAIN WITH EXTREME CARE

By the day of the operation, the Ellmans felt they had done everything they could to ensure Ari had the best place, the best doctors and the very best chances of success, Ari's mother said. Still, when they left their home at 5 a.m. on Feb. 8, 2019, they began "by far the hardest drive we'd ever taken," she said. "At the end of it, we knew we'd be handing him over and it would be out of our control."

Ari's prep for surgery began at dawn, with the setup of the same 3-D digital modeling and navigation system used to rehearse the operation, but this time it was anchored to actual landmarks in Ari's brain so surgeons could see on the monitor exactly where their tools stood relative to both the tumor and to critical brain structures.

By the beginning of the second hour in the OR, Hwang was slipping his endoscopes into each of Ari's nostrils as he began to navigate the space between Ari's nose and brain, "creating corridors through the nasal passages by opening sinuses, combining nasal passages, removing bone, and converting two separate nasal chambers into one chamber with more access to — and better visualization of — what will be the avenue to Ari's brain," said Hwang.

Two hours in, Grant and Fernandez-Miranda enlarged the corridor into the base of the skull using high-speed drills and opened the dura, the thick membrane that seals off the brain from the rest of the world. The tumor was close to the point of entry, but this part of the brain is

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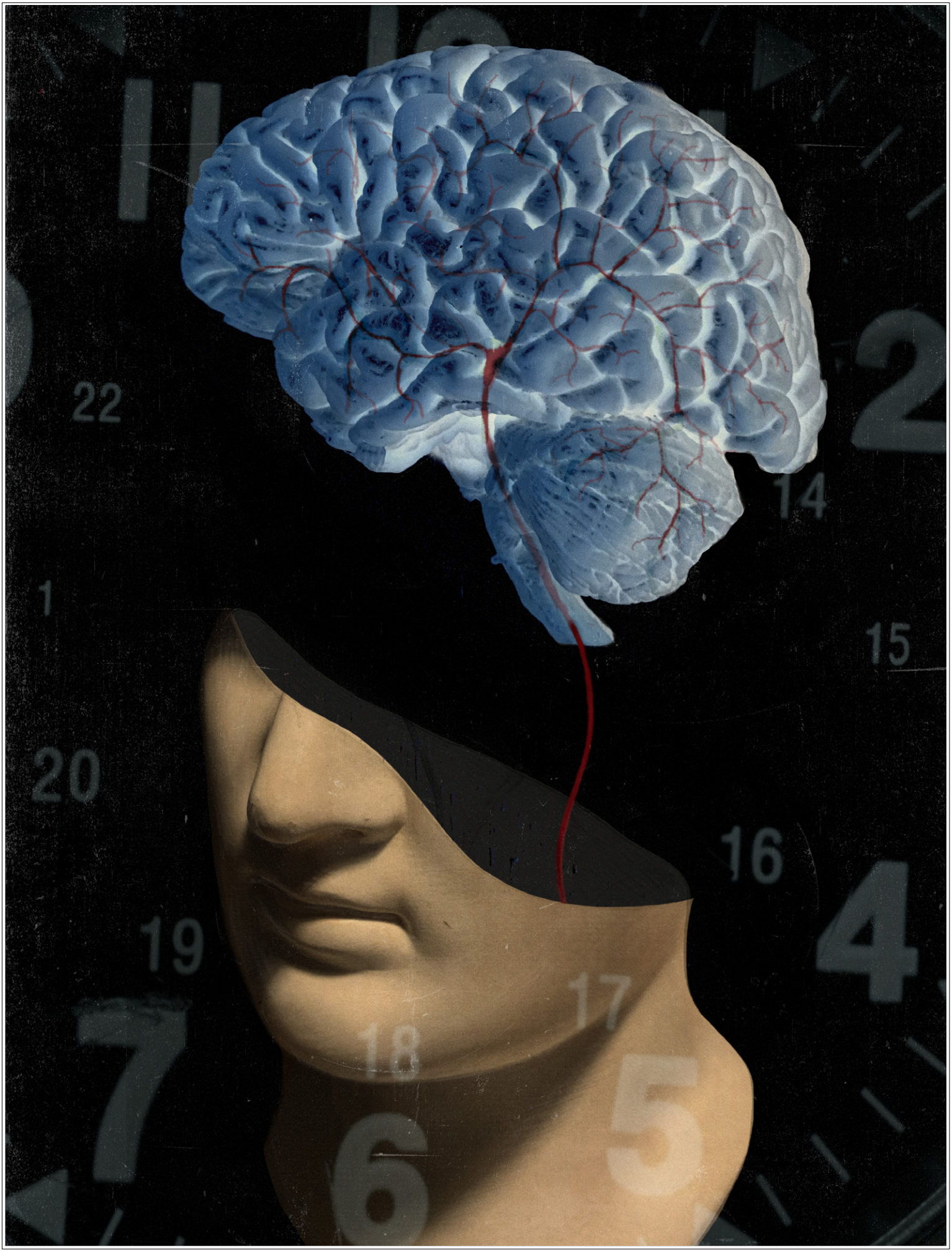

OPENING STROKE'S WINDOW

Treating stroke more than a few hours after the crisis is no longer considered absurd

By Amy Jeter Hansen

ILLUSTRATION BY JONATHON ROSEN

AROUND 10:30 P.M. ON APRIL 23, 2017, Cindi Dodd ended a phone call with her best friend, turned off her bedside light, and settled in for a night's sleep in her Salinas, California, home ahead of a surgery the next day.

The scheduled operation was a breast reconstruction following a bout with cancer, but when Dodd's husband, Rick, woke her at 5 a.m., something else was terribly wrong. She seemed to be having a seizure. She couldn't move her left arm or leg, and when she spoke, only gibberish came out.

Rick Dodd called 911 and yelled to their son to turn on the porch light for an ambulance. At the hospital, the family found out that a blood clot had lodged in Cindi Dodd's middle cerebral artery, preventing blood and nutrients from flowing to her brain. While she was asleep, the 46-year-old graphic designer had experienced an acute ischemic stroke. Cells in her brain had begun to die.

Doctors told Dodd's family they could do nothing to remove the blockage: Too much time had lapsed since she was last known to be well. According to standard guidelines, after six hours from the onset of a stroke, the risk that treatment would cause dangerous bleeding in the brain and elsewhere in the body outweighed the benefits of restoring blood flow to damaged tissue.

Her best option, an emergency physician told her husband, was to get to Stanford Health Care. There, doctors were leading a large clinical trial to determine if the narrow window of time for stroke treatment could be widened for patients under some circumstances.

Rick Dodd didn't hesitate. Within an hour, a helicopter arrived, and Cindi Dodd was on her way to Stanford Hospital.

"That's my baby. Take care of her," Dodd's mother told the flight nurse through tears.

EXTENDING TREATMENT TIMELINE

ON THE OTHER SIDE OF THAT FLIGHT, at Stanford Hospital, Gregory Albers, MD, was leading the most critical clinical trial of his 30-year career.

He became fascinated with the human brain when he was a teenager, in California's San Fernando Valley. Since completing a stroke research fellowship at the Stanford University School of Medicine in 1988, he had dedicated his work to improving the lives of stroke patients.

WHEN CINDI DODD WOKE UP AFTER HER STROKE, SHE REALIZED THAT BEING IN A STANFORD TRIAL TO EXTEND THE TREATMENT TIMELINE GAVE HER 'A CHANCE TO FIGHT FOR MY LIFE.'

LESLIE WILLIAMSON

Whenever stroke patients arrived at the hospital too late for a dismal outcome to be prevented, Albers always felt dismayed. He wondered if some patients who arrived many hours after their stroke began might still benefit if blood flow was restored to their brain tissue. And if so, was there a way to identify which patients could be helped during this longer period?

These questions would frame his professional efforts for nearly three decades, beginning in the 1990s.

During that time, through a methodical progression of research, Albers and his colleagues chipped away at the status quo of stroke treatment. They tested — then refined — a new imaging technique that could quickly reveal the damage wrought by a stroke, as well as the at-risk tissue that could still be saved. Gradually winning over skeptics, they crafted a protocol that added precious hours to the timeline for stroke care and carried immense potential to help countless future patients avoid severe disability or worse.

"It was a huge challenge," Albers said of his quest to improve outcomes for stroke patients. "We were dealing with the No. 1 cause of disability worldwide, and there was no treatment."

ADVANCING BRAIN IMAGING

THE STANFORD STROKE CENTER opened in 1992, led by Albers, neuroradiologist Michael Marks, MD, and neurosurgeon/neuroscientist Gary Steinberg, MD, PhD. The center's aim was to develop new therapies and bring them to patients. "We were not satisfied with this nihilistic approach, that stroke is something you can never treat," said Steinberg, who is the Bernard and Ronni Lacroute-William Randolph Hearst Professor in Neurosurgery and Neurosciences.

Within a year of establishing the center, its leaders were approached by Michael Moseley, PhD, a physicist who had recently joined Stanford Medicine's radiology department. Moseley was studying ways to capture images of brain damage from a stroke, and he'd made an intriguing discovery.

At the time, because of limitations of conventional magnetic resonance imaging and computed tomography, evidence of injury from a stroke didn't appear on a scan until four or more hours after a patient's symptoms began. When brain cells begin to die during a stroke, they lose the ability to maintain a balance of water inside and outside the cell. Conventional techniques could capture images of dead cells swamped with water hours later, but Moseley wanted an ear-

lier indication of what was happening.

In a late-night laboratory insight, he discovered that he could track a stroke's damage to brain tissue as it happened through an MRI technique that was more sensitive to the movement of water in cells. Scans created through diffusion-weighted imaging showed a clear difference between cells that had no active transport of water and those with normal water-shuttling activities.

In short, Moseley had found a way to watch brain cells die in real time.

To Albers, "It seemed like the holy grail."

With Moseley, Marks and other Stanford colleagues, Albers embarked upon a series of studies that used diffusion-weighted imaging to track stroke patients for weeks. The resulting images — with bright white smudges showing dead tissue, in contrast to healthy gray tissue — depicted a process that happened at different rates for different people, but often took more than a day to reach maximum size. This discovery ran counter to the prevailing belief that a stroke completed its path of destruction within one to two hours.

Watching the progression of images brought the researchers to the next logical step: "I could see dead brain, but I couldn't predict what was destined to die," Moseley, a professor of radiology, said.

They decided to follow the blood. Using a technique called perfusion-weighted imaging, they injected a contrast agent into a patient's bloodstream and monitored how long it took the contrast to reach distinct areas of the brain. If a major blood vessel was blocked, the contrast agent's journey to that side of the brain was delayed.

It was hard to tell from a brightly colored perfusion-weighted image whether tissue was dying or already dead. However, when the researchers compared it with a diffusion-weighted image, which clearly depicted dead tissue, they could determine whether there was a mismatch area — brain tissue that had not died but was marked for demise if the artery's blockage wasn't cleared.

They realized they could determine whether a person's stroke was finished. If it was ongoing, they could predict how it would play out if physicians couldn't open the blood vessel.

Their rough data suggested that about three-quarters of stroke patients could still benefit from treatment after six hours; after 12 hours, treatment could still help about half of them. This was radically different from what animal models had shown: In rats, a stroke would typically complete within 90 minutes. In monkeys, three hours was the upper limit for avoiding brain damage, according to a pivotal study.

In their 1999 paper, Albers and his colleagues predicted that late-window therapy could improve stroke outcomes, but their study was met with ambivalence from other neurologists. Some were intrigued, while many others thought this approach had no chance of success.

"Neurologists in general tend to be skeptical people," said Albers, the Coyote Foundation Professor, "and there had been a number of stroke trials in the past — many, many stroke trials that had been done in the '80s and '90s — that neurologists were initially excited about. They all failed."

A PROMISING NEW DRUG

BEFORE THE 1990s, physicians routinely let a patient's stroke run its course, convinced there was nothing they could do. This changed as scientists gained a better understanding of the rate at which human brain cells disintegrate and as doctors tested tools for restoring blood flow to oxygen-starved tissue.

A clot-dissolving drug called tissue plasminogen activator — known as tPA — showed promise. It works by activating plasmin, an enzyme responsible for breaking down blood clots. However, because tPA can increase the risk of bleeding everywhere in the body, it can cause serious bleeding complications.

In 1996, the U.S. Food and Drug Administration approved tPA for treating ischemic strokes — those caused by a blocked artery — but only within three hours of the first symptoms. After three hours, the thinking went, it was too late to save the dying brain tissue, and the risk of the drug causing further harm outweighed any potential benefit. Because many patients are unable to seek medical care immediately, the time constraint strictly limited the number of patients who could be treated with tPA.

Albers believed more people could be helped.

In 2001, after he, Moseley and their team published several preliminary studies about the new imaging technique, they were funded by the National Institutes of Health to perform a study of stroke patients who had not arrived in time to receive tPA. The patients would undergo the new imaging techniques and be given tPA between three and six hours after their first stroke symptoms.

Because tPA works for only about half of the patients who receive it, that meant the researchers could test their imaging technique in two ways. For patients with a mismatch and whose blockage persisted, they could see whether the stroke proceeded as predicted. For patients with restored blood flow, they could see if the intervention prevented damage in the brain areas predicted to be salvageable, and if those patients had better outcomes.

The results, published in 2006 as the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) study, turned out exactly as Albers and the Stanford team had hoped and predicted.

Patients with a mismatch whose arterial blockage was dissolved showed improvement in functioning, such as regaining control of their limbs, as measured on the NIH Stroke Scale. This suggested that the imaging had successfully identified salvageable tissue in individual patients and that restoring blood flow by administering tPA had saved the tissue.

What's more, the study indicated that more than half of the patients still had brain cells that could be saved five to six hours after a stroke.

"Clearly," Albers thought, "we're on to something here."

EXPANDING THE LIMITS

HIS TEAM'S NEXT STUDY pushed the envelope further.

Though the design of the second DEFUSE trial was similar to the first, there were two crucial differences. First, the time window was doubled to 12 hours. Second, patients would be treated with a new technique called thrombectomy, in which a physician threads a catheter through the artery to the clot, then deploys a mechanical device to extract it. Additionally, the team had developed an imaging software called RAPID that automatically analyzed the diffusion and perfusion images and calculated the volume of salvageable tissue; the nine medical centers participating in the study all used the new software in the trial.

Some of the researchers' peers expressed doubts about the study's premise — 12 hours was so much longer than the accepted window for stroke treatment. But when the second DEFUSE study was published in 2012, six years after the first, the findings were undeniable.

"It worked beautifully," Albers said.

Their results suggested that the window for successful treatment could be extended to 12 hours for some stroke patients. But they had not yet conclusively shown that patients selected with their imaging technique benefited from late treatment. Doing so required a randomized trial, which is what Albers wanted to do next.

'BRAIN IS OF THE ESSENCE'

IN THEORY, thrombectomy devices, with their capability to clear blockages, were the perfect instrument to help physicians save brain tissue in stroke patients. However, studies of early versions showed disappointing results. Although the devices could reliably restore blood flow to oxygen-deprived brain tissue, stroke patients' ability to function often didn't improve much.

In the years after the DEFUSE 2 study was published in 2012, manufacturers improved the devices. Meanwhile, Albers wondered if many of the patients being treated already had irreversible injury. He wanted to find out if patients who underwent a thrombectomy fared better when the Stanford team's imaging had shown salvageable tissue prior to the procedure.

Before the team could secure funding for a third DEFUSE trial, however, several studies were published that seemed to confirm Albers' theory, widening the stroke treatment window to six hours in certain cases. Two had used the RAPID software, which was now owned by a company Albers had co-founded, and these studies produced the greatest treatment benefits. Among patients with scans that showed salvageable tissue, those who received a thrombectomy within six hours of a stroke showed better outcomes than those who had not undergone the procedure. In 2015, the American Heart Association/American Stroke Association changed treatment guidelines to reflect what the studies had found.

But the Stanford researchers did not believe the issue was settled, as six hours was not long enough to get to the majority of stroke patients; many live far from a stroke center or have the stroke while they're sleeping. The Stanford studies suggested that for patients flagged through imaging, treatment could succeed up to 24 hours after symptoms began. The team was finding that "time is not of the essence. Brain is of the essence," said Maarten Lansberg, MD, PhD, a Stanford professor of neurology who joined the effort in 1997.

The third DEFUSE trial, also funded by the NIH, began in 2016 with more than three dozen medical centers participating. The randomized study focused on patients whose stroke was caused by a blood clot obstructing one of two large arteries in the brain — the middle cerebral artery or the internal carotid artery. This happens in about 1 in 4

THE STANFORD STUDIES SUGGESTED THAT FOR PATIENTS FLAGGED THROUGH IMAGING, TREATMENT COULD SUCCEED UP TO 24 HOURS AFTER SYMPTOMS BEGAN.

ischemic strokes and accounts for the most disabling strokes.

If the RAPID software showed potentially salvageable brain tissue six to 16 hours after a stroke's onset, a patient was randomly assigned to have either standard medical treatment or an alternative that included both the standard treatment and a thrombectomy. Participants were tracked for three months, the period when stroke patients typically experience most of their recovery.

Meanwhile, another study using the Stanford-designed software had been launched in 2014 by Stryker Corp., which manufactures devices for stroke care. The design of Stryker's trial, called the DAWN study, was almost identical to the DEFUSE 3 study with one significant difference: It pushed the treatment window to 24 hours after a stroke's onset, compared with 16 hours in DEFUSE 3.

After an analysis of interim data, the data safety and monitoring committee stopped enrollment in the DAWN trial early, in February 2017. Among 206 stroke patients whose scans showed salvageable brain, those who underwent a thrombectomy experienced less disability than the control group. Because the DEFUSE 3 study was so similar, the NIH placed it on hold soon afterward, in June 2017, to evaluate preliminary findings.

Those weeks were nerve-wracking for the Stanford team, who waited to see what would come next for the study they'd worked so long to begin.

"We were nervous," said Stephanie Kemp, the Stanford stroke center's program manager. "They could have said, 'You don't need any more patients. You've proven what you need to prove.' But they also could have said, 'Oh, no, you're not there yet, and you're not going to get there.'"

CHANGES IN TREATMENT GUIDELINES

IN FALL 2017, when Albers finally saw the data from 182 participants in the Stanford-led trial, he couldn't sleep.

There was no need to restart enrollment. The data showed that the imaging technique Albers and his colleagues had refined over so many years could help physicians determine when they could do more for a stroke patient and substantially improve the patient's recovery. Three months after a stroke, 45% of the patients who received a thrombectomy six to 16 hours after their first symptom were functionally independent, compared with 17% who received standard care. Among patients receiving the thrombectomy, 14% died within three months of having a stroke, compared with 26% in the control group. The team's findings underscored the results of the DAWN trial.

LESLIE WILLIAMSON

A QUEST TO EXTEND THE TREATMENT WINDOW TO HELP STROKE VICTIMS AVOID DEBILITATING OUTCOMES HAD DEFINED GREGORY ALBERS' CAREER FOR THREE DECADES.

Albers thought back across the decades — his entire career. He thought about the times he'd had to tell patients, "I'm sorry. You came in too late. We can't treat you." About how, for some future patients, the likelihood of death and disability was now cut in half.

"This is going to change the world," he thought.

The publication of the DEFUSE 3 study in the *New England Journal of Medicine* was timed to coincide with the American Heart Association's International Stroke Conference in January 2018. On the day Albers presented the results of DEFUSE 3, the association announced changes to treatment guidelines for acute ischemic stroke, recommending a treatment window for mechanical clot removal up to 24 hours after onset in certain patients with clots in large vessels.

William J. Powers, MD, chair of the neurology department at the University of North Carolina at Chapel Hill at the time, headed the committee in charge of recommending guidelines. He knew that many researchers had conducted similar

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A CONVERSATION WITH FLUTE VIRTUOSO EUGENIA ZUKERMAN ON ALZHEIMER'S,

a way through the brambles

Nearly four years ago, internationally renowned flutist Eugenia Zukerman was diagnosed with Alzheimer's disease. Almost as soon as she heard the verdict after a neuro-psychiatric exam, she sat down to write. What emerged was *Like Falling Through a Cloud*, a lyrical book of poetry that unfurls her journey through gradual cognitive impairment and memory loss.

"What seems to have saved me from crumbling and falling apart," she has said, "was music, love, poetry and, oddly, laughter."

Classical music fans know her, *The Boston Globe* exclaimed, "as one of the finest flutists of our times." Enthusiasts of the *CBS Sunday Morning* show recognize her as the show's sharp-minded arts correspondent, a role she held for more than 25 years. For the millions of people living with Alzheimer's, her poems — heartbreaking and honest — may offer hope or solace.

Contributing editor Paul Costello spoke with Zukerman at the end of 2019 when her book of poetry was first published. He checked in with her recently, just as she received her second dose of the Moderna COVID-19 vaccine. Her husband, Dick Novick, joined her on the phone and helped when she struggled for a word. This Q&A was edited and condensed from those conversations.

COSTELLO Although the Delta variant is wreaking havoc in many parts of the United States, for many of us who've been vaccinated there's a new normal. How are you doing?

ZUKERMAN I feel really good. I most look forward to seeing my grandchildren in Washington, D.C. It's torment not to be able to see and hold them.

As far as Alzheimer's, I am towards the end of the first part, but I feel I am very functional. I know what I want to do, and I am lucky that I'm able to do those things. I start my day by rolling out of bed and doing floor exercises. Of course, I do play my flute a lot. My flute is my best friend, my other. For me, it's a very positive time in my life. I feel very blessed and I try to simply live every day.

COSTELLO You said you feel you're at the end of part one?

ZUKERMAN I don't feel that I am in stage two, when one needs more help, but I know it's getting significantly closer for me. Stage three is hospitalization, and I feel I'm nowhere near that. I'm lucky. I do a lot of exercise. I have friends. I love to play with the animals. I am still performing — virtually — so for me, it has not been a terrible experience. In fact, I've learned a great deal through this disease.

COSTELLO What have you learned?

ZUKERMAN I think the important lesson is that you try your best. I want people to understand I am not suffering. It's so important to stay positive. I would say one of the most important things is to be as energetic as you can. What's been important is to also accept the fact that I'm not perfect. I am flawed.

COSTELLO Since you've written your book of poetry, what have you heard from readers?

ZUKERMAN Before the pandemic, I was doing [struggling for the words, she turns to her husband] signings, yes, signings at bookstores.

There was one very elegant man in line who bought six books. When he reached me, he said, "I can't thank you enough, because my family has never understood what I'm going through as a person who has Alzheimer's. What you told us here tonight made me understand, and I'll be able to go back to my family and they will understand more what I am going through."

That was a wonderful feeling.

COSTELLO Many people diagnosed with Alzheimer's are filled with fear and anxiety. Were you?

ZUKERMAN I was with my younger daughter when I had the diagnosis; I was not afraid. I knew that I had the condition. For some reason, I didn't cry. I think I just took it for what it was. I brought it home with me.

When I got up to the apartment and sat down at my desk, I stared at the wall for a while and, for some reason, put some paper down and started to write. That's how the book came about.

COSTELLO What were you thinking as you stared at the wall?

MUSIC, POETRY AND JOY

ZUKERMAN I wasn't really thinking about what I had just gone through. I was just thinking that this is a new set of circumstances. It's sudden … but I am not afraid. I haven't been afraid throughout this whole process.

COSTELLO One of your poems is entitled "Marbles." Why marbles?
ZUKERMAN Marbles are beautiful. They make noise. They make music. I don't know why the marbles metaphor came to me in such a strong way, but it seemed to me that what had been a very stable life was now pulling apart and rolling around like marbles.

COSTELLO The title of your book of poetry is so beautiful, *Like Falling Through a Cloud*. What meaning does that have for you?
ZUKERMAN My mother died at the age of 103. She often talked, even in the last days, of how she was floating. I had the idea of me floating and just lying up in the sky, and there's a moment in which you must fall.

I think once you have fallen through a cloud, there is a certain moment of clarity. The clarity for me was the understanding that yes, I had a condition, and yes, it was a death sentence, but I wasn't afraid. I think it's a gift. I don't know where that comes from. Because I'm not a terribly brave person, I feel as if I've handled this pretty well. The book, I think, is rather joyful.

RICCARDO VECCHIO

COSTELLO You wrote the book for yourself, as a way to channel your Alzheimer's, but you also wrote the book for other people who struggle with cognitive difficulties.
ZUKERMAN I absolutely did. I had met people who were having tremendous problems; they were terrified. I felt that it was not good to be terrified. I wanted people to understand that not only can they find their way through this, but they can come out, in many ways, stronger.

COSTELLO Speaking as a classical musician, how is poetry similar to music?
ZUKERMAN It's extremely similar. They are one and the same. I have always written poetry. Since I was a little girl, it just flowed. I thought it was magical the way you could put words on a page and make them feel really alive.

COSTELLO What is it about the flute that has so moved you?
ZUKERMAN It's given me a best friend for life. At the age of 10, I heard the flute in the local orchestra. I literally ran home and said, "I have to play the flute." I would go to school and come home and knew that my best friend was at home. I think that I have practiced every day of my life.

COSTELLO You still play professionally. As a self-described perfectionist, how do you accept those days when you're not your best because of your illness?
ZUKERMAN I think you deal with it by knowing that every day you want your best to be there, and every day it can't be there. Not for anyone. I am very clearly listening to myself now, and I know there will be a moment when I play only for myself, for my family or for my grandchildren.

I don't think I have anything to prove or win anymore. I adore music every day. I listen to it every day. It is a great strength in my life.

COSTELLO When people meet you at book signings, what do they tell you about memory loss and cognitive difficulties?
ZUKERMAN Everyone is afraid. They're afraid because they don't know what comes next. This is where music helps me a lot.

A few years ago, I was giving a talk and decided to talk about memory loss. I just started talking and telling them what was going on with me. I looked up and every woman was weeping. Weeping. I thought, "Whoa, this is amazing." Afterwards, I spoke to people individually. Some were crying because they were afraid of getting it. Others were crying because it just didn't seem right. It's a very complicated disease. You know there's going to be a definite end.

COSTELLO Since your diagnosis, what have you discovered about yourself?
ZUKERMAN That's a tough one. I've discovered that I am stronger than I thought. I've discovered I want to try, in the time I have left, to write more, keep performing, be with my loved ones. I want to live every day to the clearest of my abilities.

If anyone were to ask me or say to me, "I've just been tested, and it seems that I have cognitive impairment. What should I do?" I would say, "Live your life and live it with joy. Live with as much vibrancy that you have." I only know, for me, I felt it was really important to not give in to this disease, but to figure my way through the brambles. **SM**

Good vibrations

CAN PARKINSON'S SYMPTOMS BE STOPPED?

By Holly Alyssa MacCormick

ILLUSTRATION BY HARRY CAMPBELL

On June 17, 2018, Kanwarjit Bhutani stepped out of an elevator with his wife, unaware his life was about to change.

A woman followed the couple from the elevator to the door of their condominium in New York City. Out of the blue, she recommended that Bhutani see Stanford Medicine researcher Peter Tass, MD, PhD, about his promising treatment for Parkinson's — a vibrating glove.

Bhutani was still processing what had happened when he realized the mystery woman was gone. He had been diagnosed with Parkinson's disease nearly a decade before, but only his close family and friends knew.

"I felt that Parkinson's was something old people had. I don't want to be associated with that. I'm not old, and I was very young — only 39 — when I got the disease," he said.

For years he'd been managing Parkinson's while juggling a career as president of several companies, including Tupperware U.S., Avon and Jeunesse. Then, the disease worsened without warning.

"All of a sudden, I couldn't work," Bhutani said. "I basically went into hiding."

Bhutani scoured the internet for information on Tass' research and introduced himself over email. Within minutes, Tass replied. In August 2018 Bhutani and his wife flew to the Stanford campus in Palo Alto, California, to meet Tass, who assessed Bhutani's condition and explained the concept behind the glove.

"Most of it went over my head," Bhutani said. "It was all la la land, to be honest with you. I didn't understand much, but he said, 'It's noninvasive.'"

"It was noninvasive and it couldn't hurt him," added Bhutani's wife, Suhkpreet Bhutani. "We had nothing to lose."

Parkinson's disease attacks brain cells that make dopamine, a chemical that is key to nerve communication for functions like movement, mood and behavior. Drugs that mimic dopamine are common treatments for the condition.

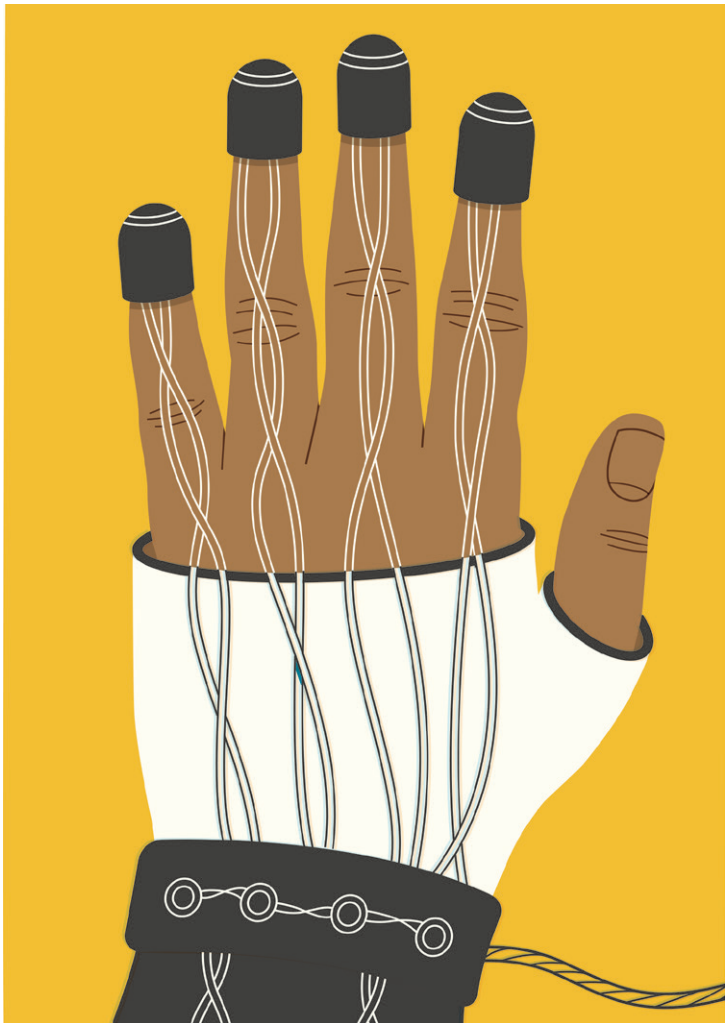
If the symptoms stop responding to drugs, deep brain stimulation is the gold standard treatment. The technique targets abnormal brain patterns with electrodes that are implanted into the brain and linked to a pacemaker-like device. Because of the risks of brain surgery, not all patients are eligible for or choose the treatment.

Yet, neither therapy is perfect. Drugs and deep brain stimulation are expensive and both can have serious side effects. They also don't always work and, even when they do, their benefits can wane. So it might be hard to imagine that a vibrating glove could be much help.

But a recent study of a small group of patients found that wearing the glove for two hours, twice a day does just that, alleviating the tremor, stiffness, abnormal walking, slow body movement and balance problems associated with Parkinson's. Although the researchers didn't set out to study other symptoms, they were surprised to find patients reported the glove also alleviated mood swings, behavior changes, depression and the loss of smell and taste.

"It seemed like magic," said Stanford Medicine neurobiologist Bill Newsome, PhD, recalling the first time he saw videos showing improvements for Parkinson's patients before and after using the glove. "But Tass' modeling studies suggest a plausible mechanism whereby fingertip stimulation could alter abnormally synchronous activity in the central nervous system."

Convincing the research community the seemingly "magic" vibrating glove has real therapeutic effects will require further testing, explained Newsome, who holds the Harman Family Provostial Professorship and directs Stanford's Wu Tsai Neurosciences Institute.



AN OLD IDEA REFINED

THE IDEA OF USING VIBRATIONS TO TREAT Parkinson's is not new, Tass explained. In the 19th century, neurologist Jean-Martin Charcot created a vibrating chair after learning that his patients' symptoms briefly improved after long, jostling carriage and horseback rides.

Charcot's vibrating chair, and the vibrating platforms and therapies developed by researchers who followed, alleviated some symptoms of Parkinson's, but the results were inconclusive and temporary.

When Tass was a medical student, he became intrigued with self-organization — the seemingly spontaneous assembly of patterns and structures, such as clouds and snowflakes. He went on to earn a doctorate in physics and a master's in mathematics for his research on self-organization, which revealed potential applications for neurological diseases, including Parkinson's.

"My goal is to create treatments that are more effective and less brutal on the body by simply utilizing the self-organization power within the body," Tass said.

HOW A BUZZING GLOVE COULD TREAT PARKINSON'S

THE SYMPTOMS of Parkinson's arise when large groups of neurons abnormally fire in unison. Using computer simulations, Tass and his team discovered that a patterned stimulus that vibrates at a frequency of 100 to 300 hertz (cycles per second) can desynchronize neuron-firing. They called this coordinated reset stimulation. Further, Tass discovered how to make the benefits of vibratory stimulus last, something that eluded Charcot and others who used vibrations to treat Parkinson's: Pauses are crucial between treatments and within stimulus patterns.

The body needs to unlearn abnormal neural connectivity patterns, Tass explained. Just as taking small breaks increases the effectiveness of study or exercise, pauses improve the treatment's effectiveness.

Tass explored possible therapeutic effects of the treatment by applying it directly to the brain with electrical stimuli via deep brain electrodes in studies in monkeys with Parkinson's symptoms (*Annals of Neurology*, 2012) and later in a study of six Parkinson's patients (*Movement Disorders*, 2014).

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ABOVE: ARTIST'S CONCEPTION OF A FINGERTIP-VIBRATING GLOVE

The man who couldn't cry

ADAPTED FROM *PROJECTIONS: A STORY OF HUMAN EMOTIONS*

By Karl Deisseroth

"Why am I here tonight?" Mateo asked.
He took his glasses off and set them carefully on the gurney.
"Because I don't know why I can't cry."

Looking at his hands, open in his lap, he considered each palm in turn, seemingly puzzled by its emptiness. Then his eyes came back up to mine, and his story began to slowly drain out, passively, by force of gravity.

He had been brought to the ER by his three brothers, who were surging about in the tiny waiting room down the hall; I was the psychiatrist summoned to evaluate him. My first impression, on stepping into the room, was that he seemed childlike — just 26 but appearing much younger, with smooth skin and rich brown eyes framed by thick black glasses; he looked as though he had lost his backpack, or perhaps was worried about his homework. And yet that impression lasted only an eyeblink.

Eight weeks earlier, he told me, his wife of a year — his pregnant bride — had been crushed and killed in their car. She was stolen from beside him late one night, as they drove in darkness on a country highway. They were returning from a weekend bed-and-breakfast getaway in Mendocino, when a white-panel van cut across their lane. Mateo jerked the wheel hard left, and their little car flipped into the median, finding a small tree stooped there that had been waiting quietly 50 years for this moment. They hung upside down for an hour, Mateo trapped beside his wife's broken body, the young family swinging quietly in their seat belts — along with the little one too, deep within her, cooling slowly along with her, unsafe in her soft embrace.

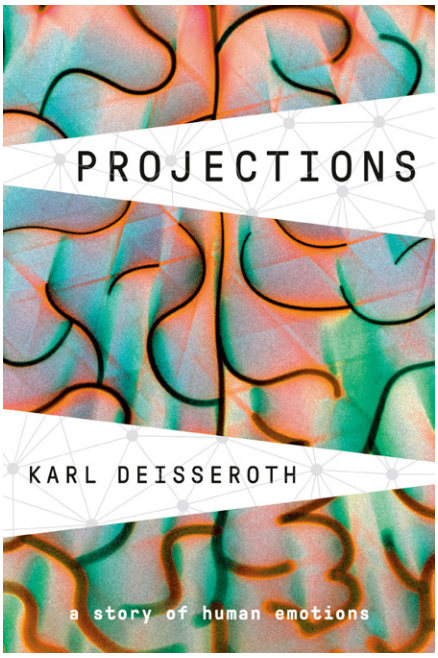
He stared at the wall now, arms empty. Two months later, there was still visceral horror in his heart — but also a relentless dry isolation. As we talked, I learned this was a man whose inner self, his emotions, had been projecting out into the world — tears had come before, in his adult life, in many moments of joy as well as sadness — but this dimensionality was now reduced, his expressions flat and colorless. He seemed set aside, set apart in time, sighted in one direction only. When I asked about his plans, there was only nothingness. Mateo could not see even a few minutes into the future, which was invisible, impossible, a featureless white wall.

Crying is significant in psychiatry; our patients experience extreme emotions, and we work with the expression of these emotions. But the reason for tears is a mystery; pure emotional tears are not clearly present elsewhere in the great ape lineage, and with all the risks of revealing true feelings in complex social environments, the poor controllability of this emotional signal seems a handicap rather than an advantage. Yet value may lie in a signal remaining largely involuntary, and thus mostly true.

Every innovation in evolution is accidental at first. Our neurons are guided during brain development by a vast diversity of path-setting molecules as strong as thread-guides on a loom — tiny signposts that send a slowly growing bundle of nerve fibers, called axons, on to the next brain region, or turn it back if it has come too far. Mutation in genes governing any of these steps, redirecting axons from emotion-regulation regions

of the brain, would be enough to bring into the world a new way of being human, with a new way of expressing feeling.

The new target here, for tears, would have been deep in the brainstem: the cells of the seventh cranial nerve, grandmaster of facial expressions but also of the lacrimal gland — the storehouse of tears. The lacrimal system likely evolved for flushing irritants from the eye, washing away particulate nuisances. With an almost-trivial rewiring, seventh-nerve control of tears would have become accessible by floods of emotion — with a tweaking of fibers already present, already projecting from emotion-control regions in the upper forebrain down to the brainstem parabrachial cells that regulate emotional changes in breathing (next-door neighbors of the seventh-nerve lacrimal cells) — and so finally wrenching, from within, the full cathartic, diaphragmatic contraction of the sob.



Mateo never did cry for his family — not that I saw, nor that he could ever tell me. In considering this, and the reasons we have for crying, it seemed to me that an odd unity links tears of sadness, when they happen, and the more mysterious tears of joy. Tears come when we feel hope and frailty together, as one. I managed to keep myself from writing this in the medical chart — and that Mateo had no hope left to cry for.

Mild improvements in material outcome that do not require a new model of self and circumstance — as with just making a bit more money in accord with known probabilities of the world — will not cause most people to cry. But when we do cry for joy — as when we feel the sudden warmth and promise of human connection, or when we see an unexpected depth of empathy in a young child — we seem to signal a flickering of hope, for the future of a vulnerable community, for humanity against the cold. We can cry at a wedding or a birth, seeing heartfelt aspiration but knowing deeply the fragility of life and love: I hope that the joy I see here will never die, I hope that the world will be kind enough to let this last forever, I hope that these feelings will survive — but I know very well they may not.

At the other, truly negative, pole of value, tears of sadness in adults also come not with mild losses from known risks but with sudden adverse personal realizations that must be addressed, and signaled (recruiting support from the self as well as from others) — like a shock of betrayal, when the hope we had for the future is shaken and our model of the world, our map of possible paths in life, must be redrawn. Large brains can contemplate many such possible actions and outcomes, ruminating and worrying, mapping out decision trees thickly ramified with possibilities projecting far into the future. But in situations where no positive outcome is possible, a passivity not only of body but also of mind can be adaptive — a deep discounting of hope, which would otherwise drain resources from our attentional and emotional budgets. Perhaps it is best to save the striving and the struggle, and to spare the trouble of tears when hope is gone.

Mateo was not suicidal, but among other symptoms of depression he had prominent hopelessness, an inability to look forward in time. Without hope for the future, Mateo could only look back. There was no point in signaling for help; his arms held nothing.

After talking it all over with Mateo and his brothers, we ended up sending him home with them — and with an appointment for follow-up care and medication — but not before I took the time to carry out an hour of predawn psychotherapy with him, right there in the ER, laying groundwork. When we can, we often steal the time to do this in psychiatry, almost instinctively, even during the besieged rush of an on-call shift. It can be hard to hold us back, as hard as it is to hold back surgeons from cutting to heal. We do this even knowing we will never see the patient again. I was discharging Mateo to the care of his family, and to outpatient treatment; in all likelihood our paths would never intersect again.

But that night, I had thought I could do something — not much, but something. And that matters — realizing at a place and moment you have been called to be whatever it is that humanity can be for a person. That is not nothing.

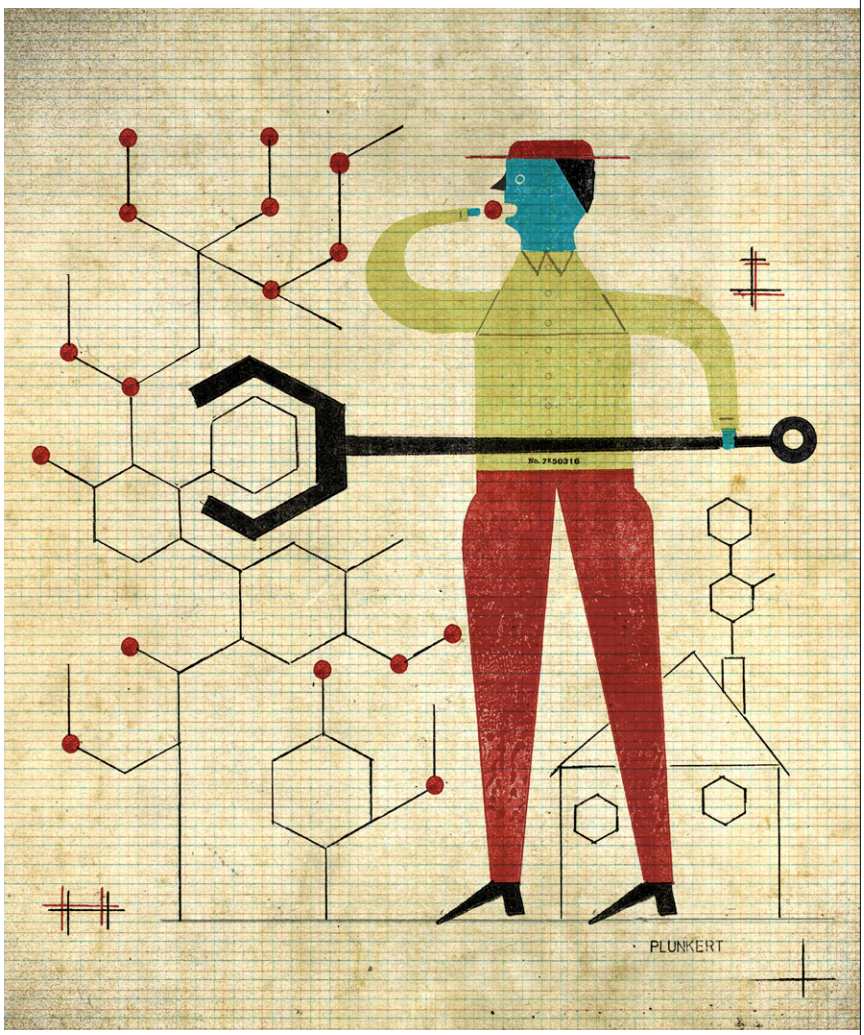
KARL DEISSEROTH *is a Stanford professor of bioengineering and of psychiatry. He received the 2021 Albert Lasker Basic Medical Research Award for research on light-activated proteins, which led to optogenetics, a technology for studying the brain.* *This essay is adapted from* Projections: A Story of Human Emotions.

plus
EXPLORING THE REALMS OF MEDICINE AND HEALING

How synthetic biology could save us

ONE BIOENGINEER'S NUTS-AND-BOLTS APPROACH TO A BIOTECH-BASED UTOPIA

By Hanae Armitage



DAVID PLUNKERT

Most bioengineers will likely tell you the basic goal of those in the field is to make new, useful stuff — yeast imbued with the power to produce medicines, synthetic tissue to help repair injuries or burns, furniture made from the fibers of fungi, that sort of thing. Drew Endy, PhD, a bioengineer at Stanford University, has a different goal:

"To create a planetary-scale civilization that harnesses bioengineering to flourish in partnership with nature," he said. "That, and a renewal of liberal democracy for the 21st century."

Mushroom furniture be damned.

The aim of Endy's bioengineering specialty, synthetic biology, is to refine the underlying fundamentals of life — like the genetic code — so that it is possible for more biotechnologies to be made real, including things that nature itself wouldn't dream of. Put simply, one of the main goals of synthetic biology is to "make the making of things" easier, said Endy.

"We tend to think of biology as something that happens to us," said Endy. "But more and more, we are happening to biology. We're in an era, scientifically, where we can express our intentions into the very kernel of life to allow for possibilities that are simply never going to exist otherwise."

Maybe that's an organism that glows in the presence of poison; crops that are suited for harsh conditions; or cells engineered to seek and destroy tumors, only to self-destruct when the cancer is cleared. The idea is to enable new solutions to our world's biggest problems — medical crises, environmental threats, humanitarian conundrums — through a means that would be infeasible through nature or improbable through more traditional laboratory techniques. He

hopes that in a few decades, biotechnology will emerge as a core pillar of society — not only as an economic powerhouse for supplying food, materials and medicines but as an intrinsic aspect of our culture. "I'm talking about a civilization in which we don't think of biotechnology products as distinct but just a normal part of life because they're everywhere and they work reliably."

Endy's current work ventures into a field of biology that's still under construction, and he's leading the effort to build the foundation by creating bioengineering-friendly organisms and systems that, quite literally, cannot fail. Every bioengineer's dream.

A PARTNER IN BIOLOGY

An engineer by training, Endy began dabbling in biology in the early 1990s, before synthetic biology came into its own. At the Massachusetts Institute of Technology, where he began his career, he helped launch the biological engineering major. Since coming to Stanford, where he is an associate professor of bioengineering, he's been recognized by the White House for his contributions to open-source biotechnology and has made a name for himself as a synthetic biology pioneer and leader. But it's not just the science that drives Endy.

"Drew is incredibly socially conscious," said George Church, PhD, professor of genetics at Harvard University and a longtime colleague of Endy's. "There's a fairly small subset of engineers in each field who are not only hacking physics, chemistry and biology but are also doing so with social structures in mind. That's Drew."

"My greatest wish is that the culture surrounding bioengineering is one of love," said Endy. If this came true, "all the good things that could be done in partnership with biology become possible." Because at its core, said Endy, love between two entities (yes, in this case, society and bioengineering) often relies on trust and partnership.

In his efforts to manifest this vision, Endy has served on the National Science Advisory Board for Biosecurity and the National Academies of Sciences, Engineering, and Medicine's Committee on Science, Technology and Law; he currently serves on the World Health Organization Advisory Committee on Variola Virus (Smallpox) Research and the International Union for the Conservation of Nature's Synthetic Biology Task Force. He and others also founded a public-benefit charity, the BioBricks Foundation, the mission of which is "building with biology to benefit all people and the planet."

It's big talk — especially because Endy admits that even he is unsure whether scientists know enough about biology, specifically genetics, to build entirely new organisms. Most every organism, including humans, contains some DNA that's basically useless; it serves no life-supporting function. It may be residual, left over from our ancestors, redundant or just a random genetic scribble. So, which are the vital bits?

The core of Endy's team's research explores taking away the guess work. The basic premise is twofold: first, parse the genetic elements critical to an organism's survival, then use that information to create organisms built only from their "essential" parts. For scientists manipulating biology to print organs from scratch or to engineer drought-resistant crops, for example, that total understanding of a living system is a be-all-end-all goal.

'If you want to build an organism, you want to definitively know what you're working with, and right now part of what bioengineers are working with is ambiguity.'

"If you want to build an organism, you want to definitively know what you're working with, and right now part of what bioengineers are working with is ambiguity," he said.

What bioengineering really needs, according to Endy, is certainty as to which genes are needed for a particular organism to survive along with what each gene is doing. So, he's working on that, aiming to establish a bare-bones version of a genome, which he's dubbed a "cleanome."

Establishing a cleanome for key organisms would allow bioengineers to build and create with more certainty and safety, he said. It could even support the adoption of bioengineering as common practice throughout society, but that's a vision of a more-distant future.

PHI-X174

To advance his ambitious idea, Endy started small — with a simple, well-studied, bacteria-infecting virus called phi-X174.

Scientists can tell where genes start and stop by looking at patterns in DNA sequences. But determining which genes are essential can be difficult. Strategies include looking across related species to spot conserved genes; searching for mutant (but still viable) versions of the organism to see how their gene patterns differ; and identifying evidence that the critical genes are making proteins.

The next step is to turn off those genes one by one, monitoring how the organism fares. If it can't survive without the gene, the researchers deem the gene essential and mark it on the organism's genomic annotation — the map charting significant elements along its DNA sequence.

"After that, most research moves on to asking what the obviously important genes do. But we're saying, 'Are we sure we've found and labeled everything that's functional in the first place?'" Endy said. In 2017, the researchers in his lab took it upon themselves to answer that question for phi-X174 and found that its genome encodes up to 315 potential genes.

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A scientist's quest to save his son from a mystifying illness

EXCERPTS FROM *THE PUZZLE SOLVER*

By Tracie White with Ron Davis

GENETICIST RON DAVIS SITS OUTSIDE THE BEDROOM OF HIS SON, WHITNEY DAFOE, IN THIS 2016 PHOTO. IT'S A FAMILY RITUAL THAT LETS DAFOE KNOW THEY ARE WAITING FOR HIS SIGNAL TO ENTER THE ROOM.

TIMOTHY ARCHIBALD

When Stanford University School of Medicine science writer Tracie White first saw Whitney Dafoe's face, she was peeking at him through the keyhole in his bedroom door. White sat, not too quietly, outside the room — something his family does to gently let him know it's time to begin his day.

Dafoe, 37, has suffered for more than a decade from what was eventually diagnosed as myalgic encephalomyelitis/chronic fatigue syndrome. The illness robbed the young photographer of his ability to work and travel, something he loved. It left him weak and unable to eat, talk or tolerate sound, vibration or touch. Even getting out of bed is painful.

On the day White met Dafoe, his family members — his father, Ron Davis, PhD, a renowned Stanford professor of biochemistry and of genetics; his mother, Janet Dafoe; and his sister, Ashley Haugen — were preparing him for a ride to a local hospital to have a new feeding tube inserted. The preparations included giving him Ativan, an anti-anxiety drug, to lessen the stress of the change in routine.

White had first visited Dafoe's home while reporting a *Stanford Medicine* magazine article about his father's search for a cure. White and Davis detailed the family's journey in a new book, *The Puzzle Solver: A Scientist's Quest to Cure the Illness That Stole His Son*, from which the following excerpts were selected.

A FAMILY WORKING AS ONE TO FIND A CURE

Ron looked up as Janet entered the kitchen; she patted him on the shoulder and took the three filled syringes. I heard her shuffle down the hall to Whitney's bedroom. The couple, married almost fifty years, often move in tandem like this. One picking up where the other leaves off. A team.

Ashley arrived dressed in black yoga pants, her long blonde hair pulled back in a ponytail. With the grace of the ballet dancer she once was, she too crossed through the kitchen to the closed hallway door that leads to Whitney's room. Her tiny, white fluff-ball of a dog, Frankie, was tucked under her arm and started to yap. Janet's head popped out suddenly from behind the hallway door. She grinned and reached for the dog. She too was dressed in black, as were Ron and I because of Whitney's sensitivity to colors. That was our uniform for the day. Janet squeezed Frankie tight, laughing as the dog's long pink tongue washed her face. Ashley set Frankie down on the kitchen floor, and together they walked back to Whitney's bedroom, with Ron following. Then

Janet waved to me to follow.

"Stay outside of the bedroom in the hallway," she instructed me. She'd told me earlier they'd discovered that Ativan did more than calm Whitney's nerves. It also seemed to calm some of his sensory processing difficulties, making sounds and movement more bearable. When he took the drug, he could communicate with his eyes and pantomime using his hands and arms and facial expressions. I watched carefully from the door as the family, huddled together in Whitney's small bedroom, gathered around his bed as if in prayer. These moments, I knew, were so rare, they were almost sacred, and emotions ran raw. Ashley sat cross-legged on the floor in front of her brother's bed, her eyes rimmed in red from tears. Ron, smiling softly, reclined on the carpeted floor just behind her, his long legs stretched out straight. His gaze drifted outside to the backyard. The winter sun sat on the leaves of an oak tree, painting the room's carpet with reds and gold. Janet stood next to the bed, beaming down at her beloved boy, waiting for him to acknowledge them. After the drug worked its way into his blood system, Whitney emerged from his comatose-like state.

His eyes opened. The family had told me that usually, at this point, he would look up at his dad with his eyebrows raised, asking, Is there a cure yet? His father would shake his head no, then make fist pumps with his hands, meaning he's working hard. And then Whitney would begin to pump his fists too, asking for his dad to work harder. Then they joined together, fists pumping out like boxers. A few hours later, as the drug began to wear off, Whitney's newfound energy would slip away. In tears, he would head back to the abyss. Ron, Janet, and Ashley all would begin to sob. And then, suddenly, he was gone, alone again in his comatose-like state.

But today was different. He raised his hands to his face and clicked an invisible camera. Ashley sprinted from the room to get a real camera, her high-end Nikon. I couldn't believe what I was witnessing. I had expected to see Whitney alert for a only few minutes; now he was sitting, smiling and interacting with his family. Tears began to fill my eyes. He was still unable to speak, but through pantomime he told them that he wanted a photograph of the family together. He could not hold the camera, but from his bed with two ice packs covering his concave stomach, he gave instructions to Ashley on just how to stage each photograph. His hands motioned his parents to move in together for a shot. The professional photographer still knew how to command a room. I could feel a hope fill the room. Ashley even laughed.

'His hands motioned his parents to move in together for a shot. The professional photographer still knew how to command a room.'

Early on, before he got too sick, Whitney had begun to document his illness with plans of someday making his own film about the disease. Now it appeared he still wanted to tell his own story. Maybe I could help him.

THIS EXCERPT TAKES READERS BACK TO BEFORE DAVIS BEGAN INVESTIGATING:

RON WOULD COME HOME in the afternoons and help Whitney put on compression socks to ease the pain in his legs. And continue to add the endless numbers of supplements and antibiotics and other drugs to his IV line. Whitney was diagnosed with sleep apnea and tried using a CPAP machine to help him breathe. After months of trying, he gave up. He just didn't have enough energy to deal with it. Ron began to panic. He watched his son wasting away and couldn't do anything to stop it.

Whitney still managed to find bits of joy listening to his music: He filled the empty hours by creating playlists on his iPod from bed. He liked to curate the lists to tell a story and named them things like Long Road Mix and Bummer Mix. He could eat some foods, although that was getting more difficult each day. Ice cream had been replaced by yogurt and constant stomach pain. But Ron was busy hatching new plans. He couldn't stand by and watch his son's endless suffering.

And so he got started on his own. I imagine him one night, shuffling out to his toolshed out back after setting up Whitney's IV, filling his water containers, and changing his socks. Ron had set up a sort of makeshift science lab on his tool bench. It was cluttered out there, so he cleared out a space on the workbench, pushing aside his old woodworking tools. He showed me the centrifuge — a tool used for blood separation and analysis. It's still there, small and round, rather old, but functional. It reminded me of one I'd used in a high school chemistry class.

"Is this where you built Whitney that beautiful oaken cradle that you guys keep inside the house?" I asked him.

"No, we hadn't moved to this house yet, but these are the same tools," Ron said, looking at one of the hammers nostalgically. He hadn't been out here for a while and was sort of embarrassed by the clutter. Plus he was always hesitant to talk about himself, so he laughed nervously when he added, "My dad was a carpenter. I'm good with my hands like he was."

That's how his scientific investigation first began. Once a week, after chatting with Whitney in his bedroom, he'd take a vial of his son's blood, then carry it with him to the work shed out back, curious to see if he could find any molecular clues to the mystery. He'd watch it spin around fast in the centrifuge, separating into its different parts, and

then he or Janet would get into the car and make the twenty-minute drive over to his lab for processing.

This is the way Ron has worked throughout his life. He would find the right tools to tinker with, in settings where he felt free to disappear into the imaginary three-dimensional worlds of scientific exploration. A place that feels safe to him, that feels like home.

… As Ron began to study his son's blood cells, he also began to worry about how he would fund any future research. He set to work making plans for experiments and more advanced testing, getting his lab involved. He knew it would take a lot of money. He made plans to run every kind of available test in his high-tech Stanford lab on Whitney's blood, searching for clues of what had gone so badly wrong in the cells' molecular pathways that could lead to treatments or even cures. The list was long and complicated. Testing would include things like cytokine analysis, genome sequencing, microbiome sequencing, metabolomics, magnetic levitation profiling, PCR assays for any viruses, antibody assays for mycotoxins, and much more.

Over the years, Ron's lab had developed a wealth of biotech inventions and advanced diagnostic testing tools. In 1989, Ron cofounded the Stanford Genome Technology Center with a large government grant to help build tools for the $3.8 billion Human Genome Project, the same project called by President Bill Clinton at its completion "the most wondrous map ever produced by humankind." Ron became director of the lab in 1992 and has remained there since. The lab made a name for itself as a think tank for the creation of diagnostic tools to help battle human illness and pinpoint disease. It also became the launching pad for biotech scientists who would go on to develop successful new startups to advance medical care.

But now he was thinking about changing the course of his research. Exactly how to launch this new project kept him up nights. He needed a plan. **SM**

From *The Puzzle Solver: A Scientist's Desperate Hunt to Cure the Illness that Stole His Son* by Tracie White with Ronald W. Davis, published by Hachette Books. Copyright © 2021.

— Contact Tracie White at traciew@stanford.edu

FEATURE

Opening stroke's window

CONTINUED FROM PAGE 31

investigations, but the Stanford team's contribution stood out.

"There's plenty of papers out there that say, 'Oh, we think we can, with 60% or 80% accuracy, identify this tissue that will live or die,'" Powers said. "But what distinguishes them — and what they really should get credit for — is being the ones who came up with a practical way to do this. They took it on, did the clinical trial, and proved that it worked."

Powers said he has integrated the approach into his own practice, as have untold numbers of health care providers. As of July 2021, the software originally developed at Stanford was being used in more than 1,800 medical centers around the world, and more than 2 million scans had been performed. At Stanford Health Care, about five stroke patients undergo a mechanical thrombectomy after perfusion imaging every week.

'A FIGHTING CHANCE'

After Cindi Dodd arrived at Stanford Hospital on that April day in 2017, a CT scan showed salvageable tissue in her brain. As part of the DEFUSE 3 clinical trial, Dodd underwent a thrombectomy to remove the clot blocking her artery.

When she woke up in the intensive care unit, her family told her what had happened. Her first thought was that she was too young for a life-threatening health scare. Then she realized the significance of the clinical trial: "It gave me the opportunity to fight for my life."

Dodd's rehabilitation was gradual, but after a year, she was back to walking, talking, driving and working.

She never met Albers in person, but on Thanksgiving Day 2018, Dodd looked up his email address and started to type. She told him about herself, that she was a wife with dreams of traveling and a mother with a fierce desire to be there when her two children graduated from college, married and had children of their own.

"I thank you for your study that gave me a fighting chance at living as a functional human being, a contributing member of society!" she wrote. "I will forever be thankful for you."

The next day, Albers replied.

"It has been such an amazing year for our group to see the dream that we have had for two decades finally come true," he wrote. "We are so grateful to patients like you, who were willing to take a chance on a new approach to treating stroke."

— Contact Amy Jeter Hansen at ajeterhansen@stanford.edu

FEATURE

A delicate operation

CONTINUED FROM PAGE 25

chock-full of essential structures, so they moved with extreme deliberation. Hwang stood alongside the other two surgeons, serving as the cameraman, doing what is called dynamic endoscopy: Directing the camera and light source by hand, he could change the angle slightly, anticipating what the neurosurgeons would need to see next. "The way we work together, and that Dr. Hwang anticipates our moves, feels almost telepathic," said Grant.

"Three surgeons and the scrub tech were all surrounding this tiny head," said Hwang. Also in the room were a neurophysiologist, a neuro-anesthesiologist and a couple of circulating nurses, and equipment specialists were coming in and out. "We really have to coordinate our movements. It's like a dance," but in an extremely confined space and one where even a small mistake could be catastrophic.

For the next 10 hours, the surgeons painstakingly removed tiny pieces of the tumor until, finally, they were shaving the last portions of it off the hypothalamus, which, among other functions, links the brain to the endocrine system. When the surgeons were satisfied that they had removed nearly all the tumor, they prepared to withdraw and close up.

Suddenly, Fernandez-Miranda saw blood leaking from an artery that must have been disturbed while they were removing the tumor. He tried closing the leak with forceps that have a bipolar electrical charge that can gently cauterize bleeding. But the effort increased the flow instead of staunching it. So the surgeon slipped in a curved aneurysm clip, which he used to clamp the side wall of the tiny leaking vessel, but without narrowing it so significantly that the change would impede blood flow. Amazingly, the clip slipped perfectly over the injury point, and Fernandez-Miranda used surgical glue to secure a muscle patch over the area. Catastrophe averted.

The Ellmans received reports on the

surgery's progress every few hours. From the waiting room, Jonathan Ellman posted updates to a WhatsApp group of hundreds of friends and family members around the world. After 16 hours of waiting on pins and needles, Ellman pressed "send" on a 9:41 p.m. post that read: "The final report from Fernandez-Miranda: 'We preserved all structures while completely removing the giant craniopharyngioma.'"

But Ari's ordeal wasn't over. After the tumor was removed, a flap of tissue was placed over the hole between the nasal passage and the brain to lock air and infection out and to keep cerebrospinal fluid in. "It's like closing a leaky roof from the inside; you're borrowing things from inside the house to try to patch it up," said Hwang.

Unfortunately, when Ari was almost ready to go home, he became somnolent and stopped talking. It turned out that because Ari was so small, the first flap hadn't fully sealed, which led to a cerebrospinal leak, meningitis and air within his brain. In another exceptional move, the surgeons performed a more elaborate repair with a bigger flap made of soft tissue taken from underneath the scalp and tunneled through the sinuses to create a strong seal.

This leak repair procedure, which had never before been tried on a child Ari's size, worked. Ari soon began to eat, talk and laugh again. Six weeks after his admission, he was sent home to restart his toddler life. He experienced a small regrowth of his tumor in 2020, and a transnasal reoperation at Packard Children's was successful, with Ari leaving the hospital after only five days. The Stanford team has since performed transnasal skull base surgeries in several other children.

Ari, now 5, continues to do well. His family has moved to Los Angeles, but he remains under the care of the Stanford team.

"The world of a 5-year-old who has gone through such a crazy health journey is a lot more complex and nuanced than any other 5-year-old's," his mother said recently. For instance, because the original tumor compromised Ari's pituitary gland, which normally produces growth hormone, he receives daily injections of the hormone to compensate. This is not his favorite activity, though he is excited about the foot of height he has gained in the last year. His parents continue helping him manage the challenges of his medical situation (such as by fielding questions like, "Why do I need shots when my sister doesn't?") while also reveling in Ari's enjoyment of normal kid stuff. He's a big fan of building intricate Lego sets, trying new sports and showing off his favorite dance moves.

"One of Ari's attributes is how committed he gets to something he's passionate about," said his father. He's recently become enamored of tennis and loves hitting balls from the ball machine on the tennis court near his grandparents' house. In fact, he'll happily swing at 500 tennis balls in a row.

"He's super determined," his mother said. "It's hard to say whether his determination was built up while he was in and out of the hospital. Or was he born this way, and the diagnosis made it even more of his thing, his skill? It's probably some of both." **SM**

Erin Digitale contributed to this article.

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FEATURE

Good vibrations

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In the 2014 study in humans, coordinated reset stimulation was applied for three consecutive days in two daily sessions of up to two hours. The researchers found that the stimulation reduced the neural synchrony associated with Parkinson's and this correlated with improvement of motor function.

Next, Tass and his team set out to find a way to deliver the stimulation without implanting electrodes in the brain. The solution was to replace electrical bursts delivered through electrodes embedded in the brain with vibratory bursts delivered through mechanical stimulators to the fingertips.

Fingertips have many sensory neurons, which means a large portion of the sensory cortex of the brain is dedicated to receiving signals from them. This is important because a noninvasive therapy must act on a sufficiently large portion of the brain to have similar benefits as deep brain stimulation. (This is also why fingertips are ideal for Braille, but not tattoos.)

The outcome of this research is a strappy, skin-exposing glove that looks like something out of a sci-fi film. The glove is lightweight and can be worn while performing regular daily activities. It's attached to a device that delivers bursts of 250 hertz (a buzz slightly stronger than a cat's purr) through pin-sized openings on plastic pads strapped to the index, middle, ring and pinky fingertips.

Each glove collectively stimulates a patch of skin smaller than a dime.

WHAT'S NEXT FOR THE RESEARCH?

In April 2021, Tass and his team published the results of pilot studies of patients — including Bhutani — with mild to moderate Parkinson's disease in *Frontiers in Physiology*. In these studies, eight Parkinson's patients received vibrotactile coordinated reset stimulation daily for at least three months (three of those patients received the therapy for six or more months).

The researchers assessed patients' motor function and obtained at-rest electroencephalographs before and after the three months of glove therapy using four subcategories — tremor, rigidity, bradykinesia (slow body movement) and axial (balance). They used EEGs, which measure brain activity, to investigate the therapy's possible effects on the abnormal, synchronous neural patterns associated with Parkinson's.

The researchers assessed the patients' movements and brain activity off medication at the start of the study, at three months, and during follow-up visits approximately every three months thereafter.

These pilot studies revealed that the vibrations were well-tolerated, produced no side effects, improved the patient's motor performance and reduced Parkinson-related neuronal synchrony in the brain.

"There's currently no middle ground between drugs and invasive treatments for Parkinson's patients," said Leila Montaser Kouhsari, MD, PhD, a movement disorders neurologist at Stanford Medicine.

"Parkinson's patients are often really suffering but symptoms, such as tremor, can vary with stress and medication fluctuations, so they may not be ready to go all in with invasive procedures. Or, because of other health problems, they may not be able to get surgery," said Montaser Kouhsari, clinical assistant professor of neurology and neurological sciences.

"Depending on how the clinical trial goes, the glove could expand what we have

to offer patients. It could be huge if it helps a lot of patients with no side effects."

For now, the glove treatment is available only to Parkinson's patients participating in a clinical trial of the device that started Aug. 1. Tass is also working with an industry partner to gain U.S. Food and Drug Administration clearance for the treatment, which he hopes to have by summer 2023.

Newsome said the new trial is one of many important next steps: "The therapeutic effects need to be documented in a larger group of patients." More research will be needed to identify which Parkinson's patients are likely to benefit from the therapy, he said.

"Although much painstaking research remains to be done, this therapy is potentially game-changing because it is completely noninvasive," Newsome said.

Before Bhutani used the glove as part of the study published this year in *Frontiers*, his Parkinson's symptoms included muscle contractions, loss of taste and smell, inability to speak above a whisper, mood swings, and obsessive-compulsive buying behaviors. Each day he took 25 medications — some to treat Parkinson's and others to alleviate the side effects of the other drugs.

At the beginning of his treatment, Bhutani wore the glove for two hours every morning, and two hours in the afternoon or evening.

Within three weeks, he said, his sense of taste and smell returned, and he was able to work in the garden again. Bhutani also reduced the drugs he was taking to 10 medications a day, and his muscles became less rigid and stiff, which restored his ability to show emotion with his face.

Bhutani still uses the vibrating glove, but not as often as he did initially because the benefits are lasting longer.

"In November 2018, I ran my first marathon," Bhutani said. "It was a dream come true."

His mood has also improved. "I feel my quality of life has come back. And I've got a very strong caregiver," Bhutani said, smiling at his wife. "She has been by my side … I'm grateful to her."

He's also grateful to the mystery woman who suggested he contact Tass in the first place. Bhutani tried to discover her identity to thank her, but he never saw or heard from her again.

"I don't know who she was, but she changed my life," Bhutani said. **SM**

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FEATURE

How synthetic biology could save us

CONTINUED FROM PAGE 39

Gabrielle Dotson, an undergraduate researcher in Endy's lab at the time, helped lead that effort. Their experiment involved building a new virus with only the 11 genes scientists had thought were functional. The idea was, if 11 genes are all phi-X174 needs, the cleaned-up virus should grow at the same rate as a normal phi-X174.

It did not: The cleaned-up phi-X174 grew at half the rate of the normal variant. So, something was missing from the annotation. The researchers discovered that "something" wasn't a gene but a genetic modifier — a stretch of DNA that influences a gene's activity. Without that modifier, the gene's function was stunted. In variants that contained the modifier, the organism grew normally.

The team published a study in the *Proceedings of the National Academy of Sciences* in 2019 providing all the DNA details that make phi-X174 tick, creating what Endy believes is the first truly validated annotation of a genome.

"With our phi-X paper, we were trying to set up a new way of thinking, showing how the genetics of natural living systems can be formally completed by building the thing from scratch," said Endy.

For years, living systems big and small have been repurposed for commercial use, like bacteria engineered to produce biofuels, said Dotson, who is pursuing her PhD at the University of Michigan, Ann Arbor.

"Applying this approach to get a complete genome annotation for organisms of interest could allow us to more rigorously redesign genomes for a new beneficial purpose," she said. "This simple virus is a proof of principle that we can build off of as we start thinking about other more complex systems."

PUTTING UP (GENETIC) GUARD RAILS

The cleanome could provide bioengineers with the materials to more easily build new "synthetic friends," as Endy puts it. But for every gas pedal, there must be brakes, so Endy and graduate student Jonathan Calles are pushing on yet another aspect of life's foundations — evolution — but from an engineer's perspective.

Conceptually, a fail-safe system could be a self-destruct button triggered when something goes wrong. Think of a rocket headed for the moon. If halfway into the stratosphere the rocket takes a sharp turn toward a big city, that's a problem. The fail-safe system in the rocket flags the dangerous reroute and explodes the rocket midair, saving the town.

That's what Endy and Calles want to do for synthetic organisms. This would be a crucial feature for say, cells engineered to seek out and attack tumor cells. You certainly wouldn't want those cells to evolve inside a patient to have new cell-killing abilities.

"If we want to be practical and moral bioengineers, which we do, and we anticipate needing to deploy bioengineering to help solve the world's problems, we need something that actively preserves whatever biological solution we've devised," said Calles. In other words, you want whatever you've engineered to do exactly what you've built it to do and nothing more.

In all organisms, DNA serves as the instructive template for proteins; any changes to those instructions, or mutations, can change the resulting proteins. In nature, mutations are common, and some help organisms evolve with new adaptations to survive.

Other mutations reduce the organism's fitness, and while one mutation might not bring down the whole organism, as more pile up, the organism is less likely to survive and pass on the changes it acquired. Because evolution depends on the passing on of newly acquired mutations, a fail-safe system would significantly slow evolution down.

In a fail-safe organism, the idea is to rejigger life's underpinnings so that any and all mutations are inherently detrimental and thus leave the organism more susceptible to death.

"I have to qualify this by saying it's kind of a crazy idea," Endy said. "We're quite literally exploring reconstructing biology's central dogma to limit evolution."

WHAT'S IN A FAIL-SAFE?

To understand how this fail-safe system should work — and why it could impede evolution — it may be helpful to put yourself in the shoes

of a ribosome, a tiny machine that operates inside cells to make proteins.

As a ribosome, your job is to gobble up the amino acid molecules specified in your genetic instructions, link them together in the prescribed order and spit out the result: one of the organism's many proteins. But you don't work alone. You have a helper, and its name is transfer RNA. Transfer RNAs hunt down amino acids and hand them to you so that you can turn them into proteins.

Transfer RNAs pair with specific segments of your genetic instructions, called codons, which code for a given amino acid.

And just to make things nice and complicated, several codons can represent one amino acid — and there are almost as many types of transfer RNAs as there are codons. That's how the natural biological system works.

In the fail-safe system, the team weeds out the transfer RNA genes so there's only one transfer RNA per amino acid.

As a result, there's only one viable instruction code per amino acid, and if a mutation occurs, it's more than likely that no transfer RNA will be available to keep the protein-making process rolling. When that happens, the ribosome is stalled and can't contribute to the cell's life. The idea is, the more mutations that accumulate, the more ribosomes will stall and the less likely the mutant cell will persist in a survival-of-the-fittest competition.

Endy's team's first fail-safe model was an engineered version of E. coli protein synthesis. Now, they've turned to the trusty phi-X174 to show how a fail-safe system would play out with a genome that has some complexities not found in other lab models — like genes that overlap.

Now, after two years, Calles and Endy are about halfway to making a fail-safe version of phi-X174. But if there's one thing they know, it's that there's more than one way that evolution could evade a system meant to stall it.

"There's this famous quip from evolutionary biologist Leslie Orgel: 'Evolution is cleverer than you are,'" said Calles. "It keeps me up at night."

THE BIG PICTURE

While the researchers spend most of their time mulling over molecules and toying with transfer RNAs, Endy keeps the grand vision: to empower the public to engineer biology in the same way they're empowered to read and write.

To what end? It all comes back to partnership with nature, democracy and helping humanity flourish in synergy with biology and the planet. The key to a synthetic biology-fueled democracy, Endy said, is having the option to change biology yourself.

He draws on history to exemplify the idea. In the early 1800s, Thomas Jefferson wrote John Adams a letter about access to land ownership for citizens.

"They could have land to labor, from which they could derive a satisfactory livelihood and eventually retire," said Endy. "This kind of option and access to a means of production is often a defense against political oppression — if the government or someone else is going to oppress me, but I can provide for myself elsewhere, I'll just leave."

Endy ponders what it means to have those sorts of options in the 21st century. The idea isn't to create an upheaval of the global economy, where everyone engineers their own food and medicine.

"I still think the power of the market should be in full play. But I also think the option to access bioengineering capacities can be a safeguard against being exploited. Another way to think of this is as an intrinsic defense against monopolies." It's also a never-ending source of problem solving.

Endy hopes for a future for society that's rooted in building a new kind of infrastructure in which it's possible to "parts kit" genomes. As in, you could buy sets of genes or the cleanome version of organisms to build your own synthetic organisms.

In concrete terms, Endy sees bioengineering as a necessary staple of any society. So, it should be possible to design and make things like food, drugs and other bio-based solutions anywhere.

"That implies we're going to have to implement a fully disaggregated workflow, where the DNA designs you come up with in one place operate reliably in another," he said. "It also implies we're going to need to fundamentally understand how biology works, through efforts like the cleanome, so that we're not doing endless tinkering and testing but designing and deploying."

It's an ambitious, unwieldy vision. But he's determined. Every email he sends ends in the same way. In place of a signature is a promise: "Our victory inevitable, our timing uncertain." **SM**

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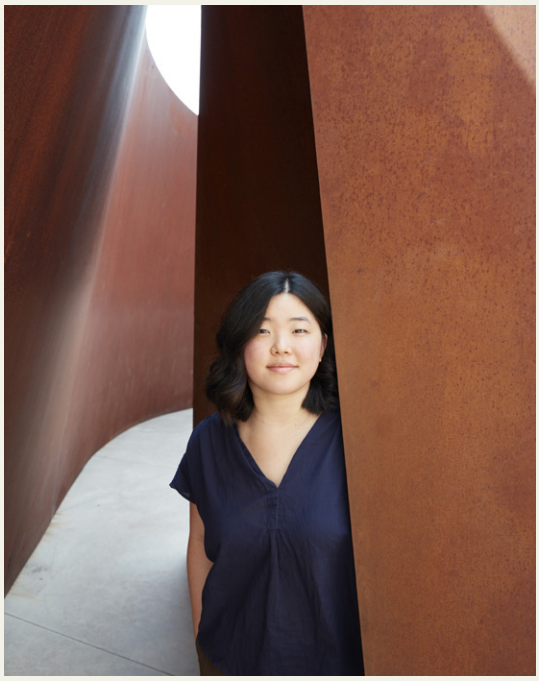
NOURISHING THE BRAIN WITH BLOOD FROM THE BELLY

A STRANGE AND WONDERFUL SURGERY FOR A RARE NEUROLOGICAL DISORDER

When Hope Kim was 6, a debilitating stroke forced her to spend a month in Seattle Children's Hospital, then years in physical and occupational therapy. Though it's rare for someone so young to have a stroke, Kim has a brain condition called moyamoya that upped the odds.

The disease is caused by blocked arteries at the base of the brain, where a tangle of small vessels forms to compensate for the low blood flow. On a scan, the tangle resembles a puff of smoke (moyamoya is a form of moya, or "haze" in Japanese).

One of Kim's uncles, a medical student at the time, recommended Gary Steinberg, MD, PhD, a professor of neurosurgery at Stanford and the director of the Stanford Moyamoya Center. Steinberg is world famous for his success in treating moyamoya.



Hope Kim's health is back as result of an unusual surgery for moyamoya disease that uses blood vessels from the omentum, in the abdomen, to bypass a tangle in the brain.

In August 2006, five months after Kim's stroke, Steinberg performed two bypass procedures, a week apart, in which he harvested a scalp artery and sewed it to a brain artery to restore blood flow to her brain. Five years later, he operated on her again, this time using blood vessels in the omentum, a sheet of fatty tissue that covers the abdomen, to supply the brain. Steinberg, one of only a handful of surgeons skilled in the technique, recently performed it on his 40th moyamoya patient, a 46-year-old woman from Florida.

"It's a good option when you're out of scalp blood vessels," he said. "The omentum is really a miraculous organ. It has a luxuriant blood supply."

After her first surgery, all was well with Kim until the summer before she began seventh grade. "My arm and leg would have spasms," she said. "And every now and then I would feel weak on that side. At first I thought it was anxiety about starting junior high."

Her mother, a nurse, suspected her neurological problems had resurfaced and brought her back to Steinberg. Kim was one of the less than 1% of Steinberg's moyamoya patients to require a second procedure. He suspects that as she grew and her brain developed, the bypass was no longer able to supply an adequate amount of blood to the right side of her brain.

The problem was that she was out of blood vessels in her scalp that he could use for another bypass. He and a pediatric laparoscopic surgeon cut a 3-foot-long flap of the omentum — still attached to the blood supply in the abdomen — and stretched it under her chest, along her neck and into the surface of her brain. Her abdomen now supplies part of her brain with blood.

Steinberg said he started using the omentum to treat moyamoya and stroke patients in the 1990s, after learning that cardiac surgeons use it to help heal chest infections or heart problems. But the large incision needed to access the omentum meant that patients endured a long and painful recovery, so he shelved the procedure for 10 years.

He resurrected it in 2000 when "the pediatric surgeons had become wizards at operating laparoscopically." With the aid of a laparoscope — a long, thin tube with a camera at the end — they could conduct surgeries through small incisions, cutting and stretching the omentum using tools inserted through the incisions.

Kim, who had her second bypass in November 2011, bounced back quickly enough to return to junior high before winter break. "Everyone was telling me to take it easy, but I felt totally healed," she said.

Kim is now 22 and this fall is starting a master's program in school counseling at Seattle University. Though she sees Steinberg every 10 years for a follow-up, she has had no more moyamoya symptoms since her second bypass, and Steinberg projects that won't change.

"I get migraines every so often," Kim said. "But that's from lack of sleep or stress, not moyamoya."

— BY MANDY ERICKSON

LESLIE WILLIAMSON

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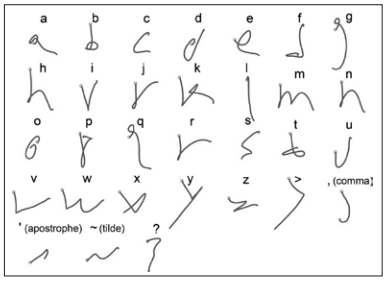
Call it mindwriting

A WAY TO COMMUNICATE FOR THOSE WHO CAN'T SPEAK OR PRODUCE TEXT IN AN ORDINARY WAY

The combination of mental effort and state-of-the-art technology have enabled a man in his 60s with immobilized limbs to communicate by text at speeds rivaling those achieved by his able-bodied peers texting on a smartphone.

In a study of the communication method, a brain-computer interface implanted in the man's brain sent signals to a computer with software that quickly converted his thoughts about handwriting into text on a computer screen. The man, who lost practically all movement below his neck because of a spinal-cord injury in 2007, produced text at a rate of about 18 words per minute. By comparison, able-bodied people of the same age can punch out about 23 words per minute on a smartphone.



For the study, Jaimie Henderson, MD, professor of neurosurgery, placed two brain-computer-interface chips, each the size of a baby aspirin, in the left side of the man's brain. The man then concentrated on writing individual letters of the alphabet on an imaginary legal pad with an imaginary pen. The chips picked up signals from neurons firing in the part of the motor cortex — a region of the brain's outermost surface — that governs hand movement.

Those neural signals were sent via wires to a computer, where artificial-intelligence algorithms decoded the signals and surmised the man's intended hand and finger motions. The algorithms were designed in Stanford's Neural Prosthetics Translational Lab, which Henderson co-directs with electrical engineering professor Krishna Shenoy, PhD.

Using this approach, the man was able to write more than twice as quickly as he could using a previous method developed by the Stanford researchers, who reported those findings in 2017 in the journal *eLife*.

The new findings, published May 12 in *Nature*, could spur further advances benefiting hundreds of thousands of Americans, and millions globally, who've lost the use of their upper limbs or their ability to speak as the result of spinal-cord injuries, strokes or amyotrophic lateral sclerosis, also known as Lou Gehrig's disease, said Henderson.

Shenoy and Henderson are the study's senior co-authors. The lead author is Frank Willett, PhD, a research scientist in the lab.

"We've learned that the brain retains its ability to prescribe fine movements a full decade after the body has lost its ability to execute those movements," Willett said.

— BRUCE GOLDMAN

FRANK WILLETT