special report

BALANCING ACT
THE IMMUNE SYSTEM

Chronic fatique syndrome
Solving the mystery

Eating without fear
Food allergy breakthroughs

Out of the blue
When the immune system attacks the brain

Osteoarthritis
Not just wear and tear

Am I losing my mind?
A conversation with author Susannah Cahalan

plus

Research re-examined
Why unvalidated claims often rise to the top

Hey, buddy
Peer support for PTSD
The last 12 years of kidney transplant patient Lupe Alcaraz’s life were awful. She was often sick, her immune system crippled from decades of taking immunosuppressive drugs. She needed steroids too, which weakened her bones. “It was just really ugly,” recalls her daughter, Cynthia Alcaraz-Jew. When Alcaraz died in 2010, Alcaraz-Jew’s own kidneys were failing — her family suffers from a genetic condition called Alport syndrome, which causes kidney, eye and ear problems. Months later, as Alcaraz-Jew, now 47, slogged through yet another year of dialysis, she got some wonderful news: Her younger brother, Xavier, could donate his perfectly matched kidney, and she qualified for a Stanford study that attempts to wean transplant patients off the immunosuppressive drugs. “I couldn’t have been happier,” she says.

Now, less than two years after her transplant, Alcaraz-Jew is drug free, living proof that an experimental treatment developed by Stanford immunologist Samuel Strober, MD, and his colleagues has the potential to improve the health of hundreds, perhaps thousands, of transplant patients. Stanford is one of just a few research institutes working to wean these patients off immunosuppressants.

Strober studied the immune system for decades before formulating the treatment, which thwarts the battle between a patient’s immune system and a donated organ. The medications dampen the response, but they can also cause heart disease, infections and even kidney failure — a bitter irony for someone who just received a new kidney, says Strober, a professor of immunology and rheumatology.

The treatment starts the day after the transplant. For 10 days, the team irradiates the primary immune organs, including the lymph nodes, thymus and spleen, then injects a serum that contains antibodies allowing it to recognize and kill a type of immune cell called a T cell.

Several weeks later, Strober’s team injects the patient with cells from the donor: a combination of mature and immature immune cells. Once injected, the immature cells, known as stem cells, must mature and mix with the patient’s cells to prevent an immune attack.

“They’ve got to stick and stay,” says John Scandling, MD, the kidney transplant specialist who works with Strober. “That’s the challenge.”

The treatment is most effective with well-matched donors, and the team has tried it only with kidneys because kidneys can be donated from a living patient, who can also supply stem cells.

Of the 24 kidney transplant patients with perfectly matched donors who enrolled in the trial beginning in 2000, 16, including Alcaraz-Jew, are living drug free, and three others are working to get off the medications, Strober says. The team is planning to publish a paper summarizing the research results in the near future.

To treat patients who don’t have a perfectly matched donor, the team has been experimenting with the amounts and types of donor cells needed.

“The idea is to make this applicable to everybody,” says Scandling, a professor of nephrology.

Now, however, Alcaraz-Jew is reveling in her hard-won health with her husband and two daughters. They recently returned from Cancún, where they swam with whale sharks, a feat that would have been unimaginable two years ago.

“It changed my life completely,” Alcaraz-Jew says. — BECKY BACH
SPECIAL REPORT

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In 2008, Stanford immunologist Mark Davis, frustrated that virtually none of the advances in basic immunology had been incorporated into standard medical practice, wrote a polemic against the reigning mouse model.

Efficient, small and amenable to the most advanced tools of genetic engineering, the mouse is at the center of modern biomedical research. And while the mouse model has been spectacularly successful in elucidating basic biological mechanisms, its clinical usefulness has been much more limited. In the mouse, we’ve cured cancer, treated spinal cord injury and vaccinated against HIV — many times over.

It seemed obvious to Mark that the prevailing research paradigm in his field was broken. Yet his piece in *Immunity* was met with disregard and disbelief. Mark, like so many of his colleagues, had built a very successful career using experimental mice. So much had collectively been invested in the mouse model that few were ready to admit it was time to explore new approaches.

Mark knew that in order for colleagues to take seriously his criticism, he needed to suggest an alternative. In “A Prescription for Human Immunology,” he proposed the human “model.” With the availability of millions of blood specimens and advanced molecular technologies, he suggested immunologists deploy a systems approach to understanding the interactions in our staggeringly complex immune system. Using advanced instrumentation and techniques that in many cases were pioneered here, the Human Immune Monitoring Center at Stanford is the only facility of its kind that allows researchers to perturb the immune system and then sit back and watch the hundreds of interactions among the moving parts.

In suggesting a focus on humans, Mark was proposing an entirely new research paradigm. But it was little more than a thought experiment at the time. Since then, important discoveries have validated his approach. One study found that our bodies build up immunity by exposure to harmless, as well as harmful, pathogens — perhaps an evolutionary clue as to why kids eat dirt. Another study linked high testosterone levels in men to a weakened immune response to the flu vaccine. It has long been known that men do not respond as strongly to vaccination as do women. The new study may explain why this is the case.

Mark’s paradigm-shifting work is the kind of scientific creativity that characterizes Stanford Medicine. In laboratories around the world, scientific progress happens when researchers pursue a novel idea. But since scientific disciplines are bound by paradigms of agreed-upon methods and models, innovation often requires researchers to pursue a revolutionary idea that proposes an entirely new paradigm altogether. Here at Stanford Medicine we are not satisfied with incremental progress, with leaving well enough alone. We’re willing to risk failure in the hope of achieving something great.

By decreasing our reliance on surrogate models of disease, we can speed the translation of advances in biomedical knowledge into tangible benefits for human health. In this way, Mark Davis’ provocation was more than a call to his fellow immunologists; it was a call to scientists everywhere.

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

Researchers previously thought kidneys stopped growing after childhood. That meant if a kidney was damaged, the harm was permanent.

Now, however, researchers at the Stanford Institute for Stem Cell Biology and Regenerative Medicine and the Sackler School of Medicine in Israel have discovered that kidneys grow continually.

“This research tells us that the kidney is in no way a static organ,” says Benjamin Dekel, MD, PhD, a senior author of the paper and associate professor of pediatrics at Sackler and head of the Pediatric Stem Cell Research Institute at the Sheba Medical Center in Israel. “The kidney, incredibly, rejuvenates itself and continues to generate specialized kidney cells all the time.”

The findings mean scientists could strive to create kidney parts in the lab and develop new methods of treating kidney disease. The study was published in Cell Reports.

The discovery won’t revolutionize kidney treatment overnight, the researchers say. They still face many hurdles, including learning how to control the growth of a variety of cells simultaneously. Dekel says they won’t be able to manufacture an entire kidney in the near future.

Stanford authors include lead author Yuval Rinkevich, PhD, a postdoctoral scholar, and co-senior author Irving Weissman, MD, professor of pathology and of developmental biology and director of the Stanford institute. — BECKY BACH

AND CHRISTOPHER VAUGHAN

100 to 1 is the ratio of microorganisms in or on a human to the human’s own cells. More at http://stan.md/1wk6qsC.
Double mastectomy falls short

IT’S A CASE where less is more, literally. • Opting to have both breasts removed after a cancer diagnosis in one breast is no more likely to prolong life than the selective removal of cancerous tissue plus radiation therapy. And a bilateral mastectomy can require significant recovery time — longer than the alternative.

The results came after a study, published in the Journal of the American Medical Association, of nearly 190,000 California women diagnosed with the disease between 1998 and 2011. The researchers, including assistant professor of medicine and of health research and policy Allison Kurian, MD, found that increasing numbers of women received a bilateral mastectomy during the study period. Younger, more affluent women were particularly likely to undergo the complex surgery. In 2011 about one-third of women under 40 had both breasts removed.

The data came from the California Cancer Registry, which holds information about all cancer diagnoses in the state — including details on a patient’s socioeconomic and health insurance status. “We can now say that the average breast cancer patient who has bilateral mastectomy will have no better survival than the average patient who has lumpectomy plus radiation,” says Kurian, a member of the Stanford Cancer Institute.

— KRISTA CONGER

Diagnosing diabetes

THE TWO TYPES OF DIABETES have different causes and different treatments. Until recently, distinguishing between the two required a slow, expensive test in a health-care facility. • Now, however, Stanford scientists have invented a hand-held microchip that can diagnose type-1 diabetes. Early diagnoses and rapid, aggressive therapies may allow patients with type-1 diabetes to live healthier lives, researchers say. • “With the new test, not only do we anticipate being able to diagnose diabetes more efficiently and more broadly, we will also understand diabetes better — both the natural history and how new therapies impact the body,” says Brian Feldman, MD, PhD, assistant professor of pediatric endocrinology.

The chip uses nanotechnology to detect the auto-antibodies that attack insulin-producing cells in the pancreas of patients with type-1 diabetes. Those antibodies are not found in patients with type-2 diabetes.

The chip was unveiled in Nature Medicine. The researchers are awaiting Food and Drug Administration approval of the device. Each chip is expected to cost about $20 to produce and can be used for upward of 15 tests. — ERIN DIGITALE

CANNABIS CONNECTION

THE BLOCKING OF endocannabinoids — the brain’s internal versions of marijuana’s psychoactive chemicals — appears to play a role in the early pathology of Alzheimer’s disease. • Research led by Daniel Madison, PhD, associate professor of molecular and cellular physiology, found that a compound called A-beta might, in the disease’s earliest stages, impair learning and memory by blocking the natural, beneficial action of endocannabinoids in the hippocampus. This midbrain structure serves as a combination GPS system and memory-filing assistant, along with other duties. A-beta is the chief constituent of the hallmark clumps dotting the brains of people with Alzheimer’s. • The Stanford group is now trying to figure out the molecular details of how and where this interference occurs. That could pave the path to new drugs to stave off the cognitive defects that characterize Alzheimer’s. • However, Madison said it would be incorrect to infer from this study that smoking pot would counter or prevent Alzheimer’s. • The study was published in Neuron. — BRUCE GOLDMAN
Radiation relief

LETHAL RADIATION exposure may seem the stuff of science fiction. But workers at nuclear power plants and people who witnessed the aftermath of the atomic bombs dropped on Japan in 1945 are certainly aware of the real-world dangers. • Now Stanford researchers have hit upon a way to possibly protect people after exposure to high doses of radiation by blocking the degradation of a small molecule in their intestinal tracts. The molecule, called HIF2, helps cells respond to stress. The approach worked unexpectedly well in laboratory mice.

The side effects of acute radiation exposure are most evident in rapidly dividing cells in the intestinal lining or bone marrow. Exposure leads to debilitating nausea, vomiting and diarrhea, and high risk of infection. Though bone marrow transplant can mitigate the bone marrow damage, there’s no treatment for the intestinal impact.

When the researchers studied the effect of total body irradiation on mice in which HIF2 degradation had been blocked, they found that over one-third survived at least 30 days — as long as they also received a bone marrow transplant. In contrast, none of the untreated mice lived longer than 10 days after exposure.

The animals were still at least partially protected from death even when the treatment was initiated up to 24 hours after radiation exposure.

Though they haven’t tested it yet, the researchers hope a strategy like theirs, which protects HIF2 with a molecule called DMOG, will relieve cancer patients from diarrhea and nausea caused by radiation therapy.

“There are a number of drug molecules that act in a manner similar to DMOG that are already in clinical trials for unrelated conditions,” says professor of radiation oncology Amato Giaccia, PhD, who led the study. “Our next step will be to test some of these molecules to see if they also offer radioprotection.” — KRISTA CONGER

GOOGLE Rx

RESEARCHERS AT STANFORD, DUKE UNIVERSITY and Google’s research arm, known as Google X, are planning an initiative to understand the molecular markers of health and the transition to disease. The study is at the early stage, with researchers planning to enroll 175 healthy participants in a pilot trial this year. The participants will undergo a physical exam and provide samples of body fluids like saliva and urine that can be examined using new molecular testing tools. The study’s results will help the researchers design and conduct a larger trial. — RUTHANN RICHTER

Let me go

MOST PHYSICIANS WOULD forgo aggressive end-of-life treatment for themselves but still pursue it for their patients, according to a recent Stanford study in PLOS ONE.

The study, led by VJ Periyakoil, MD, clinical associate professor of medicine, set out to determine physicians’ attitudes toward advance directives, documents that patients can use to indicate end-of-life care preferences. It included a 2013 survey of 1,081 Palo Alto physicians showing that most of these doctors — 88.3 percent — would choose “no-code” or do-not-resuscitate orders if they were terminally ill.

These results mirror what most Americans say they want at the end of life, but it’s not what most get. “Patients’ voices are often too feeble and drowned out by the speed and intensity of a fragmented health-care system,” she says. “The system needs to be changed.” — TRACIE WHITE
Erin keeps a photo of herself playing soccer in the living room of her tidy cottage near San Francisco Bay. It captures her image frozen in time and space, hurtling like a comet between two opponents, her white-blond ponytail fanned out like flames. • “She was a midfielder with boundless energy, lightning fast,” recalls the coach of her Big Ten college soccer team.

• Erin, in her early 30s, always assumed that soccer would be at the center of her life. As a little girl, her favorite toy was a soccer ball, a present from a cousin living in Rome. At age 4, she drew a picture of herself competing in the Olympics. In high school, she was invited to try out for the national team’s talent pool. After college, she played for the Detroit Jaguars, a semi-professional team. • But her dream of playing competitive soccer abruptly ended after a trip to Mexico in 2007. • “I was doing social work at an orphanage when I got sick,” says Erin (who asked that her real name not be used). “I passed out and was hospitalized with a high fever, low blood pressure and swollen lymph nodes. After that, I was never the same.”

• Thus began her seven-year journey battling a devastating illness with no known cause or cure. She was bedridden for all but four hours a day. She could stand only for 20 minutes.

By Kris Newby

ILLUSTRATION BY JEFFREY DECOSTER
PHOTOGRAPHY BY TIMOTHY ARCHIBALD
without fainting. But the worst symptom was the brain fog.
“It was like my thoughts were stuck in molasses,” says Erin.
No one could figure out what was wrong or how to fix it.
She was labeled with chronic fatigue syndrome. Despair set
in as the door to her old life slowly closed.

**INTERROGATING THE IMMUNE SYSTEM**
That same year a door opened on the other end of San Fran-
cisco Bay, in a windowless basement of a clinical research
building at Stanford University. Here Mark Davis, PhD, an
immunologist with a computer hacker’s mindset, was launch-
ing a center that aimed to break open the black box called the
human immune system. This dynamic network of biological
sensors, cells, secretions and genes is like a sixth sense, able
to detect microbial friend from foe in the food we eat, the
things we touch and the air we breathe. The most intelligent
facets of the immune system are still a mystery. How does it
differentiate between the cells that are part of you and the in-
terlopers? What are the steps involved in launching an army
of white blood cells to attack a microbial invader? How does
the system dial down the resulting tissue-damaging inflam-
mation? How do our traitorous cells — the cancers — make
themselves invisible to our immune system?

Davis, director of Stanford’s Institute for Immunology,
Transplantation and Infection, is in the right place at the
right time for this quest, swimming in the primordial soup of
creative disruption, Silicon Valley. At long Stanford cafeteria
tables frequented by geneticists, bioengineers, math genius-
es, computer programmers, surgeons and cancer biologists,
ideas just happen. And sometimes, visionary entrepreneurs
throw money at these ideas. Such is the case with Davis’ Hu-
man Immune Monitoring Center, which before long
had enough funding to acquire a CyTOF, a time-of-
flight mass spectrometer for high-speed acquisition of
multiparametric single-cell data. (If someone asks you if
you want one of these instru-
ments, just say yes.)

The CyTOF enables re-
searchers to detect 40 dif-
ferent components within a
single cell at the rate of 1,000
cells per second. It not only
measures static levels of pro-
teins, useful in identifying
different types of immune
cells, but it also detects min-
ute changes in signaling pro-
teins within cells in response
to various stimuli. Using this
device, a staggering amount
of data is generated. And
armed with big-data analyti-
cal methods developed dur-
ing the Human Genome
Project, Davis’ multidisci-
plinary team is trying to bring
order and meaning to the
output. When it’s all done,
the team hopes to create a map of what a healthy person's immune system should look like and a flow chart depicting how immune-system signaling pathways work.

The ultimate goal of Davis’ “Human Immunome Project” is to develop better tools to answer immunological questions no one can answer now. One of the first: What is wrong with the immune systems of patients like Erin, and how can we help them get better?

TWO YEARS INTO HER ILLNESS, Erin was broken. On any given day, she would cycle through a laundry list of symptoms: brain fog, dizziness, light sensitivity, a sore throat, nausea, swollen lymph nodes, crushing fatigue, a racing heart, ear ringing, drenching sweats and fainting.

During this time, she had lost some of her most active and athletic friends, who grew impatient with the waxing and waning symptoms that prevented her from the leaving the house on most days.

“I had times where I’d shut the blinds, lie down and hope for a better day,” says Erin. “Literally, my escape was through my dreams. I just couldn’t stand to be in my body.”

Her life revolved around doctors’ appointments. One physician ruled out infectious diseases. Neurologists examined her for seizure disorders and brain tumors. A rheumatologist evaluated her for systemic lupus erythematosus and other inflammatory diseases. An endocrinologist agreed that the origin of her fatigue was not the thyroid, the adrenals or any other gland. A cardiologist assured her it was not her heart.

None of them could settle on a definitive diagnosis, so the physicians tagged her with the insurance code for chronic fatigue syndrome, a controversial diagnosis for a set of symptoms also sometimes labeled as CFIDS — for chronic fatigue and immune dysfunction syndrome — and ME — for myalgic encephalomyelitis. The dominant moniker today is ME/CFS.

No one knows what causes ME/CFS. Some think that an infectious agent or overactive immune system triggers it. Others blame genetic flaws, environmental factors or a combination of any of the above.

Roughly 17 million people worldwide (1 million to 4 million in the United States) have ME/CFS. It strikes people of all ages and racial, ethnic and socioeconomic groups. It is diagnosed two to four times more often in women than men.

It’s a syndrome that gets little respect in the medical community because, with no tangible cause and an ever-changing constellation of symptoms, patients often get labeled as hypochondriacs, malingerers or seekers of addictive pain medications. The primary diagnostic criterion for this condition is infuriatingly vague — “six or more consecutive months of severe fatigue” — virtually unchanged since 1994.

As Erin went from specialist to specialist, well-meaning doctors grew frustrated with their inability to help her. One day Erin blacked out while driving, almost hitting a streetlight. After another fainting accident, an emergency room physician told her, “On hot days, women faint.”

“I felt objectified, like a slab of meat,” says Erin.

Finally, in 2009 Erin was diagnosed with postural orthostatic tachycardia syndrome — which accounted for her fainting spells. For treatment, her cardiologist sent her to Stanford Hospital’s cardiology clinic to see one of the nation’s few POTS specialists, cardiac electrophysiologist Karen Friday, MD.

POTS, which often accompanies ME/CFS, is a fainting disorder associated with an abnormal increase in heart rate and low blood pressure. The mechanism is unknown, but some people develop it after contracting viral or bacterial infections like mononucleosis, pneumonia or Lyme disease.

Friday prescribed fludrocortisone to manage Erin’s low blood pressure, but to explore the possibility of an underlying microbial trigger, she sent Erin to see Stanford professor of infectious diseases José Montoya, MD.

Montoya, 54, dapper in his white coat and tie and smiling widely, greeted Erin with a bear hug and told her in his thick Colombian accent, “I want to make your life beautiful again.”

“Dr. Montoya was a shining beacon of hope,” says Erin.

Montoya’s ethos to reduce patient suffering was shaped by a hardworking, single mother and the iron-fisted priests at his Catholic school in Cali, Colombia. He was accepted into medical school at age 18, after receiving the third-highest qualifying exam score in his native country that year. After medical school he went on to Tulane University School of Medicine for his residency, then joined the infectious disease division at Stanford. At Stanford he became a world-
recognized authority on infections affecting heart transplant recipients and on toxoplasmosis, a common parasitic disease.

Montoya conducted a detailed medical history and physical exam on Erin, then ordered a battery of tests for viruses, bacteria and fungi. His wide-net diagnostic approach paid off; he found two blood-borne microbes — Human Herpesvirus-4 and the coxsackie virus — known to cause chronic disease and POTS.

Though Montoya wasn’t sure if these viruses were at the root of Erin’s illness or merely collateral infections, he started her on a high dose of the antiviral drug famciclovir. Erin was relieved to finally have a physician who wasn’t going to punt her case to another specialist.

“I wanted to live my life again,” says Erin.

Montoya is one of only a handful of clinician-researchers who accept ME/CFS patients, and he currently has a waiting list of about 150.

Back in 2005, while attending a conference on toxoplasmosis in Paris, Montoya told his mentor that he wanted to research ME/CFS. His mentor scoffed at the idea, pointing to a homeless person lying in a Parisian gutter.

“That’s going to be you if you go into chronic fatigue research,” the mentor told him.

The hard truth is that most medical research labs rely in large part on U.S. government funding, and the ME/CFS research budget is insufficient to support a typical university research lab.

The National Institutes of Health, the largest funder of medical research in the United States, allocated only $5 million for ME/CFS research in 2013. (To put this in context, the annual NIH research budget for multiple sclerosis, with 400,000 sufferers, is $112 million.) The reasons behind this underfunding are complicated.

One factor is that the NIH funding process favors well-defined diseases that fit neatly into medical specialties like cardiology, cancer and neurology. Most of these medical societies have organized lobbying efforts, sometimes backed by pharmaceutical or medical technology companies. Another factor is that collectively ME/CFS patients are too sick to organize, raise money and lobby for research dollars. And then there is the stigma associated with the condition; some NIH grant reviewers are reluctant to fund research because they believe that ME/CFS is a psychosomatic, “all in the head,” disorder. (To remedy this, the NIH recently created a special emphasis panel so that researchers familiar with the condition review grant applications.)

But none of this deterred Montoya, who was driven to do something for the suffering patients queuing up for appointments.

Opportunity knocked in 2008 when a wealthy donor met with Montoya to talk about the ME/CFS problem. He asked if a $5 million donation for research could make a difference.

Montoya could hardly believe the sum, replying, “Yes, give me five years.”

With the freedom of private funding, Montoya was able to take a multifaceted and rigorous approach to analyzing ME/CFS. Traditionally, NIH funding is awarded through medical specialty groups that tend to favor research that tests one narrow hypothesis about a disease. For example, a researcher might get funded to screen blood samples for one virus, or treat patients with one drug. This approach takes a long time, and researchers typically aren’t able to share and build on discoveries for years.

Montoya’s game plan was to use a big-picture, big-data strategy to find out what was wrong with patients like Erin. His first step in launching the Stanford Initiative on Infection-Associated Chronic Diseases was to convince a dozen or so academic investigators to venture out of their comfort zones to research a wildly unpopular disease using technologies yet to be developed.

Montoya convinced experts in immunology, rheumatology, genetics, bioengineering, anesthesiology, neuroradiology, cardiology, psychiatry, infectious diseases and bioinformatics to all work together. The team members would be searching blood samples for infectious microbes, inflammation-related molecules and genetic flaws. They’d do brain scans and physical exams. They’d survey study subjects for fatigue levels and medical histories. Then they’d compare all this data with that of healthy people to see what was different. Next, he launched a Bay Area recruitment campaign for 200 patients who met the Centers for Disease Control’s definition for chronic fatigue syndrome, including Erin, and 400 age- and sex-matched healthy volunteers, all of whom agreed to donate eight tubes of blood and be
poked, scanned and surveyed over the next decade.

The most complex part of the ME/CFS initiative was the exploration into what was happening with the immune system of these patients. For this role, he needed an expert who didn’t care about the ME/CFS stigma or how things have been done in the past. So he called on Mark Davis.

**THERE WILL BE BLOOD**

Davis, in well-worn jeans and running shoes, leans back in his chair, surrounded by pillar-piles of scientific papers. At first glance one might assume that he is — in California-speak — a mellow dude.

But looks can be deceiving, because Davis, who discovered how T cells help a body fight off infections, is all about the fight. [See story, page 38.]

As if to prove this point, Davis reaches into a random stack of paper and pulls out a black-and-white photo of a collegiate fencing match.

“This is me,” he says, pointing to a man in white flying off the ground, plunging the tip of a silver foil directly between the eyes of a masked opponent. “I like to poke people.”

He then reaches into another stack of paper and pulls out the Dec. 19, 2008, issue of Immunity. It is a poke-in-the-eye to fellow immunologists, an essay titled, “A Prescription for Human Immunology.”

In this oft-quoted paper, he describes immunology as a field known for its “impenetrable jargon, byzantine complexity and acrimonious disputes.”

He also chides many of his colleagues for spending too much time on mouse studies and not enough on human studies. For immunological studies, mice are fast and easy. They can be bred with specific diseases, such as diabetes or Parkinson’s, and then dissected to evaluate the effectiveness of experimental treatments. There are relatively few regulatory, financial and ethical hurdles to working with mice. He emphasizes that lab mice live in isolated, disease-free, temperature-controlled environments, far different from the crowded, germ-ridden urban habitats of your typical Homo sapiens. (Most humans are infected with six different herpes viruses, and who knows what else.) The other problem with “mouse models” is that their common ancestors are genetically separated from Homo sapiens by some 65 million years.

“Inbred mice have not, in most cases, been a reliable guide for developing treatments for human immunological diseases,” says Davis.

Instead, he would like to shift the focus of immunology
research back to where it can do the most good — to humans and their blood. And along the way, he’d like to slay a few sacred cows of medicine.

First off, Davis believes it’s time to rethink the CBC or complete blood count, the most commonly ordered medical test on the planet. The CBC, which has changed little since it was put into mainstream use in the ’50s, provides physicians with relative numbers of a patient’s red, white and platelet blood cells. This test isn’t really “complete” and it doesn’t begin to capture the nuances of a working immune system.

As researchers gain a better understanding of this system, he’d like to develop a new set of metrics for immune system health that communicates more of a continuum of health rather than a black-and-white declaration. If the immune system is underactive, a person is open to infections, mutations and premature aging. If it is overactive, a person may suffer from allergies, autoimmune disease and excessive inflammation. Davis wants to redefine health as an immune system in balance, then develop better reporting tools to help clinicians determine if a patient is fighting a virus, a bacteria, an allergy or environmental toxins.

Davis’ FIELD OF DREAMS for this effort is Stanford’s Human Immune Monitoring Center. Launched in 2007, today the center consists of dozens of instruments that provide standardized, state-of-the-art immune system analysis at the RNA, protein and cellular levels. Its gene-sequencing instrumentation is located in a nearby building and shared with the Stanford Functional Genomics Facility. For researchers both inside and outside of the university, the center’s 15-person staff provides a one-stop shop for these services. At the start of a project, the center’s director, Holden Maecker, PhD, meets with investigators to help plan studies and determine needs, such as what samples to take, how to store those samples and which tests will best answer their scientific questions. There is also assistance on results archiving, reporting and data mining.

“We have about 60 different projects under way at the center right now,” says Maecker. These include searches for immune biomarkers for aging, Alzheimer’s, autoimmune disease, cancer, chronic pain, rejection in organ transplantation and viral infections.

“I believe this is the only facility of its kind anywhere,” says Davis.

Montoya’s chronic illness initiative is the largest project in the HIMC at this time, and the complexity of the task ahead is daunting. The staff is looking for meaningful patterns in the many components of the 600 blood samples, including dozens of cytokines, 35 cell-surface proteins, 15 or so types of

SPEARHEADING the body’s defense, the immune system launches tightly orchestrated attacks. With rapid-fire precision, it relays complex information across the body, uniting diverse tissues and cells in a single mission.

Similarly, the Stanford School of Medicine’s Institute for Immunity, Transplantation and Infection unites a diverse group of experts — blending clinicians, engineers, researchers and educators — to probe the basic biology of the immune system. They use this information to develop new vaccines, improve organ transplantation and treat autoimmune disease.

More than 100 investigators are affiliated with the institute, which grew up around the Human Immune Monitoring Center. The HIMC, launched in 2007, provides a comprehensive analysis of immune system functioning using genomics, screening services and immunoassays.

“The HIMC fills a critical need,” says institute director Mark Davis, PhD. “It is becoming increasingly apparent that the immune system is involved in almost every disease, but getting and interpreting this type of data has previously been limited to specialists.”

The HIMC ensures these tools are available to the Stanford community, Davis says.

The institute fosters the development of young researchers through grant opportunities, networking alliances and educational programs, including a summer program for high school students interested in medical research. It also operates the immunology graduate program.

One of its major goals is to revolutionize the immunology care given to average people. For example, Davis says he looks forward to the day when patients will be able to stroll into their doctor’s office and ask about the health of their immune system, just as patients today ask about their blood pressure.

That type of transformation may be possible thanks to the entrepreneurial spirit and innovative teamwork that thrives at the institute, says Cristina Tato, PhD, a research and science analyst with the institute. “We really try to leverage all of the experience of Stanford Medicine by bringing together top experts to solve problems,” she says. “It’s such an amazing organization.” — BECKY BACH
blood cells, and more than 47,000 genes and regulatory nucleic acids. The challenge is not only to quantify the normal ranges for these components, but also to understand relationships between the components and reverse-engineer the cascade of biochemical reactions that drive immune system processes. He anticipates it will take about a year to run all 600 samples through the processes.

“It’s like dumping a hundred different puzzles on the floor and trying to find two pieces that fit,” says Davis.

The workhorses for these tasks are the center’s two CyTOFs. Stanford has seven of these $630,000 instruments, more than any other academic medical center, thanks to Garry Nolan, PhD, a Stanford professor of microbiology and immunology. Nolan purchased the first commercially available CyTOF, and as an early adopter developed protocols for using it in cancer biology, immunology and cell biology. He now holds equity in Fluidigm, a company that manufactures the machines.

His enthusiasm for the technology and his willingness to share what he’s learned has catalyzed an active Stanford community of CyTOF experts.

“With seven CyTOFs on campus, Stanford continues to innovate and lead the way in ‘deep-profiling’ studies of the immune system,” says Nolan.

Through this work, the Stanford team hopes to gain a better understanding of the complex, inner workings of the immune system. This will ultimately give physicians and their patients the tools to answer the fundamental question, “How is my immune system doing today?”

PUTTING THE PIECES TOGETHER

This past March, four years after the launch of the ME/CFS initiative, Montoya held an all-day symposium to present early findings on what’s happening within the hearts, blood, brains and genomes of ME/CFS patients. The lecture hall was packed with researchers from Australia, Canada, the United Kingdom and the United States, as well as patients, all eager for any news on a research agenda that had been stalled for decades.

(These presentations can be watched at http://mecfs.stanford.edu/2014SymposiumVideo.html.)

At the end of the day, the biggest news was the identification of a number of biological markers that indicate ME/CFS patients may be suffering from out-of-control inflammation.

First up was a neuroinflammation researcher, Jarred Younger, PhD, who worked with the HIMC to measure daily fluctuations of 74 blood markers and cytokines. For this study, published in the *Journal of Translational Medicine* (http://www.translational-medicine.com/content/11/1/93),
volunteers gave blood once a day for 25 days, and reported their fatigue levels on a hand-held computer twice a day. (Younger moved to the University of Alabama in Birmingham in August.) Through complex statistical analysis, the team found 12 cytokines that were consistently elevated on days that ME/CFS patients felt the most fatigued. One of these cytokines, leptin, activates microglial cells, the brain's first line of defense against infections. When microglial cells are primed, they start pumping out signaling chemicals that generate the flulike symptoms commonly reported by ME/CFS patients—fatigue, headaches and brain fog.

Amit Kaushal, a medical resident with a PhD in bioinformatics, did the first pass on genomic analysis. For his part of the investigation, he scanned the blood of 200 ME/CFS patients and 400 healthy subjects for 47,000 gene elements, then ran this data through the Nextbio Disease Atlas, a publicly accessible database that catalogs gene markers associated with specific diseases. After analysis, he found genetic markers in the blood of ME/CFS patients similar to those in patients with well-defined chronic inflammatory diseases.

The quarterback for the search for infectious microbes is W. Ian Lipkin, MD, a renowned microbe hunter and the director of the Center for Infection and Immunity at Columbia University’s Mailman School of Public Health. He is using high-throughput sequencing platforms that enable rapid identification and molecular characterization of known and novel disease agents.

“We decided to go in without any preconceived notions about what we’d find,” says Lipkin. “Our approach is comprehensive, rigorous and quite deep.”

In the first analysis, his team found no significant differences in the types of infectious organisms present in the blood of people with ME/CFS or their matched normal controls. In the next phase he’ll search inside the blood cells and analyze the gastrointestinal microbiome for the presence of bacteria or viruses that may trigger the immunological disturbances that are so disabling in ME/CFS. The objective of this work is to identify the agents responsible for initiating and perpetuating disease. This could lead to vaccines, drugs or probiotic interventions.

While not all of these results have been published or independently confirmed, the researchers were excited about finding measurable, physical differences between ME/CFS patients and healthy controls. (Stanford assistant professor of radiology Michael Zeineh, MD, has identified structural brain abnormalities in the ME/CFS patients—findings are slated for publication in the coming months.) More pieces of the puzzle are coming together, providing other ME/CFS researchers with ideas to build on. For ME/CFS patients it was validation—theyir symptoms are real, with measurable biological markers.

EIGHT MONTHS after seeing Montoya, Erin’s recovery from ME/CFS started with fleeting windows of cognitive clarity. She was on high-dose antivirals and POTS medications for about five years, and her recovery was infuriatingly slow and inconsistent. It was like wiping off a mirror in a steamy bathroom. She saw her former self briefly, then the image fogged over again.

Montoya doesn’t know why these drugs worked for Erin, but he knew from treating other patients that beating back viral infections sometimes helps get an immune system back into balance.

Erin also believes that the antiviral and POTS drugs were instrumental in her recovery, but other factors—family support, meditation and Montoya’s coaching—were also important.

One of Montoya’s key messages to ME/CFS patients is this: If you have one good day, don’t try to make up for lost time by overexerting yourself.

“Don’t burn out your engine,” says Montoya, because the resulting crash can reset the recovery process by months.

And at appointments he would remind Erin, “Take in all the love that is all around you and use it to heal.”

During her illness, Erin’s mother became her advocate, managing her medical issues and driving her to appointments. Her father added her to his health insurance policy so she could afford the visits to medical specialists. And her sister, who is her best friend and housemate, was her wingman.

“My sister was my voice of hope,” says Erin. “She’d tell me, ‘OK, you took five steps forward and two back today, but maybe tomorrow you’ll take six steps forward and only one back.’”
It’s been seven years since Erin fell into the abyss of a mysterious illness. This girl interrupted, now a woman, is picking up the pieces of her life and starting to live again.

Today, she works as a social worker and therapist. She plays soccer in a local league. She’s also started dating again. It gives her hope that researchers are finally focused on ME/CFS and that others may be able to benefit from the treatment that has given her life back.

As she packs for a camping trip, she reflects on how this illness has changed her.

“It’s made me a person of more depth and compassion,” says Erin. “Before, I’d been so active, I didn’t have the opportunity to sit with myself in this way and take a deeper inward journey. Adventure had been the focus of my life. As I sit with clients who are coming in with devastating situations, with unknown futures, I’m able to share with them hope and the power of self-fulfilling prophesies. I help them find those things inside, spiritually, that will help them meet the adversities in their lives.”

At this point her voice becomes soft, almost a whisper, as she says, “I’ll always miss playing soccer at a competitive level, but I’ve gained so much. It’s helped me reinterpret what success looks like. It’s not everything you achieve and how many games you win. It’s the process of getting there. This is my biggest achievement — recovering from this illness.”

In soccer, a “hat trick” is where a player scores three goals in a row. Montoya achieved his first goal, the launch of the first major ME/CFS research initiative, with a little funding luck and the recruitment of a top-notch research team. With the assistance of Davis and his immune system hackers, he’s close to reaching his second goal: the identification of biomarkers and causes, which will enable physicians to provide a definitive diagnosis and treatment options to patients suffering from this debilitating condition.

The third goal of his hoped-for hat trick will be a whole new way to look at the human immune system. It’s a game changer. It will provide researchers with a new playbook of research strategies to help them discover the causes of other confounding conditions, from Lyme disease to multiple sclerosis to fibromyalgia. It will provide clinicians with a better set of metrics for assessing patients’ health. And then the patients lying in dark rooms with forgotten diseases, whose numbers could fill hundreds of soccer stadiums, will have reasons to stand up and cheer. SM

— Contact Kris Newby at krisn@stanford.edu

WEB EXTRA
Hear about Erin’s seven-year battle with chronic fatigue, from despair to recovery. http://stan.md/1uanAqX

HACKING THE IMMUNE SYSTEM

THE HUNT FOR CHRONIC FATIGUE BIOMARKERS

Chronic fatigue syndrome (also known as myalgic encephalomyelitis) is an illness with no clear-cut diagnostic criteria or cause. There are an estimated 17 million sufferers worldwide (source: NIH). The Stanford Initiative on Infection-Associated Chronic Diseases is coordinating a multidisciplinary team of experts to look for biomarkers and causes of ME/CFS and other unexplained chronic illnesses.

The study, led by professor of infectious diseases José Montoya, MD, is currently the largest project at Stanford’s Human Immune Monitoring Center.

600 study subjects
Researchers have assembled a large biological sample and data repository for 200 chronic fatigue patients and 400 age- and sex-matched healthy subjects. (Recruitment is closed.)

Immune system visualization
High-speed cell analyzers look for more than 40 molecular parameters per blood cell, enabling the creation of immune system maps that flag dysfunctional processes.

Microbe search
New rapid-gene-sequencing instruments are being used to search blood and GI tract samples for more than 20 viruses, parasites, fungi and bacteria.

Inflammation molecule tracking
Called cytokines, these molecules that regulate infection and fight cancer were tracked on a daily basis in order to find relationships between fatigue levels and immune system dysfunction.

Genetic profiling
47,000 gene elements are cataloged for each sample, then compared to a public database of genetic disease markers.

Brain scans
Imaging and electrical-activity instruments are looking for brain inflammation and abnormalities in patients.
On March 2, 2009, something snapped inside Paul Michael Nelson. In the middle of the night, his parents found the 7-year-old boy stabbing the door of the family's home office with a kitchen knife, trying to get at a computer that was off-limits after his bedtime. When they stopped him, he flopped around the floor on his knees, barking like a dog. He tore at blankets with his teeth and spoke in gibberish. • It was Paul Michael's first episode of psychosis. • “It was like he was demon-possessed,” says Mary Nelson, his mother. • The Nelsons rushed to their local emergency room, where staff didn’t seem to believe their account of the intensity of the outburst and said it must have been just a temper tantrum. The staff wrote a referral to a psychiatrist and sent him home. The next day, the Nelsons took Paul Michael to the psychiatrist. She was about to give him an antipsychotic, but changed her mind after reading his blood work. • “She said, ‘Oh, my God, he’s got low platelets; I can’t prescribe this,’ and she shuffled us out,” says Paul Nelson, the boy’s father. Paul Michael's levels of platelets, the blood cells that form clots to
stop bleeding, were far below normal, but the Nelsons were not sure why the psychiatrist thought this justified avoiding antipsychotics. After the family left the psychiatrist’s office, Paul saw his son, who seemed to have held himself together for the doctor, becoming overwhelmed. “He’s very scared; he knows something’s wrong. When she shut the door, it felt like the doctor shut us off.” When the family got home that day, Paul Michael exploded into another psychotic fury.

Sucked into the whirlpool of Paul Michael’s compulsions, rages and delusions, neither the Nelsons nor the doctors who took on Paul Michael’s case realized that the little boy’s abnormal blood work held an important clue to what was wrong. It took months and several psychiatric hospitalizations before anyone recognized that Paul Michael’s case illustrated an alarming phenomenon: Your immune system can make you crazy.

When the immune system gets derailed from its usual infection-fighting role and attacks the brain, it can trigger obsessive-compulsive actions, anorexia-like refusal to eat, severe anxiety, violent outbursts and other symptoms of mental illness, as well as a host of neurological problems — in the worst cases, seizures, respiratory failure and death. Although doctors recognize a handful of immune-mediated neurologic diseases in children and adults, their awareness of the immune connection to mental illness is limited.

That’s slowly changing. Instead of hot-potatoing such puzzling cases out of their offices, as the Nelsons’ first psychiatrist did, some physicians are working to understand the mechanisms and develop treatments for autoimmune diseases that attack not just the brain but also the patient’s personality, the intangible spark we call the self.

It’s not easy. There’s no diagnostic lab test for pediatric acute-onset neuropsychiatric syndrome, or PANS — the name for this list of devastating symptoms — and the list probably encompasses an array of similar but not identical brain diseases, most of which still have unknown causes. But in spite of the stumbling blocks and the scientific disputes they’ve engendered, answers are emerging, in large part because of a Stanford team’s efforts to conduct research and treat affected children in the country’s first clinic to address the disease.

A FAMILY’S AGONY

PAUL MICHAEL’S SECOND BREAKDOWN happened after his family returned home from that unsuccessful psychiatrist visit, March 3. It was so violent that his parents called the police. He was doing some of the same alarming things as the night before — flopping around, speaking in gibberish — but was also tearing up his room, causing his parents to worry that he might find an object there that he could use to hurt himself. Paul tried holding the little boy to calm him, but Paul Michael fought his dad with what seemed like superhuman strength. The police took him to the hospital on a 5150, California’s code for involuntary restraint of persons who are a danger to themselves or others. He was in and out of a pediatric psychiatric hospital for several months.

Meanwhile Paul and Mary began their search for answers, starting with Paul Michael’s general pediatrician and the psychiatrists, social workers and counselors they found through their health insurance provider and the psychiatric hospital where Paul Michael stayed. Most of these caregivers ascribed Paul Michael’s problems to a family history of psychiatric illness (both parents had depression and bipolar disorder in their extended families), poor parenting or outright child abuse.

The Nelsons were willing to try anything to become better parents. “If I’m doing something wrong, I want to know,” Mary says, adding that “We felt like, we’ve somehow got to try to survive because we love him so much.” But they were grieved and confused, too: “We met with counselors at the psychiatric hospital who were saying things like, ‘Mom, you’re too codependent’ — and I might be, but I knew I didn’t cause my kid to go psychotic.”

Paul ticks off the strategies they tried, following counselors’ suggestions, to improve their family environment: rewards for good behavior, lists of skills to utilize, contracts, daily affirmations … until both parents chuckle ruefully at the futility of those efforts in the face of Paul Michael’s uncontrollable compulsions and rages.

Although the suggestion that they were abusing their son
pained them, they knew why it crossed people’s minds: He was always covered in bruises. More than once, the police showed up to a scene of one parent restraining an explosive Paul Michael, and, to an outside observer, it was hard to tell what was really going on. Paul had been a San Francisco sheriff’s deputy for 27 years before retiring to return to school, so he could easily see these scenes from the officers’ perspective. There were times he found himself consoling the officers because they had never seen a young child so distressed.

At first, the only dissenting medical expert’s voice about the origins of Paul Michael’s illness came from Mary’s colleague William Benitz, MD, a professor of pediatrics at the Stanford School of Medicine, where Mary was a human resources manager in the neonatology division. Benitz urged the Nelsons to take Paul Michael to a rheumatologist who could investigate whether an autoimmune disease could be causing both their son’s very low platelet count — which could explain his constant bruising — and his sudden psychiatric symptoms.

“I have a rule of thumb for pediatric patients: They’re only allowed to have one disease at a time,” Benitz says. “It’s not 100 percent true, but for a previously healthy 7-year-old to develop what appeared to be psychiatric and hematologic symptoms from two different, independent processes didn’t make sense. There had to be a unifying diagnosis.”

Then, the Nelsons ended up at Stanford Hospital’s emergency department during one of Paul Michael’s outbursts, where they saw Richard Shaw, MD, a professor of psychiatry and behavioral sciences and a child and adolescent psychiatrist at Lucile Packard Children’s Hospital Stanford. Observing Paul Michael’s behavior, Shaw told the Nelsons that they weren’t dealing with schizophrenia or bipolar disorder; instead, he suspected vasculitis or brain inflammation. His opinion spurred the family to keep searching for a diagnosis.

**A HISTORY OF CONTROVERSY**

*When Paul Michael became sick in 2009, the concept of autoimmune psychiatric disease was barely on doctors’ radar. It wasn’t until September 2012 that Lucile Packard Children’s Hospital Stanford opened the country’s first clinic devoted to treating children with PANS, which is still the only clinic to couple the expertise of psychiatry and immunology/rheumatology for these patients. Children who meet diagnostic criteria for PANS have sudden, severe obsessive-compulsive behavior or anorexia, along with so many other problems that the child can barely function. These may include separation anxiety so powerful the child cannot bear to be more than a few feet from a parent, bizarre inhibitions about food, deterioration in schoolwork, intense insomnia or, as the Nelsons observed in Paul Michael, violent rages when the child’s obsessions cannot be satisfied.*

“In some ways, it’s like having your kid suddenly become an Alzheimer’s patient, or like having your child revert back to being a toddler,” says Jennifer Frankovich, MD, clinical assistant professor of pediatric rheumatology at the School of Medicine and one of the clinic’s founders.

“We can’t say how many kids with psychiatric symptoms have an underlying immune or inflammatory component to their disorder, but given the burgeoning research indicating that inflammation drives mood disorders and other psychiatric problems, it’s likely to be a large subset of children and even adults diagnosed with psychiatric illnesses,” says Kiki Chang, MD, professor of psychiatry and behavioral sciences.

Chang, a pediatric bipolar expert, was drawn to collaborate with Frankovich in founding Stanford’s clinic because many PANS patients are first suspected of having bipolar disorder. But although their symptoms begin as abruptly as bipolar manias, they are not manic. Talking about these mystifying children (among them Paul Michael, whom the doctors now consider their first PANS case), Chang and Frankovich realized the only thing that was clear was that the children and their families desperately needed help. Nearly everything else about PANS was up for debate. “A lot of academic physicians have said ‘This does not exist; it’s just bad behavior, and there are a lot of reasons for kids to have bad behavior,’” Frankovich says.

For many years, controversy dogged PANDAS, the provisional diagnosis that preceded PANS in the medical literature. The phenomenon, which was first reported in the 1980s by Susan Swedo, MD, now a senior investigator at the National Institute of Mental Health, included sudden emergence of OCD or tics (repetitive, hard-to-control vocal or physical movements) in the wake of strep infection. Swedo’s theory was that the body’s response to infection went awry and triggered an autoimmune attack on the brain. She succeeded in treating some cases with either long courses of antibiotics to kill strep bacteria or, if that didn’t work, various immune therapies.

However, many healthy children carry strep bacteria, one of several factors about the biology of strep that have made it difficult to clarify the bacterium’s role in the disease. So the syndrome’s critics have contended that the kids simply had run-of-the-mill Tourette’s or obsessive-compulsive disorder plus, perhaps, some behavioral problems caused by bad parenting.
The treatments Swedo proposed have risks. One of them, long-term antibiotic therapy, can favor development of antibiotic-resistant organisms. Another, treatment with immunosuppressants, puts kids at risk for serious infections. But the children’s symptoms were extremely debilitating, and the treatments seemed to help. Swedo was frustrated that, in her view, the science was being stalled by critics’ dismissal of the immune-system connection.

Frankovich and Chang acknowledge the dearth of science to explain most cases of PANS, but say that’s why Stanford’s clinic is so important: It provides a critical mass of patients for answering scientific questions. Other institutions, such as Harvard-affiliated Massachusetts General Hospital and the University of South Florida in Tampa, have joined Stanford in committing resources to study and treat the disease, and more programs are under development.

“Maybe we’ll go back and say, ‘We were wrong; it’s all parenting,’” Frankovich says, sounding simultaneously tongue-in-cheek and strained. “But we have to try.”

A DISCOVERY THAT CHANGED MINDS

The 2007 discovery of a molecular explanation for some cases of autoimmune encephalitis — a specific form of brain inflammation caused by an immune attack — has made a big difference in convincing physicians to look for autoimmune underpinnings when patients suddenly seem to go off the deep end.

In this disease, known as anti-NMDA receptor encephalitis, an antibody made by the patient’s immune system attacks a receptor for a single neurotransmitter, N-methyl-D-aspartate, producing psychiatric and neurologic disturbances. For instance, a patient may first show anxiety, paranoia and hallucinations, progressing to movement disorders and seizures. In the worst cases, patients develop irregular heartbeat and breathing, go into a coma and die. But quick diagnosis and treatment can reverse all of this. The book Brain on Fire, Susannah Cahalan’s 2012 best-seller describing her bout with the disease, raised awareness [see story page 36]. Though at the height of her illness, Cahalan was severely debilitated with paranoia, hallucinations, seizures and cognitive impairment, she received treatment, made a full recovery, returned to her job as a New York Post reporter and became an advocate for other autoimmune encephalitis patients.

PAUL MICHAEL (FAR RIGHT) AND HIS FAMILY AT HOME.
FINDING A SPECIFIC ANTIBODY that triggers PANS symptoms would make treatment much easier. But most patients have no known biomarker of their illness. In this, though, Paul Michael was lucky. At the beginning of the summer of 2009, a physician in the Nelsons’ insurance network referred him, at Benitz’s suggestion, to Frankovich. (The insurer didn’t have an in-network pediatric rheumatologist within 50 miles of the family’s Half Moon Bay, Calif., home, so he was able to go outside the network to see her.) From blood tests, Frankovich discovered that Paul Michael had elevated anti-B2G1 antibodies. These antibodies bind a specific component of cell membranes and target platelets for destruction; they are also associated with blood vessel disease that can cause neurological symptoms such as chorea, a movement disorder that can co-exist with behavior disorders. Paul Michael also had some blood markers of lupus, an autoimmune disease that can attack the brain, though he didn’t meet full diagnostic criteria for that disease.

At first, Frankovich had no evidence to prove that the anti-B2G1 antibody or lupus markers were contributing to his psychiatric symptoms, but in a sense that didn’t matter. She was a rheumatologist, and she had found an immune abnormality — autoimmune platelet disease — that clearly needed treatment.

In early June 2009, Frankovich began giving Paul Michael powerful immune-suppressing drugs. His platelet count rose and his psychiatric symptoms eased. After having spent 61 days in emergency rooms and psych hospitals between March and May, Paul Michael spent nearly all of June and July at home, visiting the emergency room only three times. Paul and Mary began to hope that things were turning around.

But then, in December 2009, Paul Michael got the flu and Frankovich stopped his immune-suppressing medications so he could recover. His body fought off the virus, but his platelets dropped and his rages surged back.

“He had a five- to six-month flare,” Mary says. “It was heartbreaking.”

“We had to start over,” Frankovich says. The second time she tried suppressing Paul Michael’s immune system, he didn’t respond to one of the medications she had used initially, so she switched to a stronger drug. In the subsequent months, Frankovich shifted the medication doses up and down to investigate whether Paul Michael’s autoimmune disease was connected to his psychiatric symptoms. His regression when he had the flu, she concluded, was not a fluke: When Paul Michael’s immune system was not being suppressed, his platelets fell and his rages became more frequent and intense. She became increasingly convinced an autoimmune process was causing both his low platelets and his psychiatric symptoms.

But she had trouble getting others to agree that there was a connection. “Even though our psychiatrist at Stanford believed the two problems were related, the non-Stanford psychiatrists the family was seeing through their insurance provider didn’t understand what was going on medically,” she says. “They were looking at this as a kid with a behavior disorder, saying it must be a parenting issue.”

By June 2010, police had responded to 5150 calls from the family 17 times. Exhausted by trying to care for him, his parents felt they had no choice but to have Paul Michael live at a psychiatric institution.

For 15 months, Paul Michael became a residential patient at Edgewood Center for Children and Families, a San Francisco facility that provides the highest level of psychiatric care available below a locked psychiatric unit. Edgewood had a much more structured, predictable environment than any family could reasonably provide at home, and unlike parents who
haviors to try to figure out how they might have sparked episodes of Paul Michael’s rage.

“We were looking for triggers, but there was no trigger,” Paul says. When the illness was at its worst, it was impossible to avoid setting the boy off. “If it wasn’t going to happen at 9 when the phone rang, it would be at 9:15 when the cat wanted to go out,” Paul says. The Nelsons eventually discarded the concept of triggers. “Now, when he’s getting edgy, we call it ‘storm season,’” Mary says.

“This illness has leveled our pride and our expectations,” Paul says.

“There has been a lot of grief for both of us, his sister and for him, too,” says Mary.

“But it’s lucky he had the clear autoimmune blood disorder, because it allowed us to use immune-modulation therapy,” says Frankovich. “Had he just come in with behavioral deterioration, he would still be in a mental hospital.”

**HUNTING FOR ANSWERS — AND TREATMENTS**

Because it’s unclear whether PANS is actually one disease or many, Frankovich and Chang are conducting research to clarify the jumbled picture presented by all 70 children they’ve seen to date at Stanford’s PANS clinic. In one study, they’re looking for genetic markers that appear more often in PANS patients, the first step toward figuring out whether certain genes increase a child’s vulnerability to the disease.

They’re also using brain imaging to ask how PANS could change two brain regions. One of these, the basal ganglia, plays important roles in fine-motor control and in fine-tuning mood and anxiety. It is also a region where the blood-brain barrier tends to break down, providing a possible entry for antibodies, which researchers suspect may attack the brain.

Figuring out whether PANS patients make antibodies against their own brains is perhaps the most important key to the disease’s mysteries. The research bears similarities to the discovery of anti-NMDA receptor encephalitis, and the path to that breakthrough may provide a road map of sorts for PANS researchers.

“You first need a critical mass of patients, but it doesn’t need to be very big,” says Josep Dalmau, MD, PhD, who led the anti-NMDA discovery. The professor of neurology at both the University of Pennsylvania and the University of Barcelona notes that his team’s first report of anti-NMDA receptor encephalitis included just four patients with very similar conditions. “In my experience you need clinics, and a good group of clinicians who can see all these patients and group them in some way.”

After grouping them, Dalmau’s team searched the patients’ cerebrospinal fluid for unusual biomarkers, finding an out-of-place antibody common to all four patients. The clincher was that this antibody attacked the brain.

“It’s very clear-cut: You see the antibody beautifully reacting with neurons, and see that the antibody binds to the brain and decreases the number of NMDA receptors,” Dalmau says. “There’s no ambiguity. We don’t see the antibodies in patients without the disease.”

There are hints that PANS may also be associated with misplaced antibodies. Madeleine Cunningham, PhD, professor of microbiology and immunology at the Oklahoma University Health Sciences Center, has developed a possible PANS diagnostic panel that tests for one brain enzyme and four antibodies against different brain proteins.

“The evidence she has published is strong, but it’s just the tip of the iceberg,” Frankovich says. “We still have a lot more work to understand what these four antibodies mean and how reliable they are in the clinical setting.” For one thing, healthy people have low levels of these antibodies; scientists still don’t understand what constitutes a critical level of these antibodies and why they enter the brain. Clinical studies at several sites around the world are attempting to independently validate the panel.

Circumstantial evidence also suggests antibodies contribute to PANS, Cunningham notes, because plasmapheresis, a technique in which a patient’s plasma is replaced with the plasma of a healthy individual, has successfully treated some PANS patients.

“Plasmapheresis removes antibodies and the person gets better,” Cunningham says.

An immune-suppressing treatment, intravenous immunoglobulin, or IVIG, may also help. IVIG, a blood product consisting of IgG antibodies from healthy donors, is infused into the patient to tamp down inflammation. Scientists aren’t entirely sure how it works, but the NIH’s Swedo is now conducting a phase-3 clinical trial of IVIG versus placebo to see if it’s an effective PANS treatment, part of her larger effort to standardize PANS therapy.

And the larger scientific community is talking more about PANS and PANDAs, too. For example, the *Journal of Child and Adolescent Psychopharmacology* is publishing an October 2014 special issue on the diagnoses.

Without a universally accepted PANS treatment, Stanford’s doctors currently approach PANS patients one symptom at a time. Depending on the patient’s presentation and
The immune system

Balancing Act:

That which does not kill you can still be plenty debilitating. A perfect example is osteoarthritis, essentially the scraping of bones against one another when one of evolution's carefully crafted masterpieces, a joint, gradually breaks down. An estimated 27 million people in the United States are diagnosed with osteoarthritis, by far the most common form of arthritis. That number is likely to increase to 50 million by 2030, due mostly to the aging of the population. • Over half of the U.S. population has symptomatic evidence of osteoarthritis by age 65, says Bill Robinson, MD, PhD, an associate professor of immunology and rheumatology at Stanford. “Virtually everybody gets it, if they live long enough,” he says. “Some of us get it while we’re still young, typically stemming from an injury to the affected joint years earlier. But far more of us get it later on.” • Who? Everyday people. “You, me, our next-door neighbor,” says Mark Genovese, MD, professor of immunology and rheumatology. Genovese, who sees a lot of osteoarthritis patients in his Stanford practice, describes the condition as ubiquitous. “As we age, it approaches 100 percent prevalence.” • You start to feel some combination of pain, stiffness and tenderness in a thumb, a knee, a hip, a toe or perhaps your back or neck. It takes

By Bruce Goldman

Illustration by Jeffrey Decoster

When

Bones

Collide

An Unexpected Fuel for Osteoarthritis
progression of osteoarthritis."

But Robinson, who also spends time seeing osteoarthritis patients, has another, revolutionary thought: that far from being the passive product of a lifetime of joint usage, the disease is driven by chronic, low-grade inflammation. He and his colleagues have shown in laboratory studies that components of the immune system are hyperactive in osteoarthritic joints and that stopping low-grade inflammation in its tracks can substantially counter disease progression.

This new thinking about osteoarthritis as what he calls an auto-inflammatory disease instead of a set of bald tires has the potential to change the picture considerably for patients. Having proved his hypothesis first in vitro at the laboratory bench and then in animal models that inflammatory processes are key to osteoarthritis progression, Robinson has passed the torch to Genovese: a classic translational-medicine hand-off, from basic research through animal models to clinical trials involving osteoarthritis patients.

THAT WHICH DOES NOT KILL ME GETS NEGLECTED

In a sense, osteoarthritis is to movement as Alzheimer’s disease is to memory. • “We can’t stop it. We can’t cure it,” says Genovese, who is also the James W. Raitt Professor of Medicine. “So instead we try to reduce pain in those who have it. But we shouldn’t mistake that for altering the course of the illness, which we are unable to do. We lack any therapies that fundamentally alter the progression of osteoarthritis.”

Loss of function in an osteoarthritic joint is typically accompanied by pain, particularly at night or with overactivity, that can range from mild to utterly disabling. The only treatments today are painkillers and, ultimately, joint replacement. Osteoarthritis accounts for one out of every four visits to a primary-care physician’s office.

With so many sufferers, you might think osteoarthritis would be a hot research area. And you would be wrong. While osteoarthritis may be a huge public-health problem, it’s not going to kill you today. So, says Robinson, it takes a backseat to cardiovascular disease, cancer, AIDS and other more lethal disorders.

“We believe we can change this paradigm that not much can be done to reverse, halt or even slow the progression of osteoarthritis,” says Genovese, who is leading a pilot study in actual patients to test Robinson’s theory. “The prevailing view today is that this is simply the result of the normal destruction that takes place in the body with aging and injury. We’re saying, yes, but the process perpetuates and feeds on itself. If we can disrupt that, we might be able to change the course of the illness.”

A key component of any joint is cartilage, a shock-absorbing material that lines and separates the two bones defining a joint so they don’t scrape together when we move. Osteoarthritis involves the breakdown of cartilage, the growth and expansion of the bone facing the joint, and the infiltration of inflammatory white blood cells; it also involves increases in inflammation-associated substances in the synovium, the surrounding pouch that supplies the relatively blood-free cartilage with nutrients. It’s not hard to imagine how either a sudden injury to a joint or the strain of its routine use over the decades, compounded perhaps by carrying extra weight, could produce osteoarthritis. But then again, not all old people — or all obese people, for that matter — get it.

OSTEOARTHRITIS IS DISTINCT from the far rarer rheumatoid arthritis, which affects no more than 1 in 100 people. The latter is an autoimmune condition that occurs when the body’s immune system mistakes proteins associated with the joints for those of a foreign invader and mounts intermittent, escalating attacks on innocent tissue. Leading the charge are the cellular and molecular warhorses of the so-called adaptive immune system: for example, antibody-secreting B cells and toxin-secreting T cells.

It turns out that rheumatoid arthritis and osteoarthritis are examples of overdrive in two quite different branches of the immune system.

A key feature of the adaptive immune system when it’s working correctly is that it precisely targets specific features of the enemy it seeks to fight, thereby sparing innocent bystander cells in adjacent and surrounding tissues. The adaptive immune response takes a week or two to get up to speed after it detects the presence of an invading organism or tumor-cell wannabe. That leaves a two-week window during which a pathogen, left unchecked, could multiply in the body to the point where it would be impervious to the adaptive immune system’s eventual response.

Filling the gap is another, far more ancient branch of the
immune system. Whereas any creature with a backbone (i.e., vertebrates) has an adaptive immune system, all multicelled creatures, from sponges to space cadets, are endowed with a so-called innate immune system. This ragtag army of cell-surface receptors, circulating warrior proteins and primitive, amoeba-like cellular thugs doesn’t customize its every response to the specific features of each offending invader. Instead, upon finding that an unfriendly bacterium or virus is afoot, it quickly mounts a take-no-prisoners response, which we call inflammation: the “calor,” “dolor,” “rubor” and “tumor” (heat, pain, redness and swelling) recorded by the Roman encyclopedist Celsus in the first century and recalled by any modern who ever skinned a knee as a careless kid or sliced a finger instead of a carrot as a harried adult. That inflammation keeps offenders at bay while the adaptive immune system is taking its time revving up. But it also wreaks collateral damage and draws in additional immune reinforcements, taking a toll on the tissue in the vicinity. Up close, not so pretty.

Rheumatoid arthritis occurs when the adaptive immune system mounts an inappropriate attack on native proteins in joint areas, while osteoarthritis, Robinson says, is an example of the collateral damage wrought by the friendly fire of inflammation. Given the quite different immune entities involved, it’s perhaps not surprising that drugs that are effective for rheumatoid arthritis don’t do much for osteoarthritis, says Robinson, who refers to the latter as an “autoinflammatory” rather than an autoimmune condition.

Robinson further distinguishes between what he calls high-grade versus low-grade inflammation. “High-grade inflammation — what you see in an autoimmune disease such as rheumatoid arthritis — is analogous to a building that’s on fire, with flames coming out of the windows,” he says. “Low-grade inflammation is more like overheated electrical wiring responsible for a smoldering carpet.” Fluid from a rheumatoid-arthritis patient’s affected joint contains 10 times as many white blood cells and immune-signaling chemicals as fluid from that of an osteoarthritis patient, he says.

Chronic low-grade inflammation is now known or strongly believed to be a driver of several other diseases once not associated with immune causation. Among them are cardiovascular disease, macular degeneration, type-2 diabetes and, lately, Alzheimer’s disease.

Next door to Robinson’s laboratory, in fact, sits the lab of neurology professor Tony Wyss-Coray, PhD. About a decade ago, Wyss-Coray began studies of neurons, laying the groundwork for the now widely accepted notion that chronic low-grade inflammation plays a key role in Alzheimer’s disease. His thinking exerted an important influence on Robinson, though Robinson was primed to find it persuasive. “As an immunologist my first impulse is to see everything as an immunological problem anyway, so it came naturally,” he says.

It’s not that Robinson came to the conclusion that injuries or age-related wear and tear have nothing to do with the development of osteoarthritis. Rather, he thinks that those events trip off what becomes a vicious cycle whereby the resulting low-grade inflammation causes further damage to the injured or worn-down joint, for example by breaking apart cells whose spilled-out chemical contents spell trouble to the indiscriminate, innate immune system. In susceptible individuals, that cycle persists, producing one Pyrrhic victory after another by the innate immune system over a person’s own joint tissue.

In a study published in Nature Medicine in late 2011, Robinson and his team demonstrated compelling evidence that inflammation is hard at work in osteoarthritic joints. First, they compared joint fluid from osteoarthritis patients with joint fluid from people without the condition. They saw numerous differences, including increased amounts of inflammatory proteins and significant upticks in the activity levels of several genes associated with the innate immune system.

In particular, the scientists noticed a general rise in the levels of a number of constituents of a 20-odd-protein complex called the complement system. This key component of the innate immune system is already plenty abundant in healthy people, accounting for about 4 percent of all the proteins in our blood. It consists of numerous closely coordinated proteins that serve as sentinels, snipers, snitches and switches amplifying or damping other players in the overall immune response, whose interactions unfold in a carefully orchestrated sequence called the complement cascade.

Next, Robinson and his associates induced osteoarthritis in experimental mice by injuring a cartilaginous shock absorber in their knees called the meniscus. (We have them, too. People with meniscal tears — about 50 percent of all of us over age 60 — are at heightened risk for osteoarthritis. Athletes and others who have meniscus surgery due to a torn...
Food allergies are a peculiar disease. Unlike other life-threatening conditions, the people they affect are completely healthy unless they are exposed to the allergen. They and their families live a life of unremitting worry, with the constant mental refrain that any mistake can be a fatal mistake. And there are always mistakes.

• For Michelle Sandberg, MD, and Marc Bodnick, it was the time their 9-year-old daughter Maya went on a skiing trip with her cousin. Her aunt let Maya pick out some malt balls from a candy bin after checking with the staff that none of the candies contained nuts, which Maya was allergic to. But the candies had been contaminated, and Maya’s face began to swell, her throat hurt and she vomited. Her aunt, an ER doctor, dosed her with Benadryl and she conked out for 14 hours.

• Kim Yates Grosso and Andy Grosso recall the time their 8-year-old daughter Tessa almost died when she ate a spring roll with “rice” noodles that turned out to be made of wheat, which she was allergic to, and she began to lose consciousness.

• When my son, Kieran, was a toddler he got hold of a cookie that contained egg and nuts, both of which he was allergic to. I grabbed it out of his hand just as he began to put the cookie in his mouth and rinsed his mouth out with water. I mistakenly believed then that an allergic reaction would be in proportion to the exposure to the allergen and, since he hadn’t bitten down on the cookie, I thought if he had

By Melanie Thernstrom
Allergen powders

The treatment retrains the immune system by gradually increasing the dose of allergy-inducing food.
any reaction, it would be slight. But as a precaution I decided to drive him to the hospital and sit in the parking lot. He was screaming energetically as we pulled out, but on the way he quieted and began to seem glazed. His face was white, spotted with crimson hives, and his lips were oddly blue. I didn’t know then that blue lips are a sign of oxygen deprivation, but I saw the terrible hives were spreading down his trunk and I stabbed him in the thigh with an EpiPen — an adrenaline-loaded syringe. (Adrenaline — also called epinephrine — interrupts the allergic reaction by relaxing airways and tightening blood vessels.)

I promised myself that day that nothing — nothing, nothing, nothing — would ever cross his lips again unless I had prepared it myself and, when he was released from the hospital the next day, I threw out all the processed foods in the house. But it was not his last reaction — by the time he was 3, he had needed an EpiPen three times.

In a severe allergic reaction known as anaphylaxis, the body misidentifies the protein of a harmless food as protein of a pathogen. The immune system mounts an attack that spirals out of control, turning into a terrible, self-sustaining feedback loop that — unless interrupted by a shot of epinephrine — causes tissues throughout the body to swell until the airways close and the heart and lungs fail.

Currently, about 8 percent of children in the United States and about 2 percent of adults have diagnosed food allergies. It’s a mysterious epidemic. The rate of food allergies has more than doubled over the past decade and appears to be rising, with the rate highest among preschoolers. (Many more people self-identify as food allergic, but they are actually suffering from food intolerances or sensitivities.) An estimated one-quarter of people with food allergies will have an episode of anaphylaxis in their lifetime. These rarely result in death — the fatality rate is hard to quantify because such deaths are often coded as cardiac ar-

rest — but they are the cause of 90,000 emergency room visits a year. Until recently, no effective therapy for the problem existed.

Maya, Tessa and Kieran were rescued from this life by being among the first children to be treated in a medical trial at Stanford of a treatment called oral immunotherapy, or OIT, led by Kari Nadeau, MD, PhD, associate professor of pediatrics at Stanford and an immunologist at Stanford Health Care and Lucile Packard Children’s Hospital Stanford. The treatment involves retraining the immune system through eating the allergen, beginning with microdoses and slowly increasing until the patient can safely eat a full serving of the food. Nadeau and her colleagues have recently discovered that the treatment changes the way patients’ genes function.

For decades, immunotherapy has successfully treated environmental allergies (giving injections of cat dander, tree grass and so forth), but has been considered too risky to try with food allergies. However, in the 1980s researchers in Europe experimented with food allergies and, in the past decade, trials conducted at Duke, Johns Hopkins, the Mount Sinai School of Medicine and other places showed that children could be safely desensitized to peanut, milk and egg. Each of these trials had involved desensitizing children to a single food at a time, yet a third of people with allergies suffer from more than one allergy.

In April 2009, Kim Yates Grosso attended a lecture on food allergies by Kari Nadeau. Afterward, she asked Nadeau what she could do for her daughter Tessa — severely allergic to milk, wheat, eggs, nuts, shellfish and some other foods. To desensitize Tessa to her major allergens one by one would take more than a decade. Nadeau promised to help her — and she did.

The two women worked together to raise the money to conduct a trial of OIT in which patients would be desensitized to up to five foods simultaneously. Yates Grosso led a volunteer coalition — the SAFAR (Stanford Alliance for Food
Allergy Research) Community Council. The council raised 95 percent of the money for the trials, with the balance made up by grants from the National Institutes of Health. So far, over 300 patients have undergone the therapy at Stanford; unlike other trials, Nadeau accepted both adults and pediatric patients. (Another 1,200 patients are on the waiting list.)

We began oral immunotherapy when Kieran was 2. The first doses — made from the protein of the allergens — are so small they look like sprinkles of cinnamon. Kieran, for example, began at 1.2 milligrams of each of his allergens: 1/7000 of an egg; 1/200 of a peanut, 1/200 of a hazelnut, 1/250 of an almond and 1/300 of a cashew. Every two weeks or so, he would return to the hospital for an “updose” in which he would try to eat a slightly larger amount. Every day at the same time, he would eat a dose at home and then we would anxiously monitor him for reactions for two hours. Like almost all the patients, he had reactions: He got hives on his face, his eyes became itchy, his tongue became swollen or he vomited. If he reacted, we would stay on that dose an extra few weeks until his body adjusted to it. (Reactions severe enough to use an EpiPen are rare; out of 309 patients, only 15 had a reaction in which an EpiPen was used.)

Tessa was in smaller, multi-allergy OIT trial in which patients received injections of an asthma drug, Xolair, that suppresses a critical antibody in anaphylaxis known as IgE. Because of this, Tessa was able to complete a treatment in just four months. After about two years of OIT, Maya switched to a Xolair trial and finished her treatment in eight months.

We pinched ourselves at Kieran’s fourth birthday, when we were able to serve chocolate cake made with eggs; on his first birthday, before we knew he had an egg allergy, a few bites of cake had put him in the hospital. Like most allergy parents, I had come to think of eggs and nuts — formerly favorite foods of mine — as positively evil and shunned them myself, even when I was traveling. Then suddenly the curse was lifted: We took down the sign on our front door forbidding them and we served peanut butter on toast for breakfast, almond and cashew butter sandwiches for lunch, hazelnuts for snack and eggs for dinner every night.

Indeed, we had to serve them (this is the catch of the treatment) because the patient needs to continue eating the food to prevent a return of the allergy. Suddenly the food that has always been strictly avoided has to be eaten every day — a surreal state of affairs. Patients must initially eat full servings of the food every day (the program is now experimenting with having patients eat them every other day instead). Eventually however, when their blood work and skin testing shows no traces of the allergy (which happens sometime between six months and three years), they can consume a much smaller amount — say a few peanuts, or the amount of egg in a muffin.

For some kids the food that once was poisonous to them still tastes like poison. Tessa, now 11, finds milk and eggs revolting — she will eat them only in the form of ice cream and egg chips. For a long time, Maya, 10, could consume her nuts only in a vanilla frozen yogurt and pineapple smoothie, but she eventually graduated to eating them straight.

“Nuts are hard to swallow,” she says. It could take her up to an hour to do so, and sometimes she would spread out eating the nuts over the entire day. “I chew them into a paste and then swallow them with water.”

When I say that I don’t find nuts hard to swallow, she thinks it over and says that, although she has been eating them with no physical allergic reaction for about nine months, “My brain makes my mouth not want to swallow them — it still feels like my throat is closing up.”

Because of kids’ aversion to their former allergens (not to mention the general difficulty of getting kids to eat anything their parents want them to), trials at other centers in the United States and Europe have lost up to a third of their patients. Nadeau and her team have gone...
to extraordinary lengths to avoid this. They bond with the patients and their families and are accessible to them day and night. When one boy decided he would take his dose only if Tina Dominguez, the program’s beloved physician assistant, would stay on the phone with him, she did it. Families can join a support group and work with a therapist to treat anxieties about eating the foods and a nutritionist to find creative ways to eat the food, such as placing nuts under the cheese on a pizza. Out of 309 patients, only 10 dropped out. (Three moved away, two suffered from unrelated health problems, two found taking the dose caused the child or their parent too much anxiety, and three were terminated because they failed to take their doses more than six days in a row.)

“For everyone who has stayed in the study, the treatment has been 100 percent successful,” says Nadeau. “It turns out that everyone’s immune system is capable of adapting — and surprisingly, it is as true of adults as children.” She and her team now have an eight-year study of OIT — the longest record in the United States — in which they found that everyone who was compliant with the treatment and continued to eat the foods has kept their allergies from returning.

What happens if the patients stop eating the foods altogether? Nadeau recently published the results of a withdrawal study, where 20 formerly peanut-allergic patients who had completed two years of OIT and were able to eat a full serving (1 tablespoon of peanut butter or 20 peanuts) without any reaction stopped eating peanuts altogether. After three months, more than half (13 out of 20) had regained the allergy to peanuts, although their reactions were no longer as severe. By six months, almost everyone (17 of 20) had regained the allergy.

**Why? How does OIT work — and why doesn’t it last without continuous exposure? Is it possible to understand at a molecular level what causes food allergies, and how OIT changes those processes?**

These are among the questions Nadeau and others at Stanford have been exploring. She is in the process of building an allergy research center that will bring together researchers and clinicians, geneticists, engineers, chemists, psychologists and nutritionists. Since October 2013, $14 million has been...
raised toward the center’s goal of $38 million.

“I am excited about the center because there is enormous clinical need,” says Lloyd Minor, MD, dean of Stanford’s medical school. “This profound increase in the incidence of serious food allergy that has occurred in a relatively short space of time is fascinating and deeply concerning at the same time.

“It is often times said and it’s true that Stanford nurtures innovation like no other place does.” Minor believes that “innovation today extensively builds on collaboration. One reason I’m so excited about the center is that, with Kari’s leadership, the center is establishing and leveraging interactions with departments around the entire university in truly innovative ways,” and he thinks the interdisciplinary approach is the best way to crack the code of food allergies.

The center will also research and treat food sensitivities and intolerances. “Our researchers are trying to understand why some people are skewed toward autoimmunity, like gluten intolerance or celiac, while others are skewed toward allergy,” Nadeau says. “Both involve misdirected immunity — one is dysfunctional and leads to autoimmunity, and one is dysfunctional in a very different way and leads to food allergy.”

Nadeau and her colleagues are also working on a type of immunotherapy that circumvents the need to eat the allergens. Patients receive injections in which the food protein — cloaked in a nanoparticle that will fool the body and thus avoid anaphylaxis — travels directly to the lymph nodes and re-educates the immune system. This approach has been tried successfully in Switzerland and Canada to treat allergies to grass pollen and cat dander, respectively.

Another focus of Nadeau’s work has been the development of a predictive food allergy test. Pilot studies have found that the test — which is being developed in collaboration with the laboratories of professor of microbiology and immunology Stephen Galli, MD, and professor of genetics Leonore Herzenberg, PhD — can identify food allergies with 95 percent accuracy using just three drops of blood from a newborn. The hope is that this test will eventually not only identify an allergy, but also predict how severe that allergy will be.

AN ENVIRONMENTAL CONNECTION?

Food allergies are thought to be largely genetic (one study with twins found them to be about 70 percent genetic and 30 percent environmental). The environmental theories include exposure to toxins, pollution, the Western diet and excessive cleanliness — “the hygiene hypothesis” — that has deregulated the immune system. But if food allergies are largely genetic, than how has there been such a rapid increase in food allergies?

Genetic changes used to be believed to take place only through natural selection, over vast periods of time. But the new field of epigenetics has discovered that, although the genetic code itself is fixed at birth, the environment can radically modify how genes behave through chemicals that attach themselves to the genes. Moreover, these acquired epigenetic changes can actually be passed on to later generations.

“What we discovered is that allergy treatment causes changes at the epigenetic level,” Nadeau says.

“As we learn the impact of these epigenetic influences we are really starting to see the richness and diversity of the interplay between our genetic makeup and our environment and the other things that impact the way our genes are expressed,” comments Minor, “and that’s fascinating scientifically and it’s incredibly important clinically.”

Nadeau and her colleagues focused on a type of white blood cell known as regulatory T cells, or Tregs. Tregs are called “peacekeeper” cells because they modulate the immune system and allergic response (preventing autoimmune disease, for example). Treg cells suppress other cells that are overactive or inflamed — a system that dramatically fails in the case of anaphylaxis. Her lab examined a gene within these cells called FOXP3. In the case of allergic subjects, she discovered FOXP3 had been disabled because it had become coated with methyl groups. Methyl groups (groups of three hydrogen atoms bonded to a carbon atom) affect different genes differently, but in the case of FOXP3, the methyl groups suppressed the gene, rendering it useless.

In a recent study, Nadeau compared blood samples from peanut-allergic patients who had been desensitized through OIT with blood from peanut-allergic patients who had not undergone the therapy. The untreated group had a high level of DNA methylation in the FOXP3 gene, but the patients who had undergone OIT had a low level. The therapy had caused the gene to demethylate and become active again. Indeed, the level of methylation in patients who had undergone OIT was so low as to be indistinguishable from that of people who had never been allergic.

Other work by Nadeau and her colleagues has found that environmental stressors such as tobacco smoke and pollution can cause FOXP3 to methylate.

People who have food allergies have a 65 percent chance of passing those allergies to their children. Will OIT change that? In animal models, the epigenetic changes last three generations — for good (in the demethylated FOXP3 gene), or for bad (exposure to toxins such as cigarette smoke and
infection sites are mouth, nose, lungs

first lymph nodes to respond

thymus

lymphatic system

bone marrow

spleen
INFECTION
The influenza virus enters through your eyes, nose or mouth and invades the cells lining your airway — the passage from your nose and throat and into your lungs. Its source was probably saliva droplets from an infected person. So far, you don’t feel sick.

A BY DAY 3
The first responders — the innate immune cells — flock to the scene. These blood cells act quickly by either killing infected cells or secreting proteins that recruit other blood cells to the infection site. Among the first to arrive are neutrophils and natural killer cells. Unfortunately, they kill some healthy cells too. This carnage is one reason your throat hurts.

BY DAY 6 OR 7
Prepped to attack, T cells travel from the lymph nodes through the blood vessels to the infection site. Other T cells remaining in the lymph nodes help B cells make antibodies with heightened affinity to the viral proteins. Antibodies are specialized proteins that circulate through the blood, stick to pathogens and trigger macrophages to engulf and destroy them.

DAYS 4-6
Macrophages and dendritic cells are also quick getting to the site of infection. While macrophages start killing infected cells, dendritic cells carry intelligence from the infection site to the nearest lymph node. The intelligence is in the form of bits of viral proteins displayed on the dendritic cell’s outer surface.

DAYS 7-10
Some B cells develop into plasmablasts. These enter the blood stream and release their antibodies, which attach to the viruses and neutralize their ability to invade cells. Macrophages make a meal of the viruses.

DAY 11
It’s likely the infection is now controlled. The immune response winds down. The cells that were activated start dying, though a small pool of memory cells linger, circulating in the blood or residing in the bone marrow.

A brief tour of the immune system
The most common entry sites for infectious agents are through breaks in the skin or through mucosal tissues, including the nose, lungs, mouth and gut.

The immune cells are various types of blood cells, all of which originate in the bone marrow. (Though before birth, for a short time blood cells originate in the liver.) Some blood cells migrate to the thymus, where they receive signals that help them become the various types of T cells.

The lymphatic system is a network of vessels that connects all lymph nodes in the body. It drains fluid from tissues and organs, and connects to the circulatory system. As a result, the lymphatic system is able to collect antigens from infectious agents (and toxins) and deliver them directly to the lymph nodes for uptake by dendritic cells and presentation to T cells.

The spleen cleans the blood of damaged immune cells and microbes tagged for destruction by antibodies. It also contains a full repertoire of immune cells ready to go to work. As such, if your first exposure to a pathogen is through the blood, the spleen will be the main site for immune response.

SOURCE: CRISTINA TATO, PHD
WRITING AND EDITING: ROSANNE SPECTOR
Imagine plunging into a hole from which you can’t escape.

A personal hell of mental illness, arriving without warning or known predisposition. And there you are, trapped. No diagnosis. No treatment. That was journalist Susannah Cahalan’s life in 2007. One minute a young professional charging uphill in the competitive New York City media world — the next minute collapsing into an inner state that defied clinical clarity. A descent from normalcy to catatonia and near death.

With the precision of an investigative journalist, she reconstructed what happened in her memoir, Brain on Fire: My Month of Madness. One reviewer wrote of the New York Times best-seller that Cahalan “describes in chilling detail her descent into an inexplicable madness…. It’s a story of everyday heroes — her family, friends and the determined doctors who steadfastly fought for her.”

Cahalan knows the terror of not knowing what ails you and dedicates the book to those without a diagnosis. Stanford Medicine executive editor Paul Costello spoke to her from her office at the New York Post where she’s back at journalism full time. “I do book reviews and a lot of science and health-related articles, which I really enjoy now — something that happened after I was sick.”

Paul Costello: One day you are a carefree New York journalist; the next day you’re consumed by a raging illness of unknown dimensions. What happened?

Susannah Cahalan: It started slowly at first, and then very quickly escalated. At first, it was just feeling off, just like having a bad day. Then, many bad days in a row. I couldn’t concentrate at work. I just thought, “Oh, I have some kind of flu, or I’m just in a bad mood.” But I also started getting paranoid. Looking back now, I didn’t connect the two and realize that that was the beginning.

Costello: As the illness proceeded you became more consumed with paranoia. You thought you were having a breakdown.

Cahalan: The lethargy was first. Then, I started noticing that I
couldn’t control my emotions. One second, I would be the happiest I’ve ever felt in my life. Beaming. Very manic. The next moment, I’m crying hysterically. I was having some cognitive issues as well. I found I could no longer hear what someone was saying and actually translate it into words.

COSTELLO: You endured a long period of misdiagnosis and no diagnosis. What’s it like to have a medical condition that you can’t explain?

CAHALAN: It is utterly terrifying and lonely. I feel for people who don’t have a proper diagnosis. It felt very claustrophobic. I was experiencing these emotions and feelings. I was hallucinating. You feel trapped inside your body. When no one can give you an answer, it just completely flips your worldview upside down.

COSTELLO: As the illness progresses, no one can diagnose it?

CAHALAN: On paper, I am perfectly healthy, but in person I can’t even put together a sentence. I am garbling words. I’m drooling. I can hardly even swallow liquids. Every panel of tests you can possibly think of was conducted on me. Nothing’s coming back. I think for doctors who face these situations it’s very frustrating.

COSTELLO: When did your illness begin to get some clinical clarity?

CAHALAN: Without a doubt it started with Dr. Souhel Najjar, a neurologist and epileptologist at NYU. He was called in on the case because he had this reputation as a maverick. He began with a wide-ranging health history — three handwritten pages of notes. At one point he turned to me and he had this eureka moment and he thought: “I’m going to do a simple test and see what happens.” He handed me a piece of unlined paper and asked me to draw a clock. It took me a few times to get the circle. Finally I drew a circle and very slowly I drew each number in. When I was finished, Dr. Najjar was so excited by what he saw. I had squished all of the numbers on the right side of the clock so that the 12 landed where the 6 should have been. It revealed to him that my brain was not seeing the world in the way it should. It was suffering from visual-spatial neglect. I was just ignoring the left side of my universe. That clock was proof to him that this was an organic disease — a neurological condition. It gave him the confidence to move forward and do a brain biopsy to confirm that.

COSTELLO: At that point he told your parents that essentially your brain was on fire?

CAHALAN: Yes. That was his layman’s term of saying there was serious inflammation in my brain and there was impairment there. Within a week of that I received the diagnosis of anti-NMDA receptor encephalitis.

COSTELLO: What have you learned about your illness?

CAHALAN: Anti-NMDA receptor autoimmune encephalitis is one of over 13 different types of autoimmune encephalitis. With anti-NMDA, the body’s immune system targets and attaches to the NMDA receptors in the brain. NMDA receptors are located all over the brain — the highest concentrations in the frontal lobes and the hippocampus. It explains why you have a lot of memory deficits and behavioral changes. The disease was only discovered in 2007. I was treated in 2009 and was one of the first 300 patients to be diagnosed with the disease.

COSTELLO: How much did good luck play a part of your survival?

CAHALAN: Luck that you ended up at the right institution for your care. Luck that your parents pursued a diagnosis and treatment with a vengeance. Luck that you ended up at the right institution for your care.

COSTELLO: Are you a different person now?

CAHALAN: My whole life is broken up into pre- and post- this disease. It has changed everything. It has changed my goals in life, where I put my energies and my interests. It has changed the way I appreciate life too. You can’t help but come away from a near-death experience and not look at your life differently.

COSTELLO: Now five years after your illness, is there anything you’d like to say to the medical community?

CAHALAN: Dr. Najjar shows the power of the patient history, the patient narrative and how important it is to listen to patients and families. The awareness that autoimmune encephalitis exists is extremely important. I have now listened to many people’s stories who have had this disease. People who are in a coma for six months, people who are very close to death, people who look like they will never return, who come back. Devastated at its height, you can recover. My final suggestion is that this disease required the cooperation of many different disciplines. There’s not just one doctor. It’s really important to learn how multidisciplinary care is really important to patient success.

COSTELLO: You never really discovered the cause of your illness. Is there a deep fear of not knowing?

CAHALAN: There is a fear. There is a relapse rate too; I think it’s about 18 percent. For the rest of my life it is a little bit of a specter following me around, the fear of it happening again. It doesn’t change the way I live my life, but it does follow me.

COSTELLO: I understand Hollywood’s interested in a film. Are you ready for your close-up?

CAHALAN: Oh, gosh. (laughs) Keep your fingers crossed for that. It’s been optioned by the actress Charlize Theron. She’s the producer. Dakota Fanning is slated to, it’s so bizarre to even say it, but yes, Dakota Fanning is attached to star as me.

This interview was condensed and edited by Paul Costello.
THE SWASHBUCKLER

HOW MARK DAVIS SNARED A GENE AND EXPLAINED ONE OF OUR IMMUNE SYSTEM’S GREATEST MYSTERIES

THE YEAR WAS 1980, AND MARK DAVIS, PHD, FRESH OUT OF GRADUATE SCHOOL, WAS HURLING HIMSELF ATHWART ONE OF THE DAY’S BIGGEST BIOMEDICAL MYSTERIES. AT HIS NEW JOB AT THE NATIONAL INSTITUTES OF HEALTH, HE HAD THE YOUTHFUL AUDACITY TO TRY TO RESOLVE THIS PARADOX: The entire human genome consists of a mere 25,000 genes or so, yet the number of different shapes those all-important immune warriors called T cells can recognize is on the order of billions. How can such a relatively tiny number of genes provide all the protein-making recipes necessary for T cells to be able to identify — and spearhead attacks on — invading pathogens and cancer cells? • Fueled by curiosity and a competitive spirit, Davis and a small team under his command solved the first part of the puzzle of T-cell diversity: They identified the gene for one of two protein chains that make up the surface receptor overwhelmingly responsible for recognizing all those pathogens and cancer cells. And they figured out how it works. Within a year or two, after Davis had joined the faculty at Stanford (where he is now director of the school’s Institute for Immunity, Transplantation and Infection), he and his teammates nailed the gene for the other protein chain. • With the T-cell receptor gene in hand, scientists can now routinely sort, scrutinize, categorize and utilize T cells to learn about the immune system and work toward improving human health. Without it, they’d be in the position of a person trying to recognize words by the shapes of their constituent letters instead of by phonetics.

By Bruce Goldman
YOUNG AND CRAZY

When Davis began at the NIH, molecular biology was in an embryonic state and lacked the sophisticated and user-friendly equipment (such as high-speed gene sequencers) that today’s graduate students take for granted. But Davis, who earned his PhD at the California Institute of Technology, was receptive to the new DNA discovery tools that were coming into use.

“I had the good fortune of being young and impressionable,” says Davis, who is now the Burt and Marion Avery Family Professor in Stanford’s Department of Microbiology and Immunology. His early-adopter attitude at CalTech in the late 1970s placed him at the forefront of an earlier discovery concerning how the genes coding for antibodies — produced by another set of immune-system heavyweights called B cells — frequently reshuffle themselves during cell division. This hugely increases the diversity of antibodies the B cells produce.

However, Japanese scientist Susumu Tonegawa, PhD, got to the finish line first and ended up winning the 1987 Nobel Prize in Physiology or Medicine for his effort.

It turns out that B cells had much to teach Davis — and the entire field of immunology — about T cells. T cells and B cells, working in concert, deserve much of the credit for the vertebrate immune system’s knack of carefully picking bad guys of various stripes out of the lineup and attacking them. Together (along with the various molecules they produce and secrete), they comprise the highly selective so-called adaptive immune system. (A more primitive, loose-cannon arm of the body’s defensive armory, called the innate immune system, resides in all multicellular animals.)

While quite similar in many respects, B cells and T cells are more like fraternal than identical twins. B cells are specialized to find strange cells and strange substances circulating in the blood and lymph. T cells are geared toward inspecting our own cells for signs of harboring a virus or becoming cancerous.

So it’s not surprising that the two cell types differ fundamentally in the ways they recognize their respective targets. B cells’ antibodies recognize the three-dimensional surfaces of molecules. T cells recognize one-dimensional sequences of protein snippets, called peptides, on cell surfaces. All proteins in use in a cell eventually get broken down into peptides, which are transported to the cell surface and displayed in molecular jewel cases that evolution has optimized for efficient inspection by patrolling T cells.

Somehow, our inventory of B cells generates antibodies capable of recognizing and binding to a seemingly infinite number of differently shaped biological objects. Likewise, our bodies’ T-cell populations can recognize and respond to a vast range of different peptide sequences.

So how does the T cell do it?

Ask a B cell.

GAME ON

By the time Davis began his NIH postdoctoral fellowship, in the lab of prominent immunologist William Paul, MD, the field had grasped how B cells manage to generate so many different types of antibodies. By studying the genes that produce antibodies, immunologists had learned not only that these genes contain a number of “mix and match” component sequences capable of rearranging themselves when B cells divide, but that some stretches along those genes are particularly susceptible to mutation. This further boosts the variety of antibody shapes in the resulting overall B-cell population, with a corresponding increase in the range of different pathogenic features antibodies can latch onto.

Although many early “T-cell receptor” sightings had turned out to be mirages, multiple labs had converged on a likely candidate protein that was composed of two separate pieces or subunits, designated the alpha and beta chains. There were still many doubters, but the protein work fueled an intensive hunt for the genes that gave rise to these two protein subunits.

“Earlier thinking had been that a T cell must use part of the antibody gene to produce its receptor for features of foreign or altered cells. But this had been shown not to be true,” Davis says.
Davis, at that time almost the only person in his immunology department at NIH making intensive use of the new molecular-biology techniques, had an idea for how to fish the gene for the T-cell receptor out of the sea of DNA that composes our chromosomes: Check for differences in activity between T and B cells’ genes by subtracting activity levels of each gene in one cell type from those of the corresponding gene in the other type. “This approach had mainly been used to look for differences between widely different cell types, for example liver versus kidney cells,” he says. “T cells and B cells are very similar in appearance, and they interact with each other. They seemed to have a lot in common. But T-cell receptor genes are active only in T cells. I thought looking at the differences between B and T cells might yield a relatively small number of genes to look at.”

He also knew the T-cell receptor, which clearly has to sit on the T cell’s surface membrane to be useful, would wind up being membrane-bound. And he suspected that its gene might be capable of rearranging itself, shuffling its component sequences during cell division like the genes coding for antibodies — so it would have to have highly variable as well as fixed stretches.

Paul was intrigued by his approach and made Davis the informal head of a small lab. Stephen Hedrick, PhD, a fellow postdoc and novice molecular biologist, wanted to learn the new technology and so joined the enterprise. By then Davis had already shown that 98 percent of the genes in B and T cells were similar or the same. Focusing on the 2 percent that were different might be where the T-cell receptor genes lay.

One night at a party of some CalTech buddies who had also come to work at the NIH, Davis spotted a research paper on a bookshelf, took a look, and read of a technique that would enable him to restrict his search to only those genes coding for membrane-bound proteins. And he had already mastered an existing workhorse method for checking for rearranging genes.

By early 1983, they had found 10 promising T-cell genes that both were active in T cells but not B cells and coded for membrane-bound proteins. In nine of them, Davis and Hedrick saw no gene rearrangement. Things looked grim, but they didn’t give up, hanging their hopes on the last one. It was giving them a hard time, though. Determining whether it was prone to rearrangement took several months.

“We knew we were in a race against time,” says Davis. “Other groups were closing in. Plus, I’d been hired by Stanford but was dragging out my stay at NIH because we were getting so close.” The breakthrough came that July Fourth weekend when Hedrick was taking his family to the zoo and Davis and Yueh-Hsiu Chien, PhD, his wife and colleague (now a professor of microbiology and immunology at Stanford), were driving to his dad’s home in Connecticut. “Steve wanted to stop in at the lab to nurse the ongoing experiment. He left his family in the car for what was supposed to be a minute or two,” says Davis. “He checked on that last gene, and kept his family waiting in the car for a long time.” This candidate gene practically screamed, “Look, Ma, I’m rearranging.” Hedrick called Davis.

“I told my dad, ‘Something big has happened. I’ve got to get back to the lab.’” And he and Chien returned to Bethesda that night, driven by the excitement of discovery and the need to beat the competition to the punch.

Soon afterward, they moved to Stanford and Davis set up his new lab, with Chien playing a major organizing role. In August 1983, Davis flew to China and delivered talks in Beijing and Shanghai about his T-cell work that the attending Chinese scientists (who were just emerging from the Cultural Revolution) had difficulty grasping, because what he was doing was so different from classical immunology. But a week later he skipped over to Kyoto, Japan, and finagled an unscheduled talk before the biggest international conference in immunology: the once-every-three-years International Congress. His report there was a sensation. The audience
understood that Davis and his colleagues had bagged the gene coding for one of the two protein subunits composing the T-cell receptor, later identified as the beta chain. They were halfway home.

A little over half a year later, Davis and his colleagues finished writing up their beta-chain gene discovery for *Nature*, publishing two articles in March 1984.

The pursuit of the alpha-chain gene, like that of the beta-chain gene, took place against fierce competition, including from MIT’s Tonegawa, who actually managed to sweet-talk Davis into sharing his protocol for isolating T-cell-specific genes.

This time, Davis had a leg up. “We had a postdoc, Nick Gascoigne, from England whose father told him that if we could get our manuscript on a plane to London, he would have his office assistant drive to Heathrow Airport, take it straight to *Nature’s* London office and plop it on the editor’s desk. We had seven papers published in *Nature* in 1984. We’d load the manuscripts onto DHL flights at 7 p.m. For the first ones, it was only six days from submission to acceptance.

“Meanwhile, we were getting all these invitations to Japan. So we went to one meeting, and Tonegawa was walking around, looking proud. ‘We have the alpha chain,’ he told us. ‘Do you?’”

“I told him, ‘No.’ He was happy about that,” Davis recalls.

During his talk, Tonegawa showed a slide depicting a number of short horizontal lines. Those lines represented sections of genes, and their relative positions constituted what, in those dark days before the advent of easy gene sequencing, passed for a “fingerprint” of that gene’s structure. The gene depicted in this slide was the one Tonegawa was so sure was the alpha-chain gene. On the plane home, Chien told Davis, “You know, that kind of looks like one of the genes we’ve been analyzing.”

“So I said, ‘OK, let’s assume that one is the alpha-chain gene, and work night and day to finish figuring out its structure and how it works.’” Davis recalls. “And we did.” So much so, in fact, that some colleagues, having passed their lab one night and noticed that the lights were out, told them later, “We thought it was a power failure.”

“It turned out to be the alpha chain,” Davis says. “We wrote yet another paper in a rush, and did another Heathrow run. A week later I get a call from the *Nature* editor saying that the journal had just received Tonegawa’s manuscript, and that he was very unhappy that ours got there first. I thought: This is divine justice!”

Their isolation of the gene coding for the alpha chain of the T-cell receptor was published in *Nature* that autumn. Tonegawa was quite magnanimous in defeat, says Davis.

**DON’T LOOK BACK**

Since those knock-down, drag-out days, Davis has made a number of important contributions to immunology — for example, at Stanford in the 1990s he developed a breakthrough methodology that can determine, from a blood sample, whether a given individual’s immune system has previously encountered a particular molecular shape (characteristic, say, of a pathogen or tumor).

But in recent years, Davis has broadened his horizons. Notably, he has been grappling with the immunology of human beings. A huge amount of immunological research over the past 50 years has been conducted on mice. “We’ve cured cancer and autoimmune disease in mice a whole bunch of times,” he says. But mice and humans diverged from a common ancestor some 60 million years ago, and a mouse’s immune system can tell us only so much about our own.

Getting a handle on how real, live people’s immune systems respond requires research on real, live people. To this end, Davis was instrumental in securing tens of millions of dollars to establish a Stanford center dedicated to measuring thousands of variables in human blood samples in order to better characterize the human immune system in all its complexity.

“T-cell recognition is a huge part of immunity,” he acknowledges. “Knowing what T cells recognize and when they recognize them is crucial. But the problems of human immunity are much bigger than T-cell receptors. I’ve sunk 30 years into T-cell receptors. But I’m thinking, is that all I want to do? I think I’ve still got a few more good experiments left in me.”

— Contact Bruce Goldman at goldmanb@stanford.edu
THE BUDDY SYSTEM

VETERANS HELP VETERANS COMBAT PTSD
ON A STIFLING HOT MORNING IN APRIL 2008 IN THE KIRKUK PROVINCE, specialist Jayson Early left his military base and headed to a nearby Iraqi police station on his first field assignment. During the subsequent 14 months he served in the country, Early worked both as a military policeman training Iraqi police forces and as a gunner manning the turret atop a Humvee. But for this assignment, he was sent on an innocuous-sounding public affairs errand to photograph a burned-out truck parked at an Iraqi police station.

“I was 19 years old,” he says, telling the story six years later, now a father of two and living where he grew up, in the small town of Hughson, near Modesto in California’s Central Valley. “I walk up to the truck with my camera thinking there is nothing there.” Then he looked inside.

“There were body parts, coagulated blood, hair all over,” he says, pausing. “I just wasn’t expecting it.” An Iraqi family had been executed in the vehicle, presumably by insurgents. Early had gone through intense military training to prepare for moments like these. He blocked any emotions. He followed orders, clicked the camera and moved on. It wasn’t until years later that he realized just how permanently those images, and many more like them, had burned into his brain.

Like so many of the 2.6 million Iraq and Afghanistan war veterans who have returned home over the past decade, Early brought his combat training back with him to the States. The hypervigilance, the

by Tracie White

PHOTOGRAPHY BY TIMOTHY ARCHIBALD

VETERANS JAYSON EARLY, LEFT, AND ERIK ONTIVEROS.
emotional numbness; the training that kept him alive on the battlefield didn’t serve him well in civilian life. The absence of the adrenaline high of battle and the closeness to combat buddies left him detached and lonely. Anxiety in crowds and flashbacks triggered by fireworks or screaming children led to isolation and self-medication with alcohol and cocaine. He had severe post-traumatic stress disorder but he didn’t know it.

“You went through hell essentially and made it out visibly unscathed,” he says, remembering when his deployment first ended and he was shipped to Germany, then home. “I was young. I just wanted to go home and have a normal life. I didn’t even realize PTSD was a real thing.”

“You went through hell essentially and made it out visibly unscathed,” he says, remembering when his deployment first ended and he was shipped to Germany, then home. “I was young. I just wanted to go home and have a normal life. I didn’t even realize PTSD was a real thing.”

For years, he pushed away family and friends who tried to help. “I coped by drinking large, copious amounts. I’d have trouble sleeping. I’d get angry and just drink that away.”

When he finally sought help for depression, PTSD and multiple addictions, it wasn’t a psychiatrist or a psychologist or a licensed counselor who broke through to him. It was his fellow veterans.

“Friends might say they understand but they don’t,” Early says. “It means a little more when a vet reaches out and says, ‘Hey I know what it’s like.’”

THE NEED TO CONNECT the waves of veterans recently returned from the war zones of Iraq and Afghanistan with mental health services has grown more urgent as the disturbing mental health statistics rise. Reported deaths from suicides are now higher than reported deaths from combat; 40 percent of the returning veterans report having difficulty adjusting to civilian society, according to a recent RAND Corporation
study. Twenty percent of veterans—almost half of whom won’t seek treatment—suffer from clinical PTSD or major depression often leading to addictions and self-isolation.

Because the stigma associated with seeking out mental health care is particularly strong within the military, veterans are one of the most difficult populations for mental health professionals to reach.

“It’s wicked difficult to treat anyone with moral injuries from combat in the traditional medical model,” says psychiatrist Jonathan Shay, MD, an expert on PTSD, who coined the term “moral injury” to refer to the psychological, cultural and spiritual aspects of combat trauma. “It destroys the capacity for trust. What it leaves is despair, an expectation of harm, humiliation or exploitation, and that is a horrible state of being.

“The traditional medical model — in an office with the door closed — is the last thing they want. I’m convinced that’s where peers come in. Peers are indispensable. It takes a community to heal these wounds.”

To bridge this care gap, researchers at the Stanford University School of Medicine and the Veterans Affairs Palo Alto Health Care System have designed a pilot program based on veterans supporting veterans. Psychiatrist and researcher Shaili Jain, MD, has spearheaded the effort, aptly called the Peer Support Program, hiring and training two veterans as certified peer support providers who travel to VA health clinics in Sonora, Modesto and Stockton — rural and underserved areas in California that are home to many returning veterans. The program, supervised by Bill Boddie, a licensed clinical social worker, was modeled after the VA’s use of peer support providers for the treatment of the seriously mentally ill.

Peer support providers connect with veterans in ways that other mental health professionals can’t, Jain says. Through phone calls and on-site support groups, they give advice on how to survive the day-to-day challenges of readjusting to civilian life based on their personal experience. Their role isn’t to provide psychiatric treatment, but to help break down the barriers that are blocking other veterans from getting the care they need. With thousands of veterans across the country suffering from PTSD relying on the Department of Veterans Affairs for care, integrating peer support into treatment is growing in popularity, Jain says.

“In addition to conducting research, Jain works as a clinician, providing psychiatric treatment to veterans in her small, closed-door office at the Menlo Park VA. “The very nature of the disorder makes veterans really mistrustful. The last person they may want to see is, well, somebody like me sitting in an office who comes from an entirely different world.”

A GOOD CONNECTION

In the years after his deployment to Iraq ended, Early found daily life a constant struggle. He tried to live a “normal” life. He got married, had two children. But flashbacks, sleeplessness and guilt consumed him. He turned to drinking and drugs. A minor stroke during his posting to Fort Riley, Kan., from Germany, ended his career in the military, and he moved back home to California, bringing his young family with him. It was his dad, also a veteran who had struggled with PTSD, who first broke through to him.

Concerned about Early’s self-isolation, his anger and drinking, his father introduced Early to one of the two certified peer support providers working in Modesto, former U.S. Marine Staff Sgt. Erik Ontiveros.

“One day my dad grabbed me and said, ‘Get dressed. We are going to Erik’s support group,’” Early says. The two drove to the Modesto VA clinic and joined the Friday morning support group. “I didn’t talk the first few sessions. I was still in that denial phase. I was thinking, ‘This is just a bunch of bull. I don’t need this, I’m fine.’ Then the other vets started talking about some stuff, and it was like ‘Holy crap!’”

Sitting in a circle with a small group of other Iraq and Afghanistan veterans, a light bulb finally began to flicker...
in Early’s brain. Maybe those 14 months in Iraq of piecing together the body parts of Iraqi civilians blown to bits, of constant adrenaline-pumping fear, of near-death experiences, bullet dodging, bomb scares — maybe all that and more could have caused some mental wounds. Maybe death and violence upfront and personal could trigger years of anger, depression, drinking and drug use even if he hadn’t been physically wounded. Maybe he did need help.

This is where Ontiveros, a fellow veteran who had been through similar experiences and received help for his own PTSD, stepped in. Ontiveros has 10 years’ experience as a Marine with three deployments to Iraq. He had been through treatment and was four years in recovery when Early joined his support group. Ontiveros knows how hard it can be for a veteran to ask for help.

“A lot of these vets don’t know there’s anything like this kind of support out there,” Ontiveros says. “They just sit alone in their garage drinking beer. I know what that’s like. I used to just sit at home drinking. I wouldn’t get off the couch. I’d go days without shaving, without taking a shower.”

Ontiveros, 33, went from being a combat vet to a stay-at-home dad virtually overnight. He left the Marines in 2009 and returned to the States for the birth of his first child. Back home he began experiencing unexpected flashbacks, anxiety, guilt. He found he missed the Marines intensely. In 2010 he admitted himself into the psychiatric ward at the Palo Alto VA for depression, PTSD and alcohol abuse, then attended the PTSD residential rehabilitation program at the Menlo Park VA for five months. When he got out, he worked as a volunteer with other veterans still in the program as part of his own therapy. That’s where Jain found him, trained him and hired him.

“I always share my own personal struggles, some of the processes I use to deal with them,” Ontiveros says about how he leads group sessions in Modesto and Stockton. “We’re just focusing on the here and now, our everyday lives — whether that may be getting out of the house, or talking to civilians, or navigating resources within the VA. It’s about adjusting to being outside the military. We have to learn how not to be military.”

It’s the shared experiences that make it work, he says. Veterans come from a military culture that the outside world doesn’t understand. They innately trust each other.

**VALIDATION**
THE NUMBER OF VETS who have been reached by the program’s peer support providers — Ontiveros in Modesto and Stockton, and Guy Holmes in Sonora — is evidence that the program is working, Jain says.

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**A POWERFUL SECRET**
WHEN A FAMILY TRAUMA IS DISCOVERED, A CAREER SWERVES TO HELP THOSE WITH PTSD

In 1947, when the father of Stanford psychiatrist Shaili Jain was just a 10-year-old boy growing up in India, a series of personal tragedies and historical events tore apart his family.

The partition of the British Indian Empire into the two nations of India and Pakistan resulted in one of the greatest forced migrations in human history. The chaos that followed resembled civil war, and the death toll of men, women and children exceeded half a million. Jain’s paternal grandfather was stabbed to death on the Pakistan side, while his children escaped across the border to India. Left an orphan with no money, Jain’s father eventually immigrated to England where he raised a family of his own.

Jain, MD, was born and raised in England, where she attended medical school, then immigrated to the United States to practice psychiatry. It wasn’t until a road trip with her father in 2007, traveling in a minivan from New York back home to Milwaukee, that he disclosed to her the full truth of their family history, which subsequently changed the course of her career.

“My family legacy was one of tragic loss and terror but it had been buried for decades,” Jain says.

Two years later, motivated by her father’s story, Jain left her comfortable private practice in Milwaukee and moved her own family cross-country to start a fellowship at the Veterans Affairs National Center for Post Traumatic Stress Disorder in Menlo Park.

“I realized that, at some level, those people who have had their lives torn apart because of traumatic incidents, in a way they’re my people,” she says. Jain is now a clinical assistant professor of psychiatry at Stanford and the program director for peer support services offered through the VA Palo Alto Health Care System.

“I became committed,” she says, “to advancing the science of PTSD and unlocking the secrets of what fosters human resilience in the aftermath of unspeakable traumas.”
“Veterans are voting with their feet,” she says. Nearly 200 at-risk veterans, those who are traditionally the hardest for mental-health providers to reach, have enrolled in the program since its inception nearly two years ago. Participant feedback has also been positive, with 75 percent of veterans reporting the service as helpful.

“We’ve been publishing on the concept of peer support in general and on the specific program,” says Steven Lindley, MD, PhD, associate professor of psychiatry at Stanford and the program’s leader. As Jain’s mentor during her fellowship at the Veterans Affairs National Center for Post Traumatic Stress Disorder in Menlo Park, he was familiar with her desire to advance the research of peer support and involved her when the Michael Alan Rosen Foundation became interested in funding the Peer Support Program.

“We’ve shown that there’s more of a bonding with the peer support specialists than with psychologists or psychiatrists,” says Lindley, director of outpatient mental health for Veterans Affairs Palo Alto Health Care System. “They’re providing the glue that helps these clients stay in treatment.”

Jain has spent the five years since she left a private practice in Wisconsin and traveled cross-country to start the PTSD fellowship researching, writing and publishing on peer support. It was the discovery of her own father’s hidden story of loss and trauma during the 1947 partition of India that changed her career trajectory and set her on a path committed to advancing the science of PTSD. [See sidebar, opposite.]

“It just moved me that I am from people who have had their lives torn apart because of traumatic incidents,” she says. “Now, as a doctor and a scientist, I have this platform. Doesn’t it make sense that I use it to help others torn apart by trauma?”

Peer support as treatment for individuals with PTSD isn’t a new concept, Jain says. But there has been little published in the scientific literature to support it as evidence-based care. She has set out to help change that, to add to the body of evidence that would encourage the use of peer support nationwide. The goal is to eventually test the effectiveness of the Peer Support Program in a controlled study, Jain says.

Another Stanford PTSD expert and psychiatrist, David Spiegel, MD, helped write the definition of the disorder for the DSM-IV and DSM-V, the handbook of mental health diagnosis for health-care professionals. He is not involved with the Peer Support Program, but is not at all surprised by its success. He saw how peer support helped Vietnam War veterans during the 1970s when he worked at the Palo Alto VA.

“The very thing that alienates these vets from society is their ticket to peer counseling,” Spiegel says. “They feel they don’t fit. The very thing that makes them feel excluded on the outside is an instant bond and connection with other vets. That’s a powerful thing.”

THE IMPORTANCE OF BEING UNDERSTOOD

That bond with other veterans is exactly what kept Early coming back to the support group in Modesto. But he was still struggling.

“At first, Jayson was just sitting back and hearing everybody else’s stories,” Ontiveros says. “Then he started opening up and talking about his feelings. His big thing was adjusting to civilian life and communicating with his wife.”

After about a month of support group sessions led by Ontiveros, Early says he began to realize that he wasn’t the only veteran struggling to deal with civilian life, a realization that helped break down his own barriers to the possibility of getting additional psychiatric help.

“Those other vets in the group around my age, they were opening up,” Early says. “They were talking about day-to-day hassles. Dealing with crowds at the grocery stores or dealing with somebody that’s incompetent at the drive-thru. Your fuse is so short to begin with, something so minor sets it off. Normal hassles that a normal person wouldn’t get upset about. I’m the kind of guy, at the grocery store if somebody bumps into me, and doesn’t say sorry, I’m going to slam into their cart and just walk away.”

Early felt a connection with Ontiveros, who told the group about his own daily struggles to communicate with his wife, to control outbursts of anger, to be willing to ask for help. Ontiveros informed the group about the other mental health services available to them. He gave tips on how to navigate the VA bureaucracy, on how to open up and trust someone other than another veteran.

“That first year back in civilian life, I really battled myself,” says Ontiveros who was a platoon leader when he left the Marines. “I felt like shit because I left my Marines. They were my family. I felt like I abandoned them. Sometimes I would phone some of them and break down and cry and say that I was sorry that I failed them as their leader, as their platoon sergeant, that I was sorry that I couldn’t be there for them.

“A lot of them understood, and they assured me that it was a good choice. That I had to be there for my family, that I had to move on.”

And Ontiveros understood what it was like for Early CONTINUES ON PAGE 53
RESEARCH

RE-EXAMINED

NEW CLAIMS
GET ALL THE ATTENTION,
EVEN IF THEY’RE EXAGGERATED
OR FALSE

BIOMEDICAL SCIENCE UNCOVERS NEW DISEASE GENES, DETERMINES WHICH CANCER TREATMENTS WORK AND HELPS US DECIDE WHAT TO EAT AND HOW MUCH TO SLEEP. BUT A CONCERN IS RISING AMONG BIOMEDICAL LEADERS: WHAT IF THE STUDIES ARE WRONG? • An emerging breed of scientists known as “meta-researchers” is taking a close look at how modern science is conducted and reported. Their analyses are sobering. They suggest that despite researchers’ best intentions, much of the published evidence guiding the health advice dispensed by physicians or on the evening news is misleading — or just plain false. • It’s not that the age-old scientific method — in which researchers make predictions about how the world works and collect data to test them — is flawed. If a hypothesis is true, subsequent experiments should confirm it. If it is false, it should falter in further testing and eventually fall out of consideration. • Reproducibility and self-correction are core features of this process. Yet to advance their careers, scientists feel compelled to publish often — and it looks better to report a new discovery instead of painstakingly confirming what another lab has reported. As a result, unvalidated claims dominate the biomedical literature while null findings — those that fail to support a hypothesis — lurk within file cabinets and hard drives.

Leaders of the U.S. National Institutes of Health acknowledge this problem, and in a January Nature commentary, NIH director Francis Collins announced plans to explore how to enhance research reproducibility. That same month, a special issue of The Lancet featured five papers outlining steps to boost value and cut waste in biomedical research. And meta-researchers around the globe are devoting serious attention and resources toward the cause.

They include John Ioannidis, MD, DSc, and Steven Goodman, MD, PhD, who co-direct the new Meta-Research Innovation Center at Stanford, known as METRICS. “Meta-research is not a recognized field, in a sense. There are no departments, yet many people work in this area,” says Goodman, associate dean for clinical and translational research at Stanford.

By Esther Landhuis

ILLUSTRATION BY KOTRYNA ZUKAUSKAITE
“Our goal is to help define meta-research as a coherent and cohesive field of scholarship and policy action.”

It’s that second component they hope will drive change. “Right now a lot of what’s done is research. There are fewer groups translating the research into actual research policy,” Goodman says. “We see METRICS as a research-to-action center where we identify key areas in which different policies might help, and work to develop those policies or develop the evidence base behind them.”

METRICS working groups will focus on improving the quality of peer review, educating scientists and trainees on statistical methods, facilitating data sharing and openness, and shifting funder and academic incentives to promote research reproducibility.

**A MEGA META-RESEARCHER**

Ioannidis plunged into the “research of research” after seeing dozens of heart patients receive angioplasty during his internal medicine residency at Boston’s New England Deaconess Hospital in the early 1990s. Known as percutaneous coronary intervention, or PCI, the procedure helps clear clogged arteries. Curiously, though, many who received the intervention had arrived at the hospital stable and symptom-free.

“I was often asking myself, ‘Why are we doing this?’ or ‘Why am I being told to do this test or give this treatment?’ It was not clear to me,” says Ioannidis, a former college math whiz in Athens, who turned to medicine “to have direct impact on human beings.” Medical decision-making seemed largely intuitive and expert-based — “mostly gut feeling and a little bit of tradition,” recalls Ioannidis, now a professor of medicine and of health research and policy at Stanford. Today he has more than 700 papers to his name. In his work, he has collaborated with scientists from various disciplines who share similar interests and concerns, ranging from clinical investigators, epidemiologists, neuroscientists, psychologists and geneticists among others.

The head-scratching angioplasty procedures during his residency prompted Ioannidis (pronounced yo-a-NEE-dees) and colleagues many years later to sift through data from 11 randomized trials comparing PCI with conservative medical treatment. The studies involved about 3,000 people with stable coronary artery disease. The bottom line: Barring the subset of patients who had suffered a recent heart attack, PCI offered no benefit. Meanwhile, millions had undergone this invasive procedure for no good reason, says Ioannidis.

Meta-analyses such as these are the currency of “evidence-based medicine,” a movement that gained traction in the 1990s and still guides medical practice today. It is fueled by the belief that physicians should not advise on instinct, or even on the basis of individual reports, but rather draw objective conclusions by synthesizing data from the wider body of published literature. Evidence-based medicine was embedded in law as part of the Affordable Care Act. Signed by President Barack Obama in 2010, the health-care reform law mandates a shift to reimbursing providers based on health outcomes rather than visits, tests or procedures.

While evidence-based medicine sounds reasonable in theory, in practice the approach is precarious, Ioannidis says. Data from individual studies comprising the meta-analyses are often unreliable — or unavailable.

Years earlier, UC-Riverside psychologist Robert Rosenthal, PhD, called this the “file drawer problem.” In a 1979 Psychological Bulletin paper, he assessed the impact of the predicament, in which journals overflow with research studies claiming effects that are not real while the many studies failing to show a statistically meaningful effect remain tucked inside file cabinets. In some cases, Rosenthal argues, it wouldn’t take many of these “filed” analyses to make a published result non-significant.

Ioannidis saw from his own research how easily it went awry. From designing experiments, running them, analyzing results and writing them up, “it was very easy to make errors,” he says. “And many of the errors I saw in other papers I was also seeing in my own work, despite very good intentions.”

Could it be that many reports in the biomedical literature are, in fact, wrong? Ioannidis wanted to see if this longstand-
ing hunch could be evaluated with mathematical rigor. Using a systematic approach, he calculated the likelihood that a biomedical research study would yield a true result, and determined how various factors, such as sample size and conflicts of interest, affect that probability. His decade-long efforts culminated in a 2005 *PLoS Medicine* essay, “Why Most Published Research Findings Are False.” By April 2014, the freely downloadable paper had received more than 1 million views — the first *PLoS* article to reach this milestone.

While scientists have long questioned the quality of biomedical research, “what John did is actually put numbers to it,” says Michael Bracken, PhD, a professor of epidemiology at Yale. “That was perhaps the most startling aspect of the *PLoS Medicine* paper — that so much of what we publish is almost certainly exaggerated or false.” The essay was “an instant classic,” says Bracken, who teaches a course in evidence-based medicine. “It became required reading for my students.”

In his 2005 essay and subsequent studies, Ioannidis used creative approaches to address the scope of the research quality problem. “He applied analytical rigor and provided a conceptual framework to address many of the issues that have been discussed,” says Deborah Zarin, MD, of the National Institutes of Health in Bethesda, Md. She oversees Clinical-Trials.gov, the world’s largest registry and results database for clinical trials and observational studies.

**A LOOK AT CLINICAL TRIALS**

Clinical trials are research studies conducted on people to test the safety and effectiveness of therapies or devices. Often costing hundreds of millions of dollars, these studies are the final crucible in the long, excruciating process by which a tiny subset of experimental treatments reaches the market. On average, fewer than 20 percent of potential medications that enter clinical testing will complete the final stages. For pharmaceutical companies that test in cell and animal models in people. It’s a high bar. Only 1 in 6,000 new compounds forms in animals often determines whether it’s worth testing clinical trials. How well an experimental compound performs in animals often determines whether it’s worth testing in people. It’s a high bar. Only 1 in 6,000 new compounds that pharmaceutical companies test in cell and animal models each year move into the first phase of clinical testing.

The problem begins with animal research, which precedes clinical trials. How well an experimental compound performs in animals often determines whether it’s worth testing in people. It’s a high bar. Only 1 in 6,000 new compounds that pharmaceutical companies test in cell and animal models each year move into the first phase of clinical testing.

But are animal experiments reliable enough to be steering the multimillion-dollar clinical enterprise? In directing many randomized trials, Bracken says “it became increasingly obvious that animal work, which we depend on, has been a very poor predictor of what happens in humans. The methods used in animal research are substantially flawed.”

Researchers seldom carry out at the lab bench the procedures and practices they routinely conduct in clinical trials. Often researchers don’t randomize the animals into treatment groups. Nor do they mask the experimenter who’s judging how the animals fare with treatment. Bracken and colleagues raised these issues in a 2004 *British Medical Journal* commentary and revisited them in a follow-up *BMJ* analysis published this May. “The trajectory is improving but is still far short of what it needs to be,” Bracken says. Recognizing the need for better education, the NIH is stepping up its efforts to train postdoctoral fellows in designing good experiments and conducting them responsibly. “There is wider rec-
ognition that people who do animal work need more training in design and statistical methods,” says Bracken.

**IMPROVING REPRODUCIBILITY**

Finally, there is a lack of reproducibility — the ability to replicate previously reported findings. It’s essential for what makes science a self-correcting enterprise. In the recent _Nature_ comment, NIH director Collins writes that the “complex system for ensuring the reproducibility of biomedical research is failing and is in need of restructuring.” The ability to reproduce published data can determine whether an experimental compound has a future — whether a company will spend big money developing it. These high stakes have prompted pharmaceutical researchers to take a hard look at the published data on potential drug targets. They asked a simple question: Is it trustworthy?

Bayer HealthCare scientists analyzed in-house target validation projects in oncology, women’s health and cardiovascular disease. In a 2011 comment in _Nature Reviews Drug Discovery_, they reported that the company’s validation teams failed to replicate published data about three-quarters of the time. A similar effort by Amgen scientists also yielded dismal results. Hematology and oncology researchers combed the literature for 53 “landmark” papers and found their findings confirmed in only six cases, they reported in _Nature_ in 2012.

Why such difficulty? Some would say science is inherently challenging. It’s an endeavor in which failures are frequent and successes incremental. Others blame misdirected incentives. “There isn’t a culture for replication. The drive is entirely toward innovation,” says Brian Nosek, PhD, a social psychologist at the University of Virginia in Charlottesville. “We are incentivized to make our research look more beautiful than it actually is. As a consequence, the published literature is a skewed representation of reality.”

Plus there’s job competition. Researchers advance their careers by publishing papers. “Whether they’re right or wrong has little consequence, especially in the short term of getting jobs and tenure,” Nosek says. “I want to get it right, but I need to survive.’ We’re faced with these sorts of decisions.”

In early 2013, Nosek and one of his graduate students, Jeff Spies, founded the Center for Open Science — a nonprofit tech startup that aims to align scientific practices with scientific values. Headquartered a few miles from the University of Virginia, the center builds open-source tools to improve scientific workflow; works with publishers and societies to develop incentives that encourage transparency; and, along with Stanford’s METRICS, supports meta-science. This includes “reproducibility projects” — large collaborative efforts in which individual studies are crowdsourced for replication by individual research teams. One reproducibility project was launched in psychology in late 2011, another in cancer biology six months ago, and future projects in neurodegeneration and ecology are in the works, Nosek says.

Because cancer biology studies are costly, Science Exchange, a network of verified research labs that run experiments on a fee-for-service basis, is conducting the replications. “Researchers can go online to find an expert to do an experiment for them,” says Elizabeth Iorns, PhD, who founded the Palo Alto, Calif.-based company in 2011. “It is a marketplace. You can search the database for whoever offers your experimental need and order it from them.”

**META-RESEARCHERS UNITE**

From initiatives that improve the quality of animal work to new policies promoting transparency and reproducibility, meta-science is slowly but surely coming of age. As for where to start and what to prioritize, “I feel a little bit like a child in a candy shop,” says Ioannidis, who receives more than 1,000 invitations each year to lecture on his meta-research. The good thing is that “many are sensitized to these issues — people who can push for transformation that could improve very different fields,” he says. METRICS plans to organize a conference in late 2015 for meta-researchers in biomedicine, as well as those who study the research process in other fields.

“There’s a lot of parallel activity going on and a lot to be learned from things that physicists and social scientists are doing, for instance,” says Goodman. “And they have a lot to learn from what’s going on in biomedicine. That’s part of the beauty of the center. We can reach across these boundaries and see what everybody’s doing and inform each other. The issues are not unique to biomedical science.”

— Contact Esther Landhuis at medmag@stanford.edu
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FEATURE
Brain attack
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what the clinical workup reveals, treatments possibly employed include immune-modulating drugs if autoimmune markers or signs of inflammatory disease are present, or antibiotics for repeated sinus or throat infections. They occasionally use limited trials of high-dose steroids to help suss out whether inflammation is behind the symptoms, an approach that’s also used for some forms of encephalitis. Chang often addresses psychiatric symptoms with lithium, which has a long history as a therapy for bipolar disorder, but may be generally protective for the brain. “We’re trying to support these children’s brains and lives as best we can,” he says.

A FAMILY LOOKS FORWARD
Today, Paul Michael is almost 13 and his condition is much better; Mary estimates he is “90 percent back.” After 15 months living at Edgewood, he moved home and spent another two years mostly as a day patient at the facility, with some shorter hospital stays when things temporarily became worse. He transitioned in the fall of 2013 to a special-needs classroom in a public school near his family’s home. He attends mainstream classes for three subjects, something the Nelsons could never have imagined during the worst days of his illness. Frankovich’s attempts at weaning his immunosuppression resulted in simultaneous flares of his blood disorder and his psychiatric symptoms, so he is now on a longer term protocol similar to that used to treat diseases like lupus. And it’s been more than a year since his last serious outburst of rage.

In other diseases where the immune system can hurt the brain, such as lupus, controlling the autoimmune attack takes up to five years. So Frankovich is not disheartened by the gradual nature of Paul Michael’s improvement. It also takes time for the bombarded brain to recover from immune attack, she points out. “It’s the same as in brain trauma; even after we get the inflammatory response under control, it still takes time for the brain to heal,” Frankovich says, adding that she thinks it is likely that Paul Michael will ultimately be able to complete school, hold a job and live independently. Paul and Mary are grateful for how far their son has come. “Now that he’s doing really well in school, and has been mainstreamed in three classes, that gives me hope,” Mary says. “I’m cautiously optimistic.” Paul Michael loves to make art and has excellent visual-spatial reasoning skills. In her office, Mary proudly displays several examples of this ability, among them a perfectly proportioned, 2-inch, orange-and-white guinea pig crafted out of looped-together rubber bands.

Paul Michael planned and made the three-dimensional critter on a rainbow loom, a tool most kids use for much simpler projects, such as making bracelets. The family has begun talking with him about careers that might put his spatial ability to use, such as engineering or art.

Of late, they’ve been granting Paul Michael more independence as well. “He walked to the store alone yesterday,” Paul says during a conversation in July 2014. “That’s freedom a teenager needs, he can do it, and he’s happy with himself. It’s a real good development.”

But Paul and Mary never feel like they can let their guard down, either. The disease could recur. The immune-suppressing medications Paul Michael takes have potentially serious side effects, including increased risk for infectious diseases and some cancers. And they worry about what happens if he stops the medications.

“He can be extremely volatile,” Mary says. “But when he’s not, he’s this perfectly wonderful, creative, artistic, loving guy.”

Seeing the struggles that patients like Paul Michael endure has convinced Frankovich she’ll be treating PANS patients for a long time, in spite of all the obstacles.

“Some days, I think ‘Why are we doing this? It’s so frustrating and hard,’” she says. “Other days, I see a kid we clearly made better. I’ve seen families crying, saying, ‘I haven’t had my kid in a year, and now I have my kid back.’ We cannot give up on this. There are so many of these cases out there.”

5M — Contact Erin Digitale at
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FEATURE
When bones collide
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meniscus develop arthritis at a rate five- to tenfold that of people who don’t.)

Sure enough, the mice developed osteoarthritis in their wounded knees. But bioengineered mice lacking their meniscus develop arthritis at a rate five- to tenfold that of people who don’t.

The discovery, and continuing progress in Robinson’s lab, justifies expanding the research focus from animal models to humans. That’s where Genovese comes in. His pilot study will test whether dialing down the low-grade inflammation in osteoarthritis patients can slow or halt progression of the disease.

CAN YOU TEACH AN OLD DRUG NEW TRICKS?
Medical science is not in the business of bioengineering people. But drugs can often achieve the same purpose. If you’re going to inhibit the complement system, you have to be careful, because complement is absolutely vital in the first days after an infection. Without it, you’d be toast before your adaptive immune system can fire up.

Various experimental anti-complement drugs have entered clinical trials for other indications, but none has really worked out yet. But in Robinson’s experimentation with animal models, a combination of two drugs with anti-inflammatory properties — atorvastatin and hydroxychloroquine (more typically thought of as treatments for high cholesterol and malaria, respectively) — had beneficial effects. Both drugs were long ago approved by the FDA for other indications, known to be safe enough for long-term use, and are now off patent and, therefore, cheap. Importantly, using the two drugs in combination gave better results than you might predict from simply adding their separate effects.

Genovese’s study — funded by SPARK (Stanford’s in-house bioscience incubator) and the Northern California Arthritis Foundation — has enrolled eight patients to date and is recruiting to expand to 16 patients, all over age 35, otherwise reasonably healthy, and showing some evidence of osteoarthritic knee damage (but not so much that hope of some repair is unreasonable) as well as signs of inflammation in that joint. Trial subjects are receiving daily oral doses of both atorvastatin and hydroxychloroquine for four months and being monitored for an additional two weeks after that for evidence of improvement in joint function, pain and the biochemical and radiological condition of their affected joints. It’s far too early to draw any conclusions because no results have been reported yet. Even with good outcomes, says Robinson, a slam-dunk proof that the drug combination safely counters osteoarthritis progression could still be five to eight years off.

Meanwhile, Robinson’s lab is chasing osteoarthritis’ inflammatory triggers upstream. “Specific molecular events appear to be very important in the inflammatory chain of events that drives osteoarthritis progression,” he says. “We are intent on learning exactly how, and why.”

That would be nice. A 2007 study estimated...
that annual costs to society then were $180 billion including visits to doctors’ offices, the stop-gap medications that at least diminish pain, time lost at work and major operations such as joint replacements (running at $50,000 to $75,000 per procedure). Those costs are surely greater now, and with an aging society, they will keep growing unless medical research generates some way of slowing or, better, reversing osteoarthritis’ advance or preventing it from getting a toehold (or a knee-hold or a hip-hold) to begin with. SM — Contact Bruce Goldman at goldmanb@stanford.edu

**FEATURE**

I can eat it

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Perhaps Tessa and Maya and Kieran will pass the de-methylated FOXP3 to their children, and spare them the burdens of their experiences.

**FEAR-FREE EATING**

Nadeau recently published a study that attempted to document the vast improvements in quality of life of patients and their families after they were desensitized. Of the 75 families who filled out a questionnaire, over 92 percent reported a significant improvement in their quality of life.

Kieran’s allergies were the deepest worry my husband, Michael, and I had ever faced that actually evaporated. “You’ll have to figure out something else to worry about now,” a friend joked. But we didn’t; it turns out our other worries aren’t as worrisome as the fear that our child may die because we were insufficiently worried, as it were, and failed to protect him. The long vigil was over.

For Kieran completing the therapy meant no longer being excluded from the food at every preschool party and gathering. For Maya it meant being able to go to sleep-away camp with her bag of nuts and eat the same food as the other campers. For Tessa it meant she was able to go on an overnight trip and feel safe being away from her family.

“She’s a completely different kid and we are a completely different family,” Tessa’s father says. “She has less anxiety, she’s more confident, more social.” For the first time, he and his wife are able to go out by themselves — something they never used to do because they couldn’t trust a babysitter with Tessa.

“Every single time she walked out the door I never knew if I’d ever see her again,” he says. Tessa didn’t feel safe either — she was afraid whenever she had to leave her family. “Now she hops out of the car with her backpack and tennis racket and runs into school without looking back,” he says.

Tessa still has some allergies and all patients are told to continue to carry an EpiPen, even after completing the therapy (rare reactions have been reported). One recent morning, Tessa couldn’t find the EpiPen kit she normally takes to school. Her mother was disappointed to see Tessa’s old desperation re-surface as she hunted for it, the emotions of the allergy experience still so powerful for her.

When asked if there were things they would miss about the OIT process, none of the kids hesitated. They would miss spending time with Dr. Kari, Dr. Sharon, Tina and the other staff, and being able to pick out presents from the giant present bucket. They would miss the extra time with their parents — for many children it was the only time they could recall being alone with both parents without competition from siblings. “And iPad time,” Maya adds, smiling, as updoses were a time her parents relaxed the usual strictures.

The kids got all the doting, praise and petting that they would get if they were being treated in the hospital for a chronic illness — except they weren’t sick so they were able to enjoy it. There were the occasional dreaded blood draws and prick tests, but in most of the updoses all they had to do was eat some protein powder mixed in applesauce or custard to be heroes. “We were the pioneers,” Maya says, “the ones that paved the yellow brick road.” “I wish I could be in the trial,” Kieran’s twin sister, Violet, says.

“I wish I could be in the trial forever.” SM

Learn more about food allergies at http://foodallergies.stanford.edu/
Contact Melanie Thernstrom at medmag@stanford.edu

**FEATURE**

The buddy system

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when, one night in March, he finally hit bottom.

“I had a really bad night,” Early says. “I drank a bottle of whiskey, and a lot of beer. My wife spoke to my dad about me getting help. I wish I could have told him; I knew they would listen to him more than they would to me. He said, ‘Look, you are going to get help or the marriage is going to be done.’”

The next day, Early checked into the Menlo Park PTSD residential rehabilitation program, the same one where Ontiveros stayed for five months. Ontiveros visited him there, and encouraged him to stick with the program early on when he wanted to drop out.

“It sucks every time you sit there and say, ‘I need help,’” Early says. “I got the program for 50 days thinking, ‘This is bogus, none of this applies to me.’” On day 51, the light bulb turned on and stayed on. Early stayed in the program for 115 days. He was released in June.

“Things don’t get completely better but every day life gets easier to cope with from the tools I learned while at the Menlo Park VA,” Early says. “That was a big realization for me. I never would have made it through the program without Erik.” Ontiveros says he told Early what he tells all his vets, what he learned the hard way.

“That label that we give ourselves of not being normal — that stigma doesn’t allow us to accept who we are. I tell them we have been in a situation that only 1 percent of the rest of the population has been in. What we have seen, the rest never do. It’s who we are.” SM — Contact Tracie White at traciew@stanford.edu

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LIFE FLIGHT AT 30

INSIDE STANFORD’S RESCUE HELICOPTER

It was May 1984. A 70-year-old woman critically injured in a car accident in Santa Cruz County became Stanford Life Flight’s inaugural patient. With that flight, Life Flight became the first helicopter emergency services program in the San Francisco Bay Area, and Stanford Hospital became the first medical center in the region to have its own helicopter and air medical transport team. Thirty years and thousands of flights later, Life Flight launches its helicopter and crew — a pilot and two nurses — up to three times a day and averages about 700 flights annually, ranging as far south as Santa Barbara and as far north as the Oregon border. Between 30 and 40 percent of those flights carry children to the neonatal intensive care unit of Lucile Packard Children’s Hospital Stanford. Adult patients are most often transported to Stanford Medicine for stroke, cardiac or trauma care.

Some of the flight nurses have been on board for years, even decades. To be considered for the crew requires years of experience, as well as extensive clinical qualifications and exceptional interpersonal skills.

“People say, ‘I bet your staff is a bunch of Type-A personalities,’” says Michael Baulch, RN, JD, Life Flight’s program manager. He dissents. “I want the Type-D personality whose heart rate never goes up. When you land on a highway where there are badly injured people, you want someone to step in and infuse a sense of calm into the situation.”

Most of the nurses have advanced certifications in flight nursing and critical care specialties, and several have graduate degrees. Flight nurses also assist when needed with trauma alerts in the emergency department and help in the intensive care units with advanced procedures, such as arterial lines and intubations.

“It’s a very collaborative, team-centered approach,” says Geralyn Martinez, RN, a Life Flight nurse since 1990. “Our job has evolved greatly over the years.”

The program now has a faster, larger helicopter than its first model with medical equipment that is compact, lightweight and rugged. “We have benefitted from war-zone medical care techniques developed by the military overseas,” Baulch says.

It’s the only flight program in Northern California able to transport critically ill cardiac patients who need advanced equipment such as an intra-aortic balloon pump. Its helicopter is equipped with instrument-aided flight technology that makes transport in inclement weather safer. The crew also wears night vision goggles for all nighttime flights to aid visibility and improve safety.

It’s one of just a few such programs with professionals qualified to insert a catheter into an artery to monitor blood pressure in critically ill patients, Baulch says. “And we have nurses who are world experts in dialing in the optimal setting for a patient breathing on a ventilator,” he adds.

Beneath all the technology and specialized training, however, remains the power of a calming voice. “A patient wrote me a very nice letter to say thanks,” says Life Flight nurse David Bevin, “because I leaned over her and said, ‘You’re going to be OK. You’re going to make it to Stanford.’” — SARA WYKES
Chronic pain, among the most abundant of all medical afflictions in the developed world, can trigger a psychic exhaustion best described by the question, "Why bother?" A new study shows that a set of changes in key parts of the brain may explain chronic pain's capacity to stifle motivation. The discovery could lead to entirely new classes of treatment for this damaging psychological consequence.

A series of experiments in mice led by Robert Malenka, MD, PhD, the Nancy Friend Pritzker Professor in Psychiatry and Behavioral Sciences, described in a study published in *Science*, showed that persistent pain causes changes in a deep-brain structure known to be important in the pursuit of goals likely to yield pleasurable results. "We showed that those brain changes don’t go away when you transiently relieve the mice’s pain," Malenka says.

The experiments also indicated that the mice’s diminished motivation to work for rewards wasn’t the result of pain rendering them incapable of experiencing pleasure or from any accompanying physical impairment, he says.

Malenka and his associates looked at lab mice enduring chronic paw pain. The scientists trained the mice to poke their noses into a hole to get a food pellet. At first, a single nose poke earned a pellet. But over time, the number of nose pokes required for a reward was increased. In essence, the researchers were asking these mice, "How hard are you willing to work for food?"

A week later, tests showed that the mice had lost much of their work ethic, which wasn’t restored even when the pain was relieved. Malenka’s group further found that chronic pain permanently changed certain connections to a deep-brain structure called the nucleus accumbens, which is involved in pleasure seeking, and that a somewhat obscure brain chemical called galanin plays a critical role in this change. The scientists identified receptors for galanin on certain nerve cells in the nucleus accumbens and demonstrated that disabling galanin’s signaling via this receptor prevented the long-term suppression of motivation seen in mice with chronic pain. This suggests that therapeutic compounds with similar effects could be developed, though they would have to be carefully targeted to avoid disrupting galanin signaling in other important brain circuits. — BRUCE GOLDMAN