

S T A N F O R D  
M E D I C I N E

Spring 2016

special report

RELATIONSHIPS  
Ties that heal

No known cure

A scientist tries to bring his son  
back from the brink

People who need people  
Why social support matters

Jessie and Glenn Close  
A conversation about  
mental illness

Finding beauty  
What one mom learned from  
her child's cerebral palsy

A doctor and his dog  
The Chihuahua will  
see you now

Can you hold it?  
Struggling with incontinence

plus

Intestinal fortitude  
Are we losing our microbial might?

Going home  
Trying to halt the drug epidemic



S T A N F O R D  
M E D I C I N E

Spring 2016



# UNDER THEIR WING

## PARENTS OF CHILDREN WITH COMPLICATED CONDITIONS GUIDE OTHERS

Michele Ashland's daughter was just a month old when Ashland learned in a phone call from her pediatrician that her newborn suffered from a life-threatening liver disease and might need a transplant to survive. She brought her ailing child to Lucile Packard Children's Hospital Stanford for the transplant, feeling overwhelmed. • "I landed here knowing nothing about liver disease, transplantation or hospitals," says Ashland, now a Stanford Children's employee. "I just thought the worst. I wondered, 'Am I signing her up for a lifetime of being in the hospital?' You feel so alone." • With help from the health-care team, Ashland taught herself about transplants and learned how to navigate the medical and insurance systems, manage her daughter's rigorous schedule of anti-rejection drugs and keep her safe from marauding pathogens, which can easily defeat transplant patients. • Four years after the 1995 procedure, Karen Wayman, PhD, the developmental specialist on the liver team, asked Ashland and other parents for feedback on the transplant process and ways to better support



families of transplant recipients. That marked the start of the parent mentor program at the children's hospital, in which experienced parents offer care-management strategies, as well as a shoulder to cry on, to parents of youngsters newly diagnosed with devastating medical conditions.

The program, the first of its kind in the country, now includes 15 trained parent mentors, who are paid for their work and are essential members of the health-care team, says social worker Lindsey Martins, who oversees the program.

The mentors, some of whom are fluent in Spanish, offer emotional and practical support to parents of children with cancer, heart disease, cystic fibrosis, diabetes, gastrointestinal disorders and other complex medical conditions, as well as those with infants in the neonatal intensive care unit. In addition to face-to-face interactions with families, the mentors helped develop guides, available in print or online, with tips on relevant issues, such as managing insurance and organizing a child's treatment and medication schedule.

"I used to think of the program as icing on the cake, but now I think it's not just icing — something extra — because how you manage things as a parent can really make a difference in your child's life," says Ashland, whose daughter is now a thriving college junior.

"When I approach families, I tell them I'm a parent and that they can talk to me," says parent mentor Teresa Jurado, whose 26-year-old son has cerebral palsy. "You see their whole face change. It seems like they relax and let down their guard. They don't have to pretend they have it all together."

Angelica Marin, a mother of three from Lathrop, California, says she was struggling to take care of her daughter, 7-year-old Valeria, who was born with a disability that restricts her ability to walk, speak and feed herself. Ashland and Jurado both helped her with the process of securing a wheelchair, set up appointments with the child's dozen or so specialists and arranged for a Spanish interpreter at a time when Marin was still learning English.

"I don't have words to explain just how much they have helped me," she says. "You feel so lost and are afraid of everything. I learned that I'm not alone."

"One piece of advice I always remember is they told me, 'Never give up. There is always a door open for you.'"

— RUTHANN RICHTER

# S T A N F O R D M E D I C I N E

SPECIAL REPORT

## Relationships

TIES THAT HEAL



All together now  
page 6

- 6 **You are not alone**  
YOUR RELATIONSHIPS, YOUR HEALTH
- 8 **The puzzle solver** *By Tracie White*  
A RESEARCHER CHANGES COURSE TO HELP HIS SON
- 16 **Come together** *By Krista Conger*  
HOW SOCIAL SUPPORT AIDS PHYSICAL HEALTH
- 20 **Silver linings** *By Kathy Zonana*  
SOMETIMES YOU FIND BEAUTY WHERE YOU LEAST EXPECT IT
- 22 **His dear Watson** *By Becky Bach*  
A DOCTOR AND HIS CHIHUAHUA MAKE EXPLAINING NARCOLEPSY LOOK ELEMENTARY
- 26 **Sisters**  
A CONVERSATION WITH JESSIE AND GLENN CLOSE
- 28 **Overflowing lives** *By Jennie Dusheck*  
HOW URINARY INCONTINENCE CHANGES US
- 32 **Moment of youth** *By Erin Digitale*  
PEDIATRICIANS FIND OPPORTUNITY IN CARING FOR AT-RISK TEENS

PLUS

- 36 **Gut bust** *By Bruce Goldman*  
INTESTINAL MICROBES IN PERIL
- 42 **You can go home again** *By Keith Humphreys*  
AN ADDICTION SPECIALIST RETURNS TO WEST VIRGINIA TO HELP

The special-needs village  
page 20



Bonds that endure  
page 8



DEPARTMENTS

- Letter from the dean 2
- Upfront 3
- Backstory 50

**At its heart, health care is about a connection — a personal relationship of trust and caring between a patient and a provider.**

When that relationship is strong, patients feel understood, and providers feel that their work has meaning. But go to a hospital or clinic today, and you are more likely to see a provider sitting in front of a computer than talking with a patient. Technology is changing the nature of the patient-provider relationship. Though technology has led to dramatic advances in patient care, patients and providers alike sometimes feel that technology is an intrusion, leaving them disconnected and detached from each other.

Concerned about how technology can inadvertently create barriers between patients and providers, Stanford's Abraham Verghese has led a national movement to renew focus on the physical exam, a dying art that was once regarded as the litmus test of physician quality and vital to patient care. Through the Stanford Medicine 25 program, he and his colleagues have taught hands-on bedside care to a new generation of doctors at Stanford Medicine and to practicing physicians around the world.



But as Abraham sees it, the decline of the bedside exam — with the potential to miss obvious diagnoses — is just one symptom of a much larger problem: the lack of humanism in modern medicine. Patients often struggle to feel a human connection with their providers in a high-tech health-care setting while providers themselves are reporting alarming rates of burnout and depression. To address these challenges to the patient-provider relationship, Stanford Medicine recently launched a new center, Presence: The Art and Science of Human Connection.

Under Abraham's leadership, Presence seeks to build upon the Stanford Medicine 25 program — fostering research, dialogue and design thinking across Stanford University's seven schools to produce measurable and meaningful change in the living laboratory of our hospitals and clinics. Drawing on Stanford's collaborative academic culture, Presence will explore and leverage innovative ideas from a variety of academic fields — everything from comparative literature to environmental engineering. Above all, Presence will define and advocate for the human experience in medicine, for both the patient and the provider.

The new center is part of Stanford Medicine's larger vision to lead the biomedical revolution in precision health. Instead of a frantic sprint to cure disease after the fact, precision health seeks to prevent disease before it strikes, treating people rather than just treating disease. Bringing the promise of precision health to patients will require the judicious use of technology, focusing on health care that is predictive and preventive, personalized and patient-centered.

Precision health requires both high-tech and high-touch approaches — or, to use the language of Presence, both the art and science of human connection. The patient-provider relationship is not merely an element of health care, it is the essence of health care.

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

# Upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD MEDICINE

## Tapping cells for clues

IN HIS ROLE AS a pediatrician, Manish Butte, MD, PhD, often will push and prod a young patient's abdomen, feeling for abnormalities. Now Butte and his colleagues have engineered a highly sensitive probe that can "tap" on living cells in a lab dish and make detailed measurements of their stiffness. The work, described in November in *ACS Nano*, is a major advance in atomic force microscopy, which itself was invented at Stanford in 1986.

Butte and his colleagues use atomic force microscopy to measure the mechanical properties of cells in much the same way as a handyman taps along drywall, listening for pitch changes that indicate the presence of wooden studs. By coupling their new, small, cellular probe with a traditional one, the Stanford scientists are able to sense faster oscillations than by using conventional devices alone. The technology allows them to examine very soft cells for the first time without damaging their delicate exteriors, and to complete measurements in minutes rather than weeks.



Andrew Wang, PhD, a former Stanford postdoc who shares lead authorship of the study, says that practical applications of the device range from a basic scientific understanding of cellular structure to immunology and oncology. "Cancers," he notes, "are often stiffer than normal, healthy tissues, and we can use that knowledge to diagnose disease. But first you have to have good data, which our device provides." He already has used an early form of the probe in work on breast cancer specimens taken from mastectomies.

2 milliseconds of light flashing every 10 seconds for an hour at night may prevent jet lag. Read more at <http://stan.md/1qyPgue>.

## Drug double duty

SCIENTISTS have long suspected a link between insulin resistance — the body's inability to process glucose efficiently, even with adequate insulin production in the pancreas — and mood disorders. Now it appears that pioglitazone, a drug that makes the body more sensitive to insulin, also can help relieve symptoms of chronic depression. The more insulin-resistant patients are, the better the drug's anti-depressant effect. Stanford researchers described their findings in November in *Psychiatry Research*. The work was led by Natalie Rasgon, MD, PhD, professor of psychiatry and behavioral sciences.

## Stem cells and sleep

ALTHOUGH hospitals take great care in finding suitable matching donors for bone marrow transplants (properly called hematopoietic stem cell transplants), those efforts may be compromised if the donors aren't well-rested prior to the procedures.

Working with mice, Stanford researchers have found that a sleep deficit of just four hours can halve the ability of stem cells to migrate to the proper spots in the recipient mice's bone marrow, where they churn out the cell types necessary to reconstitute a damaged immune system.

"Considering how little attention we typically pay to sleep in the hospital setting, this finding is troubling," says Asya Rolls, PhD, a former Stanford

postdoc now at the Israel Institute of Technology. On the other hand, she says, "It's heartening to think that this is not an insurmountable obstacle; a short period of recovery sleep before transplant can restore the donor's cells' ability to function normally."

The study appeared in October in *Nature Communications*. Rolls was a co-lead author; senior authors are Luis de Lecea, PhD, professor of psychiatry and behavioral sciences, and Irving Weissman, MD, director of the Stanford Institute of Stem Cell Biology and Regenerative Medicine.

## PUTTING C.F. TO THE TEST

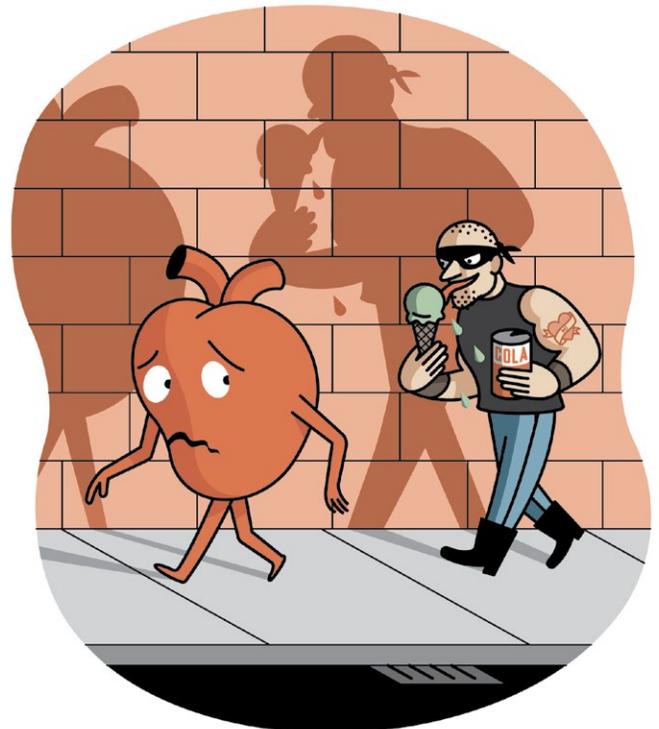
EARLY DIAGNOSIS AND TREATMENT of cystic fibrosis can make all the difference in a child's quality of life. Yet current screening tests can take up to two weeks, and may miss the disease in infants affected by rare C.F. mutations. Now, Stanford researchers have come up with a new way to extract and make copies of the C.F. gene, using the dried blood spots on cards that are collected routinely from newborns. The technique, described in February in *The Journal of Molecular Diagnostics*, is twice as fast as current methods and much better at catching rare mutations that affect nonwhite populations.

The study's senior author, Curt Scharfe, MD, PhD, an associate professor at Yale, helped develop the test while working as a senior scientist at the Stanford Genome Technology Center.

## Sugar baddy

HYPERAGGRESSIVE IMMUNE CELLS parked in arterial plaque and feasting on glucose appear to spur coronary artery disease, according to senior author Cornelia Weyand, MD, Stanford professor and chief of immunology and rheumatology, in research published in February in the *Journal of Experimental Medicine*.

Weyand and colleagues compared the blood of 140 patients who had experienced at least one heart attack with samples from 105 healthy, demographically matched control subjects. They found that the patients with coronary artery disease had immune cells that were much more likely to differentiate into damaging M1 macrophages and to carry a defect predisposing these cells to slurp up glucose. When the scientists later blocked glucose metabolism within those macrophages, their production of interleukin-6 — an immune-signaling protein infamous for driving inflammation throughout the body — dropped off considerably. "Something in there is leading to excessive IL-6 production," Weyand says, "and that something is our old friend sugar." She says the discovery could lead to new ways to prevent or treat coronary artery disease, the leading cause of death in America.



# Surgery gap

WHILE SURGERIES ARE being performed with increasing frequency in the developing world, billions of people still lack access to safe, affordable surgical care. According to a study published in March in the *Bulletin of the World Health Organization*, the estimated annual number of operations performed around the globe rose 38 percent, from about 224 million to nearly 313 million, between 2004 and 2012. Yet only 30 percent of those procedures took place in countries spending less than \$400 per capita annually on health care — nations that together account for 71 percent of the world's population.

The study, which looked at data from 194 members of the World Health Organization, also found that 30 percent of surgical procedures in the developing world are cesarean sections. This suggests that other significant surgical needs, such as traumatic injuries and cancer care, are being given low priority, says Thomas Weiser, MD, an assistant professor of surgery at Stanford and the study's lead author. "Surgery is a very unsupported discipline in some parts of the world, in terms of infrastructure," he observes. There's also "obviously a brain-drain issue," he says, "as trained providers leave their home countries to practice elsewhere."

## TB GAME CHANGER

IN 2014, THE World Health Organization challenged researchers around the globe to develop better diagnostic tests for active tuberculosis, a disease that kills 1.5 million people every year. Two years later, Stanford scientists have come up with an answer: a simple blood test that can distinguish patients with active TB from those who have latent TB or other diseases, or have been vaccinated.

The test, developed in the lab of Purvesh Khatri, PhD, assistant professor of medicine, works by identifying changes in expression of three genes that occur inside human cells after TB infects the body. It's reliable for testing adults and children, even when resistant strains of TB are involved, and in individuals who have HIV, whose TB can be missed with traditional tests. It also can be used to monitor patients to see if they are getting better, and to see how well they are responding to different treatments.

Khatri says the test's high degree of accuracy should be especially helpful in monitoring the effectiveness of treatments during clinical trials. It also has the virtue of simplicity: There's no need to collect sputum (a task that can be difficult with young children and asymptomatic adults), and it could even work in clinics lacking electricity once solar-powered machines to measure gene expression are available. A paper describing the team's work was published in February in *Lancet Respiratory Medicine*.



## Vitamin defense

MICE FED a diet deficient in vitamin D and then injected with breast cancer cells developed tumors an average of seven days sooner than mice on a normal diet, and their tumors were significantly larger after six weeks than in the animals with adequate vitamin D, according to a study in March in *Endocrinology*. The study linked vitamin D levels with the expression of the ID1 gene, known to accelerate breast-cancer metastasis: Low vitamin D correlated with higher expression of the ID1 gene. People at risk for the disease should address vitamin D deficiencies but they shouldn't go overboard on supplements, says the study's leader, Brian Feldman, MD, PhD, assistant professor of pediatrics. That's because excess vitamin D has been linked to kidney and cardiovascular damage, he says.

The study linked vitamin D levels with the expression of the ID1 gene, known to accelerate breast-cancer metastasis.

**YOU ARE NOT****A L O N E**

YOUR  
RELATIONSHIPS,  
YOUR  
HEALTH

"We enter the world alone, we leave the world alone."

It's a well-known saying, but it's simply not true.

Humans, even the most solitary, are social creatures from day one.

Each of us enters the world determined to bond with our mother — typically, we reach for a breast, latch on and stare into her eyes with a hard-to-resist gaze. Levels of hormones that influence stress and pain rise and fall in response to our interactions with mom and, soon, other people we encounter.

Relationships continue to affect our physical well-being throughout our lives — and as medical researchers are finding, we neglect this at our peril. Connections with others alter not only our production of hormones but the actions of immune cells and the pattern of our sleep cycles. Supportive relationships, not surprisingly, can improve mental health, but they can also enhance physical health. So when health problems interfere with relationships, we suffer not only from the illness but from the loss of connection.

Relationships are hard to quantify or control. There's no blood test for a healthy level of support from friends or family. There's no pill that treats loneliness. But you'll learn in the pages that follow that relationships wield mighty influence over our health and our lives — something we'd be foolish to ignore.

ILLUSTRATION BY BRIAN CRONIN





RONALD DAVIS, A RENOWNED GENETICIST, OFTEN SITS OUTSIDE HIS CRITICALLY ILL SON'S BEDROOM DOOR.

# THE PUZZLE SOLVER

A RESEARCHER  
CHANGES COURSE TO  
HELP HIS SON

*For three years, Whitney Dafoe's world has been a darkened room at the end of a hallway in the back of his childhood home. An insidious disease, one with no known cause or cure, has slowly stolen his life from him, turning his body into a prison.*

He doesn't eat. An IV line delivers nutrients and liquids and medicines to keep him alive. He doesn't speak. He's unable to write. Any motion exhausts him. Eye contact hurts him. He can't bear to be touched.

Last December, in desperation, he used Scrabble tiles to communicate, laboriously lining them up to spell out: CANT TAKE CARE OF MYSELF; DONT KNOW WHAT TO DO. At the end of the month, emaciated due to his inability to digest food, he selected five final tiles and spelled out: D, Y, I, N, G. Then he rang a bell for his father.

"My son Whitney woke me this morning to inform me that he is dying," his father, Ron Davis, PhD, posted on the Facebook page for the Stanford Chronic Fatigue Syndrome Research Center that day. "Whitney

**BY TRACIE WHITE**

PHOTOGRAPHY BY  
TIMOTHY ARCHIBALD



## **‘TO DIE OF THIS ILLNESS IS ATYPICAL;**

**HOWEVER, TO HOVER IN AN IN-BETWEEN STATE WHERE ONE EXPERIENCES A “LIVING DEATH” FOR YEARS OR DECADES IS QUITE TYPICAL.’**

*Whitney Dafoe*

has severe chronic fatigue syndrome (CFS). He did not say he is dying — he cannot speak. He did not write he is dying — he cannot write. He used Scrabble tiles to spell out his message. I did not answer him — he cannot tolerate anyone speaking to him.”

As paramedics wheeled Dafoe into the back of an ambulance that day, he opened his eyes, and for the first time in three years, stared awestruck at the wide, blue sky.

Each weekday, Davis, a renowned geneticist, takes a break from his job as director of Stanford’s Genome Technology Center, arrives home at 2:30 p.m. for his shift caring for his son, drops his comfortable, old, brown, brimmed hat on the kitchen counter and walks down the darkened hallway to his son’s bedroom door.

He doesn’t enter the room right away. Instead, he sits on a chair outside the door in the hallway, watching through a keyhole for Dafoe to find the strength to sit up and pull a blanket over his shoulders, signaling that it’s OK to come

inside. Dafoe can hear Davis in the hallway. He knows he’s there. And slowly he prepares. Sometimes Davis waits, and he waits, and he works, and he thinks, and he puzzles over the mystery behind the closed door.

Over his 50-year career, Davis, a professor of biochemistry and of genetics at Stanford, has become one of the world’s pre-eminent solvers of what others call unsolvable puzzles. In 2013, *The Atlantic* magazine ranked him among the world’s greatest living inventors. His biotech methods helped launch the field of genomics, making terms like “artificial chromosomes” and “genome editing” part of the lexicon. A substantial number of the major genetic advances of the past 20 years can be traced back to Davis. And now, his research has expanded into a whole new arena — the search for a molecular cause for his son’s illness, and from that, a cure.

Davis is grappling with the most vexing puzzle of his life. And it’s personal.

Each day has become a race to unravel the mystery of chronic fatigue syndrome, the disease that is killing his 32-year-old son, a freelance photographer who was forced to move into his childhood home five years ago when he was no longer able to care for himself. It's a puzzle that Davis ruminates over day after day, his mind humming along in high gear, constantly shifting through data, hypothesizing, analyzing.

At night, he dreams of science experiments. Each morning he awakes hopeful, with a new piece of the puzzle to fit into place, or an old one to throw out, and he heads back to work.

When you are a man of science, a world-class puzzle solver, how can you not solve this, the most important puzzle of all?

**CHRONIC FATIGUE SYNDROME**, also called myalgic encephalomyelitis or ME/CFS, is a disease that has baffled many, one that waxes and wanes, with no definitive tests for diagnosis, and symptoms that vary from patient to patient. Key to diagnosis is an inexplicable exhaustion that lasts for at least six months, and isn't alleviated by rest. Unrefreshing sleep, unexplained pain in multiple systems of the body, cognitive impairments referred to as "brain fog" and digestive ailments are all common symptoms. And then there is "the crash."

Laura Hillenbrand, best-selling author of *Seabiscuit* and *Unbroken*, who has lived with CFS for 29 years and spent many of those years bedbound, describes "the crash" — known in scientific terms as "post-exertional malaise" — as an invisible line you know is there, but you're not sure where exactly. Any expenditure of energy, however slight — walking up stairs, say, or in severe cases like Dafoe's, watching someone walk into your room — could push you over the line. Once that line is crossed, the setback can be devastating.

"The exhaustion is so profound it's a struggle to breathe, a struggle to just lie

there; it takes every effort just to stay alive," Hillenbrand says. "This can go on for months or years. ... You have to be so careful with every little bit of energy. You just don't know what your line is."

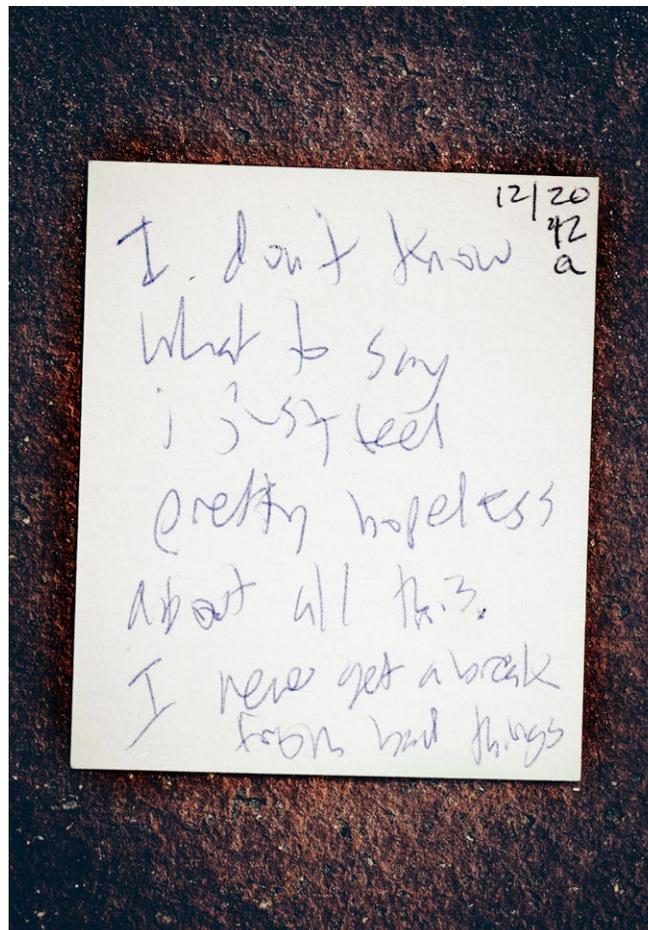
The inability to pin down the disease with a lab test and its often misleading name have resulted in patients getting labeled as malingerers or sent to psychiatric care by doctors who are unable or unwilling to help. The relatively small amount of federal funding has limited research to help find cures.

The National Institutes of Health allocated only \$6 million in 2015 for research into CFS, which has roughly 2 million sufferers. (To put this in context, the annual NIH research budget for multiple sclerosis, with 400,000 sufferers, is \$94 million.) A historical lack of acceptance within the medical establishment for CFS as a biological illness has resulted in a woeful underfunding of research, Davis says, but he notes signs of change. Davis served on a panel convened by the Institute of Medicine (recently renamed the National Academy of Medicine) to redefine the illness. The

panel's report, published in February 2015, cemented the definition of CFS as a "serious, chronic, complex, systemic disease." In turn, the report spurred the NIH to launch an internal study to analyze CFS biomarkers and promise to bolster research for this "elusive" disease. Most patients, including Dafoe, spend years undergoing fruitless tests and bouncing from doctor to doctor before finally getting a diagnosis.

"We don't have a definitive lab test, so often the attitude is that these people are crazy," Davis says. "Whitney was told that it's all in his head, that he was just depressed."

For Dafoe, the illness started more than a decade ago at 21, or possibly even earlier than that with a bad case of mononucleosis in high school, followed by a spell of headaches and dizzi-



**WHEN SPEAKING BECAME TOO EXHAUSTING  
FOR WHITNEY DAFOE, HE COMMUNICATED WITH NOTES.  
NOW HE IS TOO WEAK EVEN TO WRITE.**

ness after a trip to Jamaica during college. More signs of illness arose when he was 23. He'd been in India for several months when he began experiencing stomach pain, bloating and nausea. Two years later, he caught a cold and never felt normal again. He lost the strength to travel, he couldn't set up his camera equipment, eventually he couldn't prepare his own food, and digestive ailments made it difficult and ultimately impossible to eat.

Dafoe was an adventurer, the complete opposite of a so-called malingerer, says his sister, Ashley Davis. He traveled to all 50 states, studied Buddhism in India and Nepal, ran a campaign office for Barack Obama and took photos at his first inauguration, lived with a shaman in the Ecuadorian rainforest, helped build a nunnery in India, rode a motorcycle in the Himalayas.

But by 2013, Dafoe had become bedbound. Pain in his legs when he walked had hobbled him. In his last entry on his photography website, in June of that year, he wrote:

*Really sick. I can't talk. Can't type/text enough to communicate. Haven't had a conversation with someone in six months... To die of this illness is atypical; however, to hover in an in-between state where one experiences a 'living death' for years or decades is quite typical.*

That was three years ago. Since then, Dafoe's condition has steadily declined.

**SINCE DAFOE** was an infant, his family has lived in an elegant, old, brown house in the Palo Alto neighborhood known as Professorville, a short distance from the Stanford campus. Bright Bud-

dhist flags decorate the semicircular porch in the daylight hours and twinkling white lights strung across the front yard brighten it at night.

It's a large house overflowing with a lifetime's worth of science books, much-loved paintings, Dafoe's award-winning photographs — decor that tells the stories of the two now-

grown children — Ashley, once a ballet dancer, and her older brother, a Little Leaguer. (Their parents decided to share their last names between their children, the mother's to Whitney, the father's to Ashley.) Author Gertrude Stein's brother once lived in the home, starting a history of opening its doors to charitable and political events — one that the fit the family well. Ron and his psychologist wife, Janet Dafoe, PhD, kept their doors open wide to new ideas, to debate — politics, philosophy, science, medicine. Friends. Family.

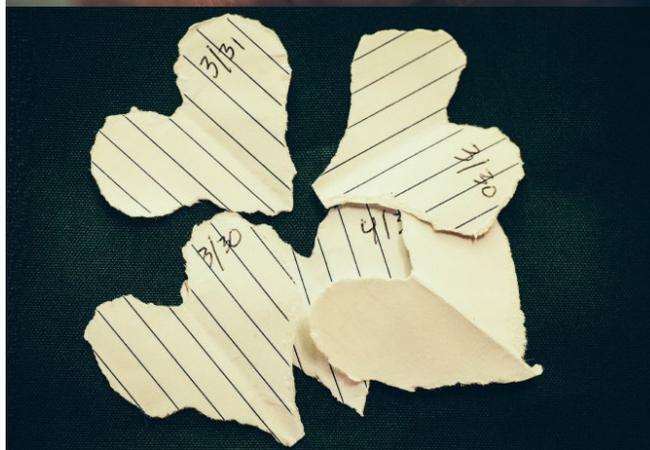
But the house has grown painfully quiet in the years since their son moved back in. A hand-scrawled note taped to the front door explains: "Please do not knock or ring bell before 3 p.m. Call or text. Very sick person."

Inside, the back of the house has become a hospital wing for Dafoe.

The family did reopen its doors last summer, holding a CFS fundraiser that drew about 100 people, including the mayor of Palo Alto, and plenty of media attention.

Every member of the family — led by Dafoe when he still had the strength — has become a CFS activist, fundraising for research, improving public awareness of the

**RON DAVIS TAKES A SHIFT EVERY DAY CARING FOR HIS SON, WHO HAS CHRONIC FATIGUE SYNDROME, GIVING HIS WIFE A MUCH-NEEDED BREAK. SON WHITNEY DAFOE SAYS THANK YOU WITH CUT-OUT HEARTS.**





## **'RON FEELS A HUGE AMOUNT OF RESPONSIBILITY**

**AND STRESS. HE ALSO HAS TO KEEP ALL HIS OTHER GRANTS UP. HE SPENDS ALL THE WAKING HOURS HE CAN THINKING ABOUT CFS RESEARCH.'**

*Janet Dafoe*

disease, doing media interviews and supporting Davis in his mission to find a cure.

“Ron feels a huge amount of responsibility and stress,” Janet Dafoe says, adding that her husband had an aortic valve replacement in December 2015, returning to his research as soon as he possibly could. “He also has to keep all his other grants up. He spends all the waking hours he can thinking about CFS research.”

In 2013, Davis launched the Stanford Chronic Fatigue Syndrome Research Center, which operates within the Stanford Genome Technology Center. As director of the scientific advisory board for the Open Medicine Foundation, whose mission is to find a diagnosis, treatments and a cure for CFS, he assembled a team of scientists from Stanford, Harvard and other institutions and helped the foundation raise more than \$2 million in donations. The donations enabled the team in February to launch a “big data” study

of 20 homebound patients with severe CFS. He’s brought together some of the world’s top scientists for a think tank to work on the problem, among them Nobel laureates Paul Berg, PhD, professor emeritus of chemistry at Stanford, and James Watson, PhD, chancellor emeritus of Cold Spring Harbor Laboratory; and Stanford colleagues Craig Heller, PhD, professor of biology, and Michael Snyder, PhD, chair of the genetics department.

But progress toward discovering a cure, or even a cause, for CFS is moving far too slowly for a father whose son is critically ill. Like other scientists who enter new research territory to help a loved one, Davis is pushing particularly hard for results. Twice he has submitted applications for CFS research funds to the NIH, without success.

“It’s enormous pressure,” he says. “We have to figure this out very quickly, because millions of people are suffering and my son is dying.”

**TO IMAGINE THE STATE** of Davis' mind when he's thinking about CFS, it helps to look at a complex chart stored on Laurel Crosby's computer in the basement of the Stanford Genome Technology Center. Crosby, PhD, an engineering research associate who works in the Davis lab, has spent three years attempting to deconstruct Dafoe's CFS symptoms into molecular mechanisms. The chart is a depiction of the key biochemical processes at work in Dafoe's body. It resembles an enormous dot-to-dot puzzle gone awry. All the lines are connected but no picture emerges. Now imagine this enormous dot-to-dot puzzle, called a human metabolic pathway

## CHRONIC FATIGUE SYNDROME RESEARCH AT STANFORD

There's nothing easy about researching chronic fatigue syndrome. There's no clear disease definition, no diagnostic test and not enough government funding to solve those first two problems. That's why two studies led by Stanford researchers, funded mostly by private donations, are giving CFS patients hope.

The Stanford ME/CFS Initiative, composed of investigators from multiple universities, is several years into a blood-biomarker analysis of 200 CFS patients and 400 age- and sex-matched healthy control subjects, under the guidance of Jose Montoya, MD, professor of medicine, and Mark Davis, PhD, professor of microbiology and immunology. The team's first published study identified 12 elevated cytokines, the infection-fighting proteins in blood, which could serve as potential markers of disease severity. Other research discovered structural brain abnormalities in the CFS patients, illuminating another diagnostic possibility. And now team members are analyzing study participants' blood and gastrointestinal microbiome for bacteria, viruses and other factors that could trigger immunological disturbances.

The second is a "big data" study entailing a broader and deeper analysis of 20 severely ill CFS patients. Researchers led by Ron Davis, PhD, professor of biochemistry and of genetics, are collecting blood, urine, saliva, sweat and stool samples, as well as monitoring sleep, brain signals and cognitive performance. Relying on genomic analysis and an international team of experts, Davis aims to create a comprehensive picture of what is going on inside CFS patients. *(See the main story for details.)*

Good news for chronic fatigue syndrome researchers came in October 2015, when the National Institutes of Health announced an initiative to invigorate CFS research. The NIH launched an internal study to analyze CFS biomarkers and increased the annual research budget by \$1 million, to \$7 million in 2016. The Stanford researchers are hoping to tap this funding to continue studying CFS and ways to diagnose and treat it. — KRIS NEWBY

chart, rotating in three dimensions. It's this structure that is constantly whirling in Davis' imagination. He's searching for gaps, for missing pieces, for answers.

"This is Whitney's biochemistry written out," Crosby says, pointing to the computer screen. "You can see evidence of vitamin and nutrient deficiencies because he's being fed intravenously. You can see deficiencies in metabolites that are supposed to go to make energy. The question is whether the machinery is inherently broken, or the system is just out of gas."

"If you look at Whitney's metabolic testing, it's amazing that his body works at all," Davis says. Of the 700 measurable biochemicals or "metabolites" plotted on the chart — including amino acids, carbohydrates, lipids and nucleotides — Dafoe has abnormal levels of 193. "Maybe low metabolite levels are keeping him sick?"

Like Crosby, Davis thinks the energy production system holds a promising clue. He spends a lot of time pondering the inability of the energy-producing structures within his son's cells, the mitochondria, to do their job.

"Everything points to dysfunctional mitochondria," Davis says. "But what is the molecular reason for the dysfunction? Given that there are over 1,600 genes involved in the workings of mitochondria, finding what's wrong is a daunting task. Some kind of infection or trauma or stress might trigger a series of events that causes the body to go into an altered state."

Davis suspects the answer to the CFS riddle lies somewhere in its molecular underpinnings. In his lab, researchers are looking for answers in the metabolic system. But he's exploring all possibilities; other scientists he's recruited — from Stanford, the University of Utah, Harvard University, the University of California-San Diego and other schools — are lending their expertise to investigate other systems of the body, including the immune system and the nervous system. So far, Dafoe's



C O N T I N U E S O N P A G E 4 5

RON DAVIS AND JANET DAFOE HAVE CONVERTED THE BACK OF THEIR HOUSE TO A HOSPITAL WING OF SORTS, BUT IT REMAINS A HOME. THEY WATCH THROUGH A KEYHOLE FOR THEIR SON TO SIGNAL HE'S READY FOR THEM TO ENTER.



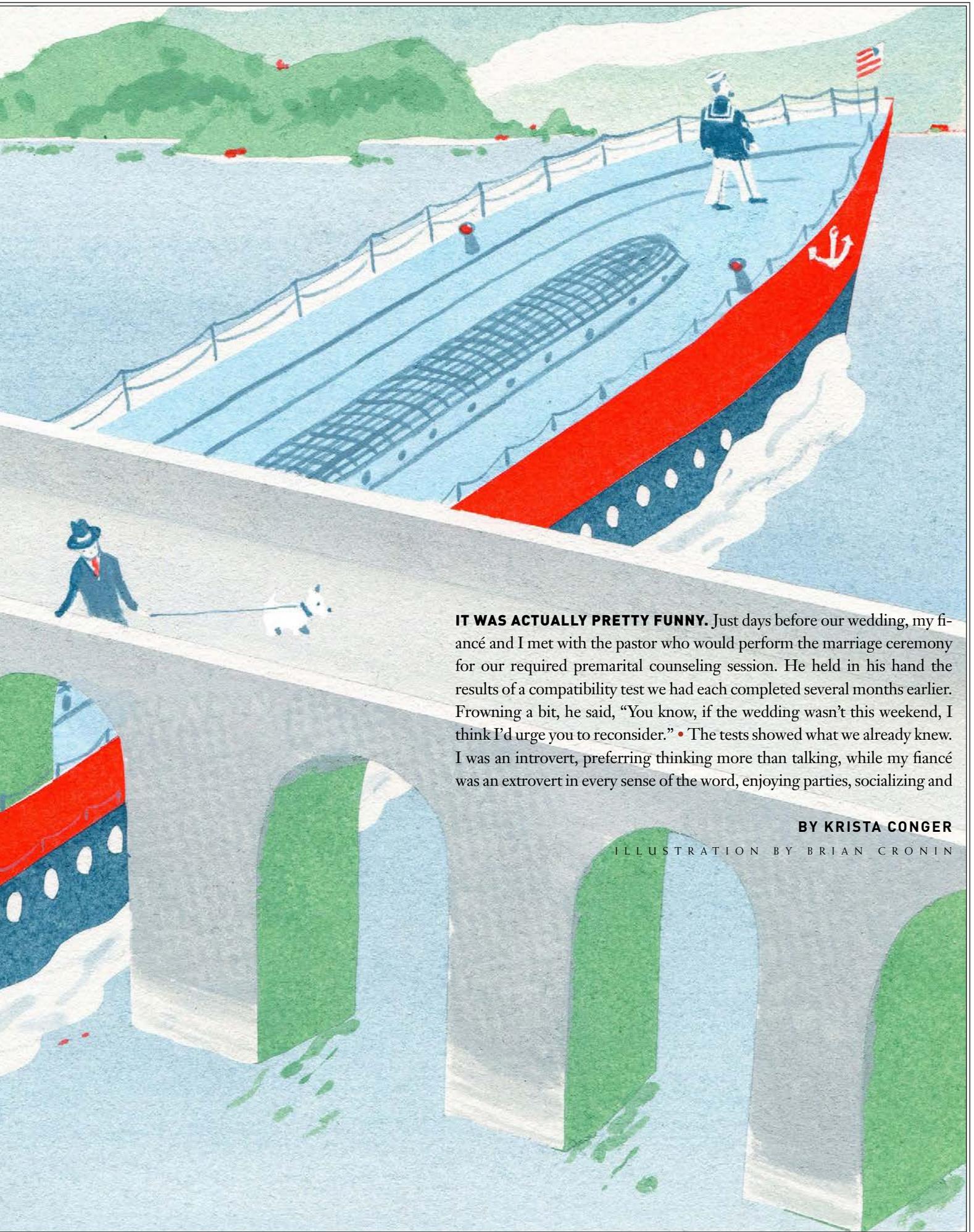
RELATIONSHIPS

Ties that heal

# COME TOGETHER

HOW SOCIAL SUPPORT AIDS PHYSICAL HEALTH





**IT WAS ACTUALLY PRETTY FUNNY.** Just days before our wedding, my fiancé and I met with the pastor who would perform the marriage ceremony for our required premarital counseling session. He held in his hand the results of a compatibility test we had each completed several months earlier. Frowning a bit, he said, “You know, if the wedding wasn’t this weekend, I think I’d urge you to reconsider.” • The tests showed what we already knew. I was an introvert, preferring thinking more than talking, while my fiancé was an extrovert in every sense of the word, enjoying parties, socializing and

**BY KRISTA CONGER**

ILLUSTRATION BY BRIAN CRONIN

leadership positions. On paper, our relationship was doomed.

That was 25 years ago. My husband and I are still together, and while our married life hasn't been without rocky patches and comical situations brought about in part by our vastly different personalities, we've always been there for each other.

Now a growing body of research suggests that healthy relationships with spouses, peers and friends are vital not

Cheryl Koopman, PhD, emeritus professor of psychiatry and behavioral sciences at Stanford. "But our interactions with others, be they friends, spouses or caregivers, are vitally important."

Researchers like Spiegel, Koopman and Firdaus Dhabhar, PhD, Stanford associate professor of psychiatry and behavioral sciences and a member of the Stanford Institute for Immunity,

## 'I CAME INTO THE GROUP ABSOLUTELY GOBSMACKED.

just for mental, but also for physical health. And this effect extends beyond nagging your husband to go to the doctor or reminding friends to take their medications or check their blood sugar.

It's increasingly evident that involvement in social networks can directly affect the levels of stress hormones in our blood, the location of critical immune cells in our bodies and even the circadian rhythms that govern our sleep cycles. Depression and anxiety, which correlate with isolation, can worsen health outcomes. Conversely, strong peer support has been associated with greater longevity in some groups of breast cancer patients.

"It's becoming very clear that positive social relationships may help people live not just better, but also longer," says David Spiegel, MD. Spiegel, the Jack, Samuel and Lulu Willson Professor, is the medical director of the Center for Integrative Medicine and the director of the Center on Stress and Health at Stanford Medicine.

"These interactions can lower stress, increase happiness and even improve sleep — all of which appear to help people stay healthy and recover from disease and trauma by affecting key biological parameters."

Surprisingly, this effect also extends to our friends and even the complicated tangle of relationships that make up our social network. In fact, some research suggests that healthy behaviors like regular exercise, as well as more risky practices such as smoking, alcohol use and overeating, can spread through our friends and our friends' friends, and even our friends' friends' friends, with a marvelously shocking facility. In other words, it's possible you are who you hang out with, regardless of how self-directed you may feel.

"We tend to think of ourselves in this culture as individuals, rather than as being embedded in relationships," says

Transplantation and Infection, are learning how social relationships and emotional states keep us healthy, or make us sick.

"Reducing depression, which is also often associated with social isolation, for example, predicts longer survival in cancer patients," says Spiegel, "and cancer patients with abnormal patterns of expression of the stress hormone cortisol die sooner than others. Even sleep and wakefulness are important. If you sleep better at night, with fewer disruptions, you may actually live longer than those patients who don't. It's important to understand exactly how social support affects our biology and our health."

**T**HE IDEA THAT relationships can affect physical health is not new. But the magnitude of the potential impact was first hinted at in studies Spiegel conducted in the late 1970s in 86 women with metastatic breast cancer. That study, which was published in *The Lancet* in 1989, found that women who were randomized to participate in a weekly psychotherapy group of women with similar cancer diagnoses lived an average of 18 months longer than those who did not participate in the intervention.

"At first we were warned that bringing women with a similar diagnosis together would demoralize them, as they watched their friends struggle and die," says Spiegel. "But exactly the opposite occurred. They encouraged one another and grew as they learned to face others' and their own mortality."

A number of subsequent studies, however, yielded mixed results as to whether participation in a peer support group increased survival of cancer patients. A study published in 2007 in *Cancer* by Spiegel of 125 women

with various forms of breast cancer failed to show any survival benefit in those randomized to receive group therapy versus others who received educational materials only — except in one subgroup of 25 women with an especially intransigent form of the disease. Members of that subgroup who participated in psychotherapy support groups lived an average of 30 months, which was about

ous illness of my own before. I was very reluctant to speak at first. But as I watched and listened to the other women in the group, I began to think ‘I can do this. I can take this journey.’ And I began to realize who I was in this new life.

“One thing I remember so clearly that David said to the group was, ‘I want you all to turn around and look at the black raven that is sitting on your shoulder. Look at it. It’s

## **I WAS LITERALLY SPEECHLESS... BUT AS I WATCHED AND LISTENED TO THE OTHER WOMEN IN THE GROUP, I BEGAN TO THINK, “I CAN DO THIS.”**

21 months longer than those who received educational literature alone. Moreover, support group participants overall reported a reduction in fear, anxiety and pain.

One possible reason for Spiegel’s conflicting results, he believes, is that breast cancer treatments improved significantly during the decades since the original study was conducted. If women with metastatic breast cancer were living longer in general, an effect of peer group participation may have been masked. Furthermore, the subgroup that benefited had a type of breast cancer that lacked estrogen receptors, so they could not benefit from powerful new treatments that block the effects of hormones on tumors.

All told, nine out of 16 recent studies conducted by researchers worldwide suggest that support groups guided by a psychotherapist can help cancer patients live longer. But regardless of the effect on life span, Spiegel feels the benefit of professionally led peer group therapy focused on building new bonds of social support, improving communication with family members and health-care professionals, and allaying fears and anxiety is unquestionable.

“The power of group support makes tremendous sense to me,” Spiegel says. “We are social creatures. Throughout evolution, we’ve relied on the ability of our relatively large brains to form connections with others and build networks of support that help us deal with threats, nurture our young and help us stay alive.”

Many of the women in Spiegel’s support group studies have since died from their disease. Those who are still alive say their participation instilled lessons and skills that helped them live more fully while also supporting one another.

“I came into the group absolutely gobsmacked,” recalls Jennifer MacLeod, who was diagnosed with metastatic breast cancer in 1993 and was a participant in the study published in 2007. “I was literally speechless. I had never dealt with a seri-

ous illness of my own before. I was very reluctant to speak at first. But as I watched and listened to the other women in the group, I began to think ‘I can do this. I can take this journey.’ And I began to realize who I was in this new life.”

death. It’s time to think about making changes in your life to eliminate toxic relationships,” says MacLeod. “That statement echoed deeply with me.”

**B**UT HOW MIGHT THIS WORK on a biological level? Dhabhar’s research addresses how emotional states directly impact the body, and his findings are telling. Reducing the amount of stress, pain and anxiety experienced by the patient directly affects key physiological parameters, he’s learned.

“We’ve found that levels of stress can impact recovery from surgery and how well our bodies mount an immune response after vaccination,” says Dhabhar, who is also a member of the Stanford Cancer Institute, Bio-X and the Neurosciences Institute.

It’s well-known that chronic inflammation can cause long-term damage to the cardiovascular system and other organs. Dhabhar has shown that long-term stress and disorders such as depression and PTSD can increase the levels of inflammatory markers in a person’s blood. And he’s shown that naturally anxious mice — those that choose to remain in an enclosed area rather than explore new terrain — not only develop more numerous skin cancers when exposed to ultraviolet light than their more laid-back peers, but may also be more likely to experience the metastasis of these tumors over time. These stressed-out mice also had higher levels of cortisol and of immune-suppressing cells, which could tamp down a successful immune attack on a newly formed tumor.

Dhabhar’s research on mice and humans shows that not all stress is harmful, however. Short-term stress in the face of a sudden challenge or an unpleasant event can actually be adaptive — providing a boost of stress hormones and

C O N T I N U E S O N P A G E 4 6

# SILVER LININGS

SOMETIMES YOU FIND BEAUTY WHERE YOU LEAST EXPECT IT

*"Why are we doing this MRI?" the anesthesiologist asks.*

*"To figure out why he has hypotonia," I say.*

*"Does anyone think he could have a mitochondrial disorder? Because anesthesia carries significant risks if he does."*

*"No, everyone thinks he has cerebral palsy."*

*"Oh," the anesthesiologist says, then turns to me and pauses. "Are you in the medical field?"*

NO, I'M NOT IN THE MEDICAL FIELD. I'm a lawyer-turned-magazine editor, and this is the second time in May 2005 I've had to answer questions about whether it's safe to sedate my 11-month-old for a brain MRI. I feel unprepared for this, the confirmation that my second child has permanent brain damage that will affect his ability to walk, speak and use his hands.

Two hours later, my son is sleeping off the anesthetic, and I'm wishing I'd never heard the term "pediatric intensive care unit." I go into the bathroom and notice an original drawing on the wall, donated by a pair of major Stanford benefactors. Their names grace buildings and programs, but they have a reputation for making smaller gifts, too: undergraduate Shakespeare outings, wildflower seeds to plant in traffic medians — and, apparently, art in unlikely places where people most need to see it. I'm touched by how fine-grained their generosity is. As I view the drawing, I take a couple of deep breaths.

I had been looking for an instruction manual. My kid has the most common childhood physical disability — the prevalence is 3 in 1,000 — but there was no comprehensive summary of the services we should pursue and the additional risks we should assess. I had appointments with three different public agencies, but I couldn't tell you how, or if, they worked together. I had a tote bag of paperwork — reports, referrals and insurance denials — and a billing specialist on speed dial. And I came to think that would be it. I'd have to

fight for every morsel of help my son needed, feeling indignant on behalf of families less well-equipped to navigate this patchwork system.

I did not anticipate the love.

First, an occupational therapist gathered my baby into her arms. In one hour, she assessed his needs and our family habits, and wrote out a three-page list of exercises for us to do. Then she asked us if we could come back two days hence, even though he was entitled only to weekly appointments. She wanted to sew him a tiny pair of hand splints. She just needed to know what color.

I felt the same embrace from nearly everyone who worked with him. The speech therapist who had to hand him over to the school district at age 3, and couldn't call me to debrief her final session because she was crying so hard. The first-grade teacher who tried to transfer to second grade, just so she could watch over him for another year. The pediatrician who sat shoulder to shoulder with me while we phrased justifications for durable medical equipment that would pass insurance muster. The fifth-grade teacher who wrote to my son, at the end of the year, "Thank you for teaching *me*." The classroom aide who stayed by his side for nine years, from preschool through sixth grade, tweaking everything — his desk, his pencil case, his lunchbox — so he could access them more independently. (She's not accompanying him to the hormonal milieu of junior high, though. We all have our limits.)

BY KATHY ZONANA

PHOTOGRAPH BY TIMOTHY ARCHIBALD



RAISING A CHILD WITH CEREBRAL PALSY OPENS A WINDOW INTO HUMANITY FOR EDITOR KATHY ZONANA, HERE WITH HER SON.

The physical therapist who named her son after mine.

My son has in his corner 12 physical therapists, nine speech-language pathologists, eight occupational therapists, seven doctors, six classroom aides, four assistive-technology consultants, three resource teachers, two adaptive swim instructors, two yogis, one myofascial release therapist, one farmer and all of the children's librarians at the Mountain View Public Library.

But for his disability, we would never have gotten to know most of these remarkable people. I tend to focus on big change — advocating for and communicating with as many people as possible. They focus on individual potential. The county therapists and I have developed a symbiotic relationship: They refine my son's gait and help him figure out how to tie his shoes; I lead legislative letter-writing campaigns to protect their program from budget cuts.

If I could rub a magic lamp, I'd enable my son to sing in musicals and run around the bases and shade his drawings with colored pencils — and so would he. As that first occupational therapist said to me, "We'll try to make him perfect, and if we can't, we'll work with what we've got." When I watch them work with what they've got — which is pretty close to perfect, in its own way — I am grateful to have this window into

humanity, to witness how devoted and caring people can be.

My son's therapists used to encourage his imagination. When he selected a ball and bat to play with, they'd ask him if he wanted to play baseball when he grew up. When he displayed his appetite for all things food-related, they'd suggest he could be a chef. I winced — I'm not big on obscuring the truth — but I also saw beauty in their approach. He'd realize soon enough how his limited speed and dexterity would circumscribe his occupational choice. For the moment, we'd let him dream.

These are the people who see possibility. They see improvement. (If you ever want to observe gradations of movement that look infinitesimal to the untrained eye, hang out with a pediatric occupational therapist sometime.) They see hope.

Two years ago, I was talking with one of my son's team members, an augmentative communication consultant who worked exclusively with children who had cerebral palsy and significantly impaired speech. She had just watched one of her former clients graduate from UC-Berkeley. "I don't get to go to many college graduations," she said. Her eyes filled with tears as she glanced over toward my son's fourth-grade classroom. "I was thinking, his will be next." **SM**

— *Contact Kathy Zonana at [kathy@stanford.edu](mailto:kathy@stanford.edu)*

# HIS DEAR WATSON

A DOCTOR AND HIS CHIHUAHUA MAKE EXPLAINING  
NARCOLEPSY LOOK ELEMENTARY

BY BECKY BACH

PHOTOGRAPHY BY LENNY GONZALEZ

There's Watson and Crick. Holmes and Watson. And Watson and Mignot. Or, more properly, Watson, the narcoleptic Chihuahua, and Emmanuel Mignot, director of the Stanford Center for Sleep Sciences and Medicine.

- Mignot found Watson (or, perhaps, Watson found Mignot) in 2014, not long after the passing of his dog Bear, a stately, black Belgian schipperke, who was also narcoleptic. Still grieving, Mignot received a call from a veterinarian in Vermont familiar with Mignot's work who had a very sleepy Chihuahua puppy in need of a home. Mignot had doubts, major ones: It felt too soon for a new dog. And he'd never particularly liked Chihuahuas.

But the narcolepsy connection proved too strong. Mignot, MD, PhD, a professor of psychiatry and behavioral sciences, has devoted his professional life to researching and treating the debilitating sleep-inducing condition, and in 1999 discovered the gene that triggers narcolepsy in dogs. Bear was the last of the Stanford research dogs, a colony of pups — at one time nearly 80 — that were bred and used to study the genetics of the disease. The dogs were beloved: They received names and

EMMANUEL MIGNOT BRINGS WATSON TO THE SLEEP CENTER TO MEET PATIENTS LIKE JACKSON, A 10-YEAR-OLD WITH NARCOLEPSY  
WHO HAS TRAVELED FROM FLORIDA FOR AN APPOINTMENT WITH HIM.



were usually adopted out as pets after they had contributed to the research. Once Mignot unraveled the genetics of hereditary narcolepsy, the colony was of little use to researchers, and Mignot adopted Bear in 2007, putting an end to an era.

Mignot and his wife, artist Servane Briand, love dogs. Their life together has nearly always included one, or two. Soon after they were married they adopted Hiatus, a wire-haired dachshund. He was their only non-narcoleptic dog, although he did love naps. Then came Bear and Watson.

“They are the perfect companions — they are always ready to have fun and welcome you home. They are just perfect,” Briand says. So, just weeks after the breeder’s call, Mignot was on a flight to the East Coast, returning to California with a new, football-sized family member — “a little bundle of happiness” — named after the Sherlock Holmes character, the IBM computer personality and the geneticist. Watson has lived up to his name, even teaching Mignot a thing or two about narcolepsy.

**A RECENT** morning found the doggie-doctor duo in a small bedroom in the Stanford sleep center’s Redwood City clinic, as a classic Bay Area traffic jam played out through the window on Highway 101 below. They were there to meet Jackson and his family, who had traveled from Florida the day before for an appointment with Mignot. A slender, bespectacled boy of 10, Jackson had been diagnosed with narcolepsy only the year before. Although Watson moonlights as an ambassador of narcolepsy — helping children understand and cope with the disease — he is a family pet, pure and simple. When he doesn’t tag along with Mignot to work, he can be found accompanying Briand to her art studio (“He’s a wonderful studio dog,” she says — he’s even depicted on the wall), or enjoying an afternoon siesta with Mignot on the couch.

The family — mom, dad, Jackson and his school-aged sister — had agreed to come to the clinic early for the opportunity to meet Watson. As they crowded into the small room, Mignot lifted up an unzipped dog carrier (Watson’s “Cadillac”), and Watson — all ears and muzzle — tentatively stepped out. “It’s a bit early for him,” Mignot apologized, pressing the dog against his chest, kissing him and cooing to “Watsonay” — or “Watsonet” as he’d spell it in French. (Mignot, a native of France, asserts that French is the best language for expressing tenderness. And it ensures that Watson, and only Watson, receives the message: “To be honest, I do confide in him.”) As the children gingerly reached out to pet the Chihuahua, Mignot pulled out several small baggies packed with chicken and dog biscuits. Watson watched

eagerly, his tail wagging frantically. Mignot placed a sliver of chicken on his finger, holding it in front of Watson’s twitchy, wet nose. Watson inhaled, then staggered backwards, struggling to remain standing as he scarfed up the meat. The family watched, rapt. Again, Watson’s hind legs seemed to buckle as Mignot dangled the meat before him. “Look, Jackson!” his mom exclaimed, “Doesn’t that look familiar?” Jackson nodded, smiling shyly.

To this crowd, Mignot had no need to explain what was happening. Excited by the food, Watson was having cataplectic attacks. When he experienced strong emotions, the dog’s muscles went limp and his eyelids drooped. Within seconds, Watson would regain command and lunge for the food. Then, he’d struggle again. At one point, Watson froze for about 30 seconds, allowing Mignot to lift him up — immobile, paws dangled in the air. A gentle tickle awoke the pup, whose tail quickly regained its whapping rhythm. To cope with the attacks, Mignot says, Watson sometimes backs into a surface he knows will support him. Jackson nods knowingly. He tries to ward off his own attacks by shaking or smacking his lips, he says. But unlike Jackson, Watson doesn’t receive medication, Mignot explains. He doesn’t have to go to school or work and he can nap frequently during the day. Again, Jackson nodded, stroking his new friend’s back.

Jackson, like many who visit the Stanford Center for Narcolepsy, has been treated elsewhere first. The disease is relatively rare — affecting 1 in 2,000 people — and most physicians don’t receive adequate (or any) training in narcolepsy, Mignot says. In humans it results when immune cells mistakenly attack nerve cells that produce hypocretin, a compound that promotes wakefulness, in the brain. There’s currently no way to correct the disorder. For now, doctors treat the symptoms, which include daytime sleepiness, other sleep disturbances and cataplectic attacks, with a combination of sedatives, stimulants and antidepressants. This balancing act can leave patients amped up on powerful stimulants, which can produce new behavioral symptoms.

**MIGNOT**, the Craig Reynolds Professor of Sleep Medicine, is hopeful that in Jackson’s lifetime a drug will be developed that can directly deliver hypocretin to the cells that need it. Several groups are making inroads testing substances using animal models, Mignot says. Until then, Watson assists him in spreading the word about narcolepsy and helping patients, particularly children, learn to cope with their symptoms. Accounts and videos of Watson’s attacks have spurred some people suffering from the disease to reach out to Mignot. “I know

it's done some good," he says. But he wants everyone to understand that although Watson's cataplectic attacks may seem charming, for a child or even an adult they are scary, disruptive, embarrassing and sometimes dangerous.

Wiggly Watson — "He moves his tail so much sometimes you have the feeling his behind is going to flop off," Mignot says — seems unaware of his serious mission. He has a sense of his condition, though, Mignot says. Wat-

ally terrible, it makes even your good times bad."

Mignot also observes how Watson's attacks grow more frequent as he tires, and how he feels better after a bit of exercise — lessons he's applied to improve care for his patients. And Watson spurs him on, reminding him how much remains unknown about narcolepsy. While in humans, narcolepsy is an autoimmune disease, in dogs, the disease can also be caused by malfunctions in the protein that receives

'HE GETS SO EXCITED WHEN WE PLAY — HE LOVES  
TO HIDE HIS PIG — AND THEN HE SUDDENLY COLLAPSES.  
IT'S SO HARD. I KNOW HE WANTS TO  
CONTINUE TO PLAY AND SOMETIMES HE JUST CAN'T DO  
ANY BETTER THAN THAT. I FEEL BAD ABOUT THAT.  
I UNDERSTAND IT'S THE SAME WITH KIDS.'

son's attacks can be sparked by food, or an appealing toy (his favorite is a brown, squeaky pig) or even simply spotting Mignot when he returns home from work. "He knows when he's going to get excited; he braces himself," Mignot says. "Sometimes he avoids certain positions." And when he does fall, it's not far — Watson's a Chihuahua, after all. He tires easily on long walks, but Mignot or his wife can easily scoop him up (an effort that was much more challenging with the 15-or-so-pound Bear). They are working hard to socialize Watson, who at first was nervous about meeting new people or dogs. It's working, according to Briand: Friends have told them they have a "well-adjusted Chihuahua," a high compliment, she says, laughing. Mignot is particularly pleased that Watson enjoys snuggly naps, something the dignified Bear considered a bit too intimate. "Watson is totally attached to us," Briand says.

Mignot says having narcoleptic dogs has shown him, in a way a half-hour meeting with a patient never could, what life with narcolepsy is really like. Watson can't do anything for very long. "He gets so excited when we play — he loves to hide his pig — and then he suddenly collapses. It's so hard. I know he wants to continue to play and sometimes he just can't do any better than that. I feel bad about that," Mignot says. For humans, narcolepsy intrudes just when they let down their guard a bit, to laugh with friends or enjoy a tasty snack. "I understand it's the same with kids," he says. "It's re-

the hypocretin signal, a condition called hereditary narcolepsy. Mignot doesn't know which type of narcolepsy Watson has, but he suspects a faulty hypocretin receptor protein because the symptoms appeared when Watson was just a puppy. The autoimmune form takes some time to develop. Human patients are most commonly diagnosed between ages 7 and 25, according to the National Institutes of Health, although many experience symptoms for several years before receiving an accurate diagnosis.

**SOMEDAY,** Mignot would love to find funding to enhance Stanford's previous genetic work on dogs with narcolepsy. He's still collecting blood samples from dogs with narcolepsy that he learns about. Mignot believes that by sequencing the genomes of dogs with autoimmune narcolepsy, researchers could discover a new immune gene that contributes to the disease. "It could tell us something different than we could learn by studying humans," he says.

Until then, Watson will remain a pampered — albeit sleepy — pooch, a confidante, playmate and inspiration, and perhaps the best-known, four-legged narcolepsy mascot around, largely inseparable from his best buds Mignot and Briand, spreading the word about narcolepsy together, one baggie of chicken treats at a time. **SM**

— Contact Becky Bach at [retrout@stanford.edu](mailto:retrout@stanford.edu)

# SISTERS

Their family name was ironic, as they were hardly close growing up.

Jessie and Glenn Close and their two siblings were raised oddly and chaotically, living for a while scattered about in an isolated, 400-room hotel in Switzerland. One of their lives is quite familiar:

Glenn launched a stage and screen career, becoming a huge star who garnered accolades and awards along the way. Jessie, the baby of the family, lived a much darker life — single mother, battling alcoholism and struggling with undiagnosed bipolar disorder. Sadly, she also spent part of a lifetime looking for love in all the wrong places.

*Resilience* is the title of Jessie's harrowing tale of what it's like to live with a mental illness and recover. It's also an apt description of the relationship between these two women, a bond weathered by time and tragedy yet bound by love.

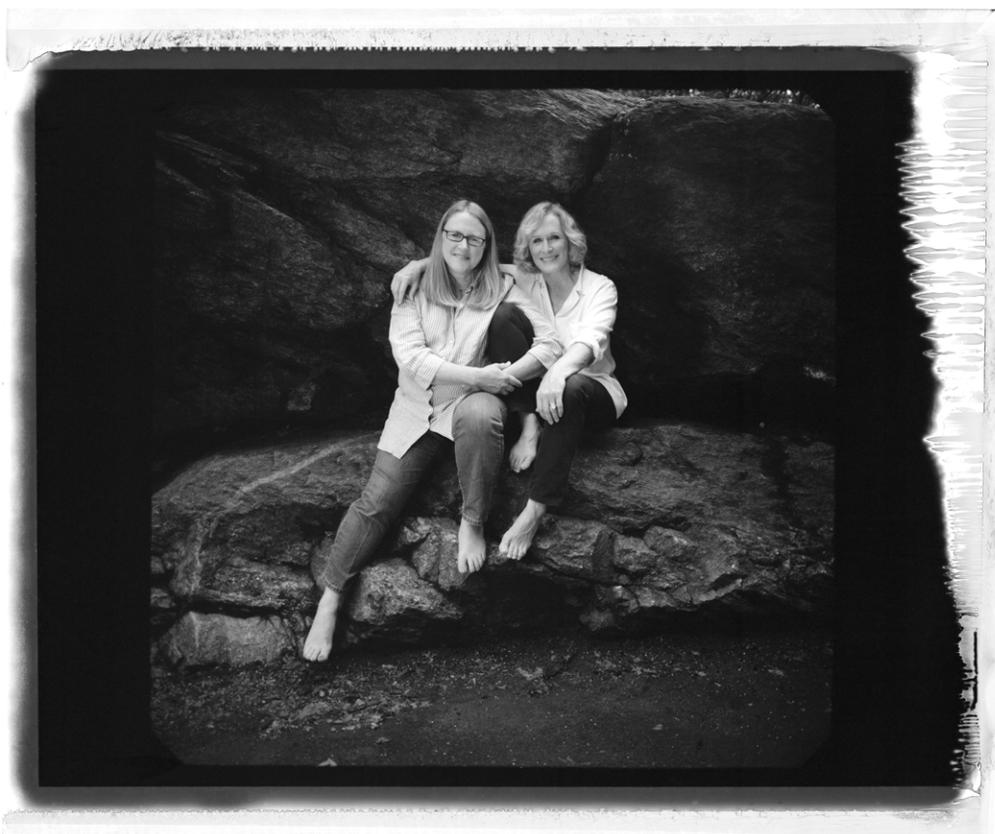
Glenn has put her star power on the line and founded a national organization — Bring Change 2 Mind — to challenge the notion of mental illness as a personal failing. Together with Calen Pick, Jessie's son who is living with schizophrenia, the Close sisters hope to dispel the portrait of the mentally ill as dangerous, unpredictable, irresponsible or incompetent. They aim to start a larger conversation. As Glenn says, "One in four people are diagnosed with a mental illness at some point in their lives, so why in the hell don't we talk about it?" A great question. So why don't we?

Glenn and Jessie spoke with the magazine's executive editor, Paul Costello.

**COSTELLO:** Can you talk about your relationship as sisters? How is it meaningful?

**JC:** Well, Glenn gave me my life back. When I told her in 2004 about the voice in my head going over and over and over that I should kill myself, she put her arms around me, told me how much she loved me and that she would help. I really don't think I could have told anybody else. She's so loving, empathetic and nonjudgmental. She's a fabulous, lovely woman.

**GC:** I don't know why but I always felt like I was Jessie's custodian. We



were brought up in a cult, basically, broken apart as a family, and we weren't given the tools of how to take care of each other. But there was something about Jess that always moved me. She was so original, magical and funny. I found out the depths of what she'd been through in her life when I first read the galleys of her book. I was absolutely pulverized about how easily she could not have been here.

**COSTELLO:** Glenn, you recently wrote a powerful article and it opened by saying, "I come from a family that had no vocabulary for mental illness." Most families don't have that vocabulary. How do we change that?

**GC:** I think it's by getting stories out. It takes courage. You have to have members of your family as courageous as Jessie and Calen to talk about what they've experienced. I know it's a big, huge step as

it's hard enough for people within families not to be stigmatized. I don't know what will be the actual tipping point to really challenge stigma except the hope that people will be honest in their own families and start a conversation so they can get the help they need.

**JC:** In writing my book, I wanted to put a human face on mental illness. I was hoping that if someone is living with bipolar disorder and they recognize themselves they would get some help. A story I like to share is about my son Calen. When he started dating his now-wife, Meg, she told her parents she was dating a young man who lived with schizophrenia, and they were horrified. I asked Meg, "What changed their minds?" She said, "They met him."

**COSTELLO:** Jessie, why did it take so long for your mental illness to be diagnosed?

**JC:** I was just considered wild and irresponsible. I don't think it even occurred to anyone that I needed help. That's the shame. People need to wake up to the behavior of their family members. When Calen was sick and the word schizophrenia was thrown around, I couldn't even hear that word without literally bursting into tears. If you have a family member who you're worried about, take the time to sit down and learn about mental illness. If you thought a family member had cancer, you wouldn't hesitate to make them go to a doctor. Mental illness is just as prevalent as cancer. It's a bad deal for our society to be so blindfolded to this problem.

**COSTELLO:** Are you hopeful that the knowledge we gain from discoveries about the brain will lessen the stigma against the mentally ill?

**GC:** Absolutely. I hope so. The more people understand that it's a part of the human condition because we are so delicately wired, the better. Our brains are just a phenomenon of nature. More often than not, there are things that can go awry. The more we can understand that having a mental illness is not aberrant with being a human being, then hopefully it will change perceptions.

**COSTELLO:** Jessie, how did stigma impact your life?

**JC:** When my youngest and only daughter was 10, I was properly diagnosed with bipolar disorder. I was afraid that if my daughter's friends' parents found out that I lived with a mental illness they would not let their daughters play with mine. I had no comforting words — not only from larger society, but from anybody — telling me, "It's OK. It's just an illness. You can handle it. You can recover." I tried to hide it.

**GC:** I recently did an interview and spoke about my mild depression. It was tough. It gave me an inkling of how courageous Jessie and Calen are to talk about the most scary diagnosis of all, schizophrenia. The mere word, schizophrenia, is stigmatized.

**COSTELLO:** Are there some heroes that you think are really challenging the misconceptions?

**GC:** I think it really helps when you have someone like the New York Jets wide receiver Brandon Marshall talking about his mental illness. It's very powerful, as in his profession, football, you're supposed to be invincible. It really does help to have someone who is considered one of our great athletic heroes come out and say, "I have this illness, and I am getting help." I hope more people do that.

**COSTELLO:** Glenn, what's Hollywood's role in perpetuating myths about mental illness?

**GC:** Hollywood is always looking for antagonists in its storytelling. And, unfortunately, somebody who is considered mentally ill can be made into a scary antagonist. It's the easiest path to put a gun or, as in *Fatal Attraction*, a knife in somebody's hand. I hope there will be fewer of those films, as they just perpetuate stigma in a terrible way. There are good examples, though. Claire Danes' character on *Homeland* is living with bipolar disorder. Films have made heroes of people dealing with mental illness. We just need more.

**COSTELLO:** Since you have been involved in mental health, do you look at roles you might consider differently now?

**GC:** Absolutely. I've turned down parts I thought irresponsible. I don't want to perpetuate the really dangerous stigma around mental illness in the work I do.

**COSTELLO:** What do you each personally hope to accomplish in the area of mental illness?

**GC:** I want to stir an open conversation about mental illness so we talk about it like we do any other chronic illness. Calen, Jess and I went to Washington and talked to legislators about mental illness. I know we think, "Oh, Washington is so broken." But those of us who care deeply about certain issues, you show up, and it can make a difference. Calen's story about how he fought so hard to get well made a difference in our conversations in Washington. Telling his story was just so effective because it's authentic.

**JC:** I was untreated for my mental illness for most of my life, but these last few years, I am the luckiest woman alive. I am making up for lost time. I hope that the programs of Bring Change 2 Mind will change

some minds. I hope that children grow up knowing that mental illness is simply an illness. I hope that if somebody in high school is feeling suicidal, they will talk to somebody about it. I hope that science will give us breakthroughs and we will find better treatments and possible cures.

*This interview was condensed and edited by Paul Costello.*

## WEB EXTRA

Hear the full conversations at <http://stan.md/1UnQJQF>  
More information: [bringchange2mind.org](http://bringchange2mind.org)

# OVERFLOWING LIVES

“I’M GOING TO TELL MY MOMMY AND DADDY THAT YOU STILL WEAR DIAPERS!” It was Rachel Hayes’ nephew, a toddler, who had pushed open the door of the bathroom to discover her in a diaper. He stood in the doorway ready to give her a scold; he himself was trying to move from diapers to the toilet and was shocked to discover his aunt’s secret.

Rachel Hayes (a pseudonym) is a university professor with multiple sclerosis, a disease that often causes urinary incontinence. She wears diapers every day. Patiently, she talked to the boy. “I told him his parents already knew that I wear a diaper and that when I was his age, I learned to use the toilet like a big girl. But a long time later something broke in me.”

The boy was satisfied, but it left Hayes with that uncomfortable feeling of not being a grown-up. “It was a moment,” she says. “Incontinence makes me feel less adult.”

**SELF-IMPOSED SECRECY** Many of us experience urinary incontinence at some time in our lives. Estimates run from 20 to 50 percent of the people not living in institutions. The numbers are much higher for those in nursing homes. It’s common among young adults and ever more common as we age. Yet adult diapers are too often the stuff of jokes instead of serious discussion, and many people suffer silently.

Incontinence has deep effects on our self-image; on our relationships with partners, family and friends; and on the way we conduct and live our lives — even who we are. At its core, incontinence affects not only our relationships with others, but our relationship with our own bodies, plunging us back into childhood anxieties most of us think we left behind when we mastered toilet training.

To avoid embarrassment, many men and women give up favorite activities like running, dancing or going to movies and concerts. Others “pad up” and carry on as normally as possible. Sometimes the

BY JENNIE DUSHECK

ILLUSTRATION BY GISELLE POTTER

HOW  
URINARY  
INCONTINENCE  
CHANGES  
US



challenge is the logistics of incontinence — the diapers and the need to be near a bathroom at all times. It's having to jump up in the middle of a movie two or three times to go to the bathroom.

But the secrecy, the sudden unexplained exits from a friendly social situation, and the background shame people carry around with them create barriers to intimacy of all

Enemchukwu says studies report poorer marital relationships and overall quality of life, libido and sexual satisfaction in women with incontinence. "Embarrassment and shame are common themes," she says.

The mechanics of men's incontinence sometimes differs from women's. But the overlap in both symptoms and causes

## SHE SAYS SHE DOESN'T WANT TO DISAVOW HER

kinds. Many people go decades without telling their closest friends or even their own doctor.

In a study of 131 women living in Israel under age 65 who had urinary incontinence, three-quarters delayed seeking help for at least a year and nearly half put off telling their doctor for three years. Doctors estimate that half of men and women who have incontinence never look for medical help, most likely because of embarrassment and the belief that the condition is an inevitable part of aging, childbirth or, in some cases, a neurologic disease like Hayes' M.S.

Stanford professor of obstetrics and gynecology Bertha Chen, MD, says, "Patients don't want to feel embarrassed about talking to their doctor and then have the doctor say, 'There's nothing I can do for you.'"

Chen, an expert on urinary incontinence who is researching treatments with stem cells, says that 50 to 60 percent of women experience incontinence after giving birth. For many, that's just a few drops when they laugh; it doesn't affect them much and they can heal with time and exercise. But others have more severe incontinence that medical care could treat or even cure, says Chen.

By age 65, about 30 percent of men and 55 percent of women experience some degree of incontinence, according to the Centers for Disease Control and Prevention. By age 80, more than half of men and women have incontinence, in about equal proportions. For men and women in the last decades of life, severe incontinence can drastically alter quality of life and contribute to the likelihood of entering a nursing home.

### LEFT OUT: SEX, ACTIVITIES, TRAVEL AND RELATIONSHIPS

**E**kene Enemchukwu, MD, an assistant professor of urology at Stanford, says some of her female incontinence patients say they don't want to be intimate with their spouses because they are afraid they will leak. "And you find the same thing for men with incontinence," she says.

is huge and the resulting effects on self-image don't differ much, say doctors.

Incontinence can have profound effects on sexual relationships. But many partners who communicate well can overcome those embarrassing moments. Dealing with the outside world can, in many ways, be much more complicated.

Rachel Hayes' incontinence began about two years after her initial M.S. diagnosis 17 years ago. At first it was a minor annoyance, but as the disease continued to damage her nerves, her incontinence has become more frequent. "Now I don't leave the house without being fully padded at all times, so it's less of a moment-by-moment social problem," she says. But she still has occasional accidents. A large amount of urine means changing her pads and finding a discreet place to dispose of an adult-sized diaper. "I always have this anxiety, which doesn't add to my social charm."

Some situations are just inherently problematic. "The way the bladder muscles work, if I'm sitting listening to a lecture at the university, I'm fine. But as soon as the lecture is over and everybody stands up, I have to split for the bathroom." It's socially awkward, she says, to be the one who never hangs around to talk with other faculty.

"There are things I avoid I wouldn't otherwise," says Hayes. "In summer, someone will say, 'Let's go swimming,' and I'll stay on the beach.

"I feel like I would be more social if there wasn't this added layer of complexity. I can't be spontaneous."

Incontinence means getting to the bathroom quickly, whether to avoid an accident or to deal with the fallout of an accident. Travel — whether a two-hour drive to the shore or a three-week trip to India — makes that tough or impossible. In a new place, it's not always clear where the bathrooms are, or even if there are any. And carrying enough adult diapers or disposable underwear means more suitcases and the risk of running out in a place where you can't buy more.

Hayes' academic interest in identity gives her special insights into her incontinence, too. She says that people who

are older tend to think of themselves as disabled. Meanwhile, people who are disabled tend to think of themselves as older. In both cases, they are distancing themselves from their situation, saying to themselves, “This is not part of who I am,” says Hayes.

She says she doesn’t want to disavow her incontinence but

affects feelings of self-worth.”

Jane Eden (a pseudonym), a Midwestern health writer, is facing the question of a nursing home for her elderly mother, Sam (also a pseudonym). Sam lives with Eden’s sister, who does most of the work of caring for her. At 100, Sam is active for her age; a personal trainer comes once a week to help her

## INCONTINENCE BUT TO ACCEPT IT. ‘I AM AN INCONTINENT PERSON,’ SHE SAYS.

to accept it. “I am an incontinent person,” she says.

For many, our very relationship with the bathroom changes. Many people suffering from urge incontinence find themselves rushing to the bathroom, only to get there a little too late. Others, especially men with hesitancy issues, may find themselves unable to empty their bladder, forcing them to return again and again. And still they leak.

### THE NURSING-HOME DILEMMA

**O**ne of the most profound effects of urinary incontinence on relationships comes when people can no longer care for themselves. At best, they become a burden to their family. At worst, family is overwhelmed and gives up.

Having incontinence doubles a woman’s risk of ending up in a nursing home and triples the risk for men. It’s not necessarily a direct cause. Instead, incontinence is associated broadly with frailty and dementia, independent risk factors for nursing home placement.

Incontinence in the aging is tangled up with many other problems. Says Chen, “I’ve had numerous incontinence patients who, as they age and develop hip problems or arthritis, basically stay home because they can’t get to the bathroom quickly.” Psychologically, when people are confined to home, she says, it promotes depression, which is common in the elderly.

Self-esteem declines, Chen says, and people who are incontinent begin to think about themselves in a different way. Their relationship with themselves changes. “They are not confident about going out; they worry how they smell. These are all things that make the person spiral downward, not feeling very good.”

Eric Sokol, MD, associate professor of obstetrics and gynecology and co-chief of urogynecology and pelvic reconstructive surgery at Stanford, agrees. “We have patients every day who say they feel embarrassed and ashamed. In fact, there are validated studies that show that depression is much more common among patients with incontinence. It really

exercise. But she’s frail, incontinent and increasingly demented. When Sam’s incontinence first started, Eden was worried about how to bring it up.

“I noticed my mother was starting to stuff little wads of toilet paper in her pants and also walking fast to go to the bathroom,” says Eden. Because her mother had already broken some bones falling while rushing to answer the telephone, Eden wanted to find a way to stop this hurrying to the bathroom.

Among the elderly, rushing to the bathroom is a leading cause of falls, and falls lead to fractured hipbones, which lead to hospitalization, rapid decline and death.

“I was really worried about having that delicate conversation. So I said, ‘Mom, why don’t we just get some pads for you so you don’t have run to the bathroom and that way I don’t have to worry about you.’ And she was just like, ‘Fine, that sounds like a great idea.’”

But as the incontinence has become more severe, it’s been harder for Eden to cope. “She needs so much help in the bathroom now.” Eden, an accomplished athlete, gets serious back pain from just a day or two of getting her mother onto the toilet, cleaning her up and then back off five times a day.

Most days, Sam sits all day, which leads to pressure sores, which make her vulnerable to infections. That means that on each trip to the bathroom she needs a thorough cleaning and treatment with creams. Even with outside help, the trips to the bathroom constitute an exhausting, backbreaking regimen for her two daughters.

Eden is on the fence about moving her mother to a nursing home. Asked about it, she thinks for a while and then says that as long as her mother has the strength to sit down on the toilet on her own and to at least help stand up from the toilet, Eden is willing to keep caring for her. The weekly visits from the personal trainer help keep her mother strong enough to do that. And when her mother is too weak to do that?

“Things could change,” Eden says slowly.

C O N T I N U E S O N P A G E 4 8

# MOMENT OF YOUTH

PEDIATRICIANS FIND OPPORTUNITY IN CARING  
FOR AT-RISK TEENS

# O

ne person in Jessica Villeola's life gives straight-up answers to her questions. He makes her laugh when she feels down. If she needs advice, he'll offer it. When she describes the void he filled in her life, that of an adult who was really paying attention, she says, "It was like I found a friend." • "When Jessica first came to the Teen Van in 2008, we talked about her goals," says Seth Ammerman, MD, clinical professor of pediatrics at the Stanford School of Medicine. "She had some good goals: finishing school, working in health care. I pointed out that those were really cool things, things that she could accomplish." • But Villeola, who was 16 at the time of that conversation, was too preoccupied to think much about a career. She had thyroid problems, symptoms of depression and no way to pay for a doctor's visit. Ammerman directs the Mobile Adolescent Health Services Program, a mobile health

BY ERIN DIGITALE

ILLUSTRATION BY GREG CLARKE

clinic known to its patients as the Teen Van. It's a service of Lucile Packard Children's Hospital Stanford and provides free health care for about 400 at-risk teens and young adults per year. Villeola went because she needed a doctor.

Ammerman's approach to patients like Villeola — simultaneously low-key, friendly and sincere — is intended to help struggling teens reshape their lives. Instead of being overwhelmed by patients' problems, which range from poverty and uninvolved families to homelessness and trouble with the law, doctors like Ammerman see their interactions with at-risk youth as an opportunity to form a uniquely powerful type of doctor-patient relationship.

So, when he first meets them, Ammerman does far more than pinpoint patients' chief medical complaints. He asks them to name their strengths. To articulate their goals. Then he says, "What do you want to work on first?"

"They've never heard of this," Ammerman says. "They've only heard how they screwed up."

**JUST KIDS** Kids who've screwed up are Arash Anoshiravani's specialty. Anoshiravani, MD, medical director of the Santa Clara County Juvenile Custody Institutions and clinical assistant professor of pediatrics at the School of Medicine, began working with incarcerated teens during a medical-school rotation in Los Angeles County. He was hesitant to go; the world of lawbreaking teenagers seemed remote from his own Southern California upbringing, where he earned good grades and competed on the water polo and swim teams at a Catholic all-boys high school before attending Stanford and Harvard.

But when he got to juvenile hall, his view of young inmates shifted.

"I was struck by how normal they were," he says. "These kids, had they been plopped into a different life or a different family, could easily have done what I was doing instead of being locked up."

Anoshiravani's instinct for social justice was spurred by hearing his patients' accounts of the violence and chaos they endured in their homes and neighborhoods. Although he saw many disadvantages to putting young people in jail, he became convinced that doctors could play a uniquely helpful role inside the justice system.

"When they're in detention, these kids are sober or becoming sober, and all those peer influences — gangs, friends, their drug dealer, intimate partners who pressure them to do things that are not good for them — are not there," Anoshiravani says. Unlike most adults working in juvenile halls, doctors have no disciplinary responsibilities. While police,

lawyers and probation officers are trying to collect evidence to prosecute young inmates, physicians aren't trying to get them in trouble. Doctors can encourage teens to reflect on what they want from their lives. "It's a huge opportunity," Anoshiravani says.

It isn't always easy. One 15-year-old gang member, charged with assault with a deadly weapon, showed such hostility during a hospital visit that Anoshiravani began to question his own safety.

"He was a big kid, probably 6 feet tall and muscular, and



visibly angry," Anoshiravani recalls. "His fists were clenched. He had hurt people multiple times, and now he was talking about how he wanted to kill members of a rival gang."

Anoshiravani took a step back from the patient and said, "Hey, let's talk about something else. Three years from now, what do you want your life to look like?"

The boy wasn't sure.

"OK, how about this? When you were 4 or 5, what did you want to be when you grew up?"

"I wanted to be a firefighter."

"Why?" said Anoshiravani.

"Because I wanted to help people and save lives," said the patient.

"But ... now you just want to kill people," Anoshiravani said. "What happened?"

The patient was silent. Tears welled in his eyes. "When I

was 7, I was walking from my house to school alone,” he said. “Four or five big kids, 13-year-olds from the opposite gang, came to beat me up. From that time on, all I’ve wanted to do is hurt them back.”

“That just blew me away,” Anoshiravani says.

Few doctors who work with adults would consider it part of their jobs to ask *What did you want to be when you were 5? Why a firefighter?*

“For an adult, they’re maybe cheesy questions, but for an adolescent, these are *the* questions,” Anoshiravani says. “Is their life what they wanted or not? And the reality is that these are the questions that matter when it comes to their health. Their health problems are almost invariably related to behavior, and their behaviors are related to how they perceive themselves and their lives.”

## PAYING ATTENTION

It’s hard to know how frequently doctors have a lasting impact on high-risk teens’ futures. There is no research tracking long-term outcomes of such doctor-patient relationships; adolescent medicine researchers, including Ammerman and Anoshiravani, focus instead on their patients’ considerable unmet health needs. (Among their projects are a paper by Ammerman describing patients’ misconceptions about the “morning after” pill and another by Anoshiravani showing that incarcerated teens have much higher rates of mental illness than those outside the justice system.)

So, instead of a “meta” view that could be afforded by research, physicians can only rely on to their own individual experiences with patients like Jessica Villeola.

“In some ways she’s a typical patient because she had so many things going on,” Ammerman says. He had first treated Villeola as a preteen at a San Francisco clinic, the Mission Neighborhood Health Center, but got to know her better when he recommended she visit the Teen Van after her family lost their health insurance. When Villeola showed up at

the Teen Van, she needed blood tests to monitor her thyroid function, evaluation and treatment for menstrual irregularity, allergy treatment and advice on healthy weight loss. And there was the most challenging problem: She screened positive for moderate-to-severe depression.

“If you try to get the patient to change everything all at once, it’s overwhelming and never works,” Ammerman says. He asks patients to prioritize, then gradually address each problem. It takes a lot of time — Ammerman spends an hour on each appointment instead of the 10 to 15 minutes typical in other health-care settings, and patients often return over months or years — as well as a team of people. The van has a driver/registrar, a medical assistant, a social worker, a registered dietitian and a nurse practitioner, as well as partnerships with many Bay Area community organizations that serve at-risk youth, including schools, social-service agencies and homeless shelters. The van’s primary sponsors are the Lucile Packard Foundation for Children’s Health and the Children’s Health Fund. Samsung, along with Caroline and Fabian Pease and the Westly Foundation, funded a new mobile clinic, which went live in October.

Helping young patients also requires a light touch. Fortunately, Ammerman has no difficulty tapping his sophomore side; one recent afternoon in the Teen Van, he looked up from his computer to solemnly announce to a patient that “splinter-free toilet paper was invented in Green Bay, Wisconsin, in the early 20th century.”

“There has gotta be some lightheartedness so that patients can get a feel for you, too,” Ammerman says. “You have to show that you’re interested in them not just for their problems, but that all of what makes them up is important.”

For Villeola, receiving counseling with the van’s social worker, Patty Sotominder, as well as an antidepressant prescription and checkups with Ammerman for her medical problems, gradually shifted her sense of flatness and isolation.

‘EVEN IF I DIDN’T WANT TO TELL THEM WHAT  
WAS GOING ON, THEY KNEW IF THERE WAS SOMETHING  
GOING ON WITH ME. AND EVEN IF I  
DIDN’T HAVE ANY ILLNESS, I COULD GO AND TALK  
TO THEM AND GET EVERYTHING OUT.’

"When I was depressed, I would basically be on my own planet," she says. "I would not feel social; it would just be me in my own enclosure." Her emotional reactions were so blunted that she remembers feeling like "a body with an empty soul."

At home, Villeola, the oldest of seven siblings of a single mother, had difficulty getting the emotional support she needed. Her mom was stretched thin by being the sole provider for their family, and the two sometimes clashed. "My mom got upset when she found out that I was using birth control," Villeola says. "It was for my own good, but she didn't understand." Villeola found it easier to confide in the people at the Teen Van, who always had time to pay attention. "Even if I didn't want to tell them what was going on, they knew if there was something going on with me," Villeola says. "And even if I didn't have any illness, I could go and talk to them and get everything out."

Ammerman kept reassuring her that he saw progress, remarking that Villeola was remembering to take her thyroid medications, was gradually losing weight, had brighter moods. "When you're living it day to day, people around you may notice that you seem better before you do," he says. "I kept the focus on the small but positive changes she was making, small steps that would ultimately make a big difference."

**AN OPEN DOOR** Anoshiravani's relationships with teens can have a double-edged quality because the kids he gets to know best are those who are incarcerated for long periods or repeatedly arrested.

"For a lot of these kids who come back over and over, we are their medical home. They think of us as their clinic, which is sad," he says. But those kids do trust him. He can ask tough questions such as, "What are you gonna do when you get out if your friends offer you drugs? In the past, the easiest choice was to use; are you ready to say no this time?"

Sometimes the patient is willing to trust him quickly, possibly even at the medical checkup required for every new juvenile inmate. Anoshiravani's favorite example was a 17-year-old girl who had landed in juvenile hall after years of cycling through foster homes.

"She was really alone in the system and didn't feel like she had anyone in her life who cared about her," he says. As they talked, he asked, *What do you want to be when you're grown up?*

"I want to be a nurse or a pediatrician," the patient said.

"You know, it's interesting," Anoshiravani replied, "Dr. Klein, who held my job for more than 30 years before he retired, told me that there were 13 Stanford medical students who rotated through our clinic and told him that they

had been in juvenile hall as teenagers. So it's not impossible. Your dream could happen."

"Do you have any medical books I could borrow?" the patient asked.

Anoshiravani walked her down the hall to his office, where she chose a book on the sociology of health. A few days later, it was returned along with a tiny book review she'd written on a Post-it note. She asked for another book. She'd stop by every so often when she got stuck in her reading to ask what something meant.

**ON THE OTHER SIDE** Villeola, too, had health-care aspirations. She started investigating certified nursing assistant programs, and Ammerman encouraged her to apply.

Partway through her training, she was caring for an elderly woman with worryingly high blood pressure. She called Ammerman. "I gave her some advice about the best way to recheck the patient's blood pressure and told her that if it was still high, she really needed to call the patient's own doctor," he says. She's since asked him other medical questions, too, often about concepts she's learning. "I think it's a cool thing that she feels comfortable to call and ask," Ammerman says. In 2015, Villeola completed her CNA training and passed a state-level certification exam. Now 24, she reports she's happily married to her high-school sweetheart. Her depression and medical issues are under control, and she knows she can go back to the Teen Van, which serves patients up to age 26, if she has any questions.

At work, Villeola provides assisted-living support for seniors, helping them with daily tasks such as bathing and dressing. Some of her elderly patients remind Villeola of the time when her own motivation was at its lowest ebb. "It's something I used to see in myself, needing help to get up and do a lot of things when I was depressed," she says.

Does she think of her work as "paying it forward"? "Yes."

**EPILOGUE** By the time Anoshiravani's patient who wanted to become a pediatrician turned 18 and aged out of juvenile hall, she'd borrowed five of his books. "The last one was the clinical anatomy book all of us used in med school," Anoshiravani said. "It's an 800-page book with a lot of medical words."

When the patient was leaving, she asked if she could keep it. Anoshiravani said yes.

He tried to contact her to be interviewed for this story, but couldn't reach her. He hopes she's doing OK. He doesn't know. **SM**

— Contact Erin Digitale at [digitale@stanford.edu](mailto:digitale@stanford.edu)

# GUT

# BUST

## INTESTINAL MICROBES IN PERIL

Let's be clear:

Justin and Erica Sonnenburg, both PhD, are not advocating a return en masse to the hunter-gatherer lifestyle that has characterized 95 percent of our species' evolutionary history.

Modern society is great!

The benefits of industrial civilization are too numerous to name. Here are just a few: Abundant food supplies. Clean water. Indoor plumbing. Centralized heating. Refrigeration. Public sanitation. Vaccination. Antibiotics. An understanding of the value of hygienic practices such as washing hands and brushing teeth.

They add up to much lower infant mortality rates and three- or fourfold increases in overall life expectancies. The risks of dying from warfare or homicide have diminished in modern times. And when they do occur, we have the mass media and the Internet to trumpet the news to the four corners of the Earth.

But in mastering our environment, we've also changed it.

We've all heard the arguments that the last few centuries of urbanization and industrialization have disrupted many ecosystems, some irreversibly.

The Sonnenburgs — Justin is a Stanford associate professor of microbiology and immunology and Erica is a senior research scientist in his lab — are concerned about an ecosystem nobody ever really used to pay much attention to, mainly because it was too hard to see. To do that, we need to look deep inside ourselves.

**BY BRUCE GOLDMAN**

PHOTOGRAPHY BY TIMOTHY ARCHIBALD





CAMILLE, CLAIRE, ERICA AND  
JUSTIN SONNENBURG REAP  
WHAT THEY SOW: A HIGH-FIBER  
DIET FOR A HEALTHY GUT.

We're not talking about introspection or meditation. Look lower. Peer deeply into your bowel. Therein lies one of the most crucial of all ecosystems: your intestinal microbiota, a collection of trillions of one-celled creatures, mostly bacteria. Copious studies have implicated the gut microbiota in training the human immune system, guiding our tissues' maturation, preventing pathogenic invasions and even manipulating our thought processes.

**T**he Sonnenburgs are concerned that our modern ways — and most particularly our diet — have caused the diversity of our intestinal biota to shrink substantially. Worse, new experiments they've conducted suggest that this shrinkage may be handed down over the generations.

In recent years, technological advances pioneered by David Relman, MD, a professor of microbiology and immunology and of medicine at Stanford, have enabled scientists to conduct accurate censuses of our resident microbes. Relman — borrowing a method first put to use by micro-ecologists exploring microbial diversity in soil, bodies of water and so forth — employed rapid gene-sequencing techniques to accurately identify and count microbes from human tissues and fecal samples based on genetic “bar codes” unique to each microbial species. Before that, such censuses were conducted by culturing these microorganisms, but numerous species failed to thrive in culture, resulting in a drastic undercount.

Now we know that hundreds, even thousands, of distinct bacterial species inhabit every healthy individual's large intestine. Far from being parasitic, this community of microbes, mainly bacteria, gets along with us so well it might be viewed as an additional organ.

If your heart or your lungs or your liver or your pancreas were losing substantial amounts of cells, wouldn't you be concerned?

That's what seems to be happening to the gut communities of people who live in industrialized societies, says Justin Sonnenburg. A study performed in his lab and published in *Nature* in January 2016 suggests that a pervasive lack of fiber in the typical diet in industrialized societies

may be to blame, and that this ongoing mass extinction in our guts could be passed along to future generations. (Technically, the term “fiber” denotes any complex carbohydrates we eat but can't digest. By that definition, sawdust is fiber, for example. But Justin Sonnenburg is chiefly concerned only with the fiber our resident bacteria *can* digest. Think fruits and vegetables, not sawdust.)

If that suggestion turns out to be true, then once an entire population has experienced the loss of key bacterial species, simply “eating right” may no longer be enough to restore these lost species to the guts of individuals in that population. Those who live in advanced industrial societies may already be heading down that path.

### THE DIE-OFF WITHIN US

When it comes to diet and intestinal microbes, we denizens of the industrialized world are the abnormal ones.

Human beings have relied on hunting and gathering for 95 percent of their evolutionary history. A half-dozen studies in recent years have compared the diets and microbiota of hunter-gatherer and rural agrarian populations from Africa, South America and Papua New Guinea with those

of citizens of industrialized countries in Europe or North America. These studies have shown that the diversity of bacterial species inhabiting the intestines of individual members of traditional cultures — whose own numbers, ironically, are rapidly declining — greatly exceeds that of individuals living in modern industrialized societies. (One such comparison tallied about 1,800 bacterial species, on average, in the guts of Guahibo Amerindians of Venezuela, but only 1,200 in those of United States residents.)

In fact, these studies indicate the complete absence, throughout industrialized populations, of numerous bacterial species that are shared among many of the hunter-gatherer and rural agrarian populations surveyed, despite those latter groups being separated from one another

by vast geographic expanses for tens of millennia.

But hunter-gatherers' life spans are a lot shorter than those in industrialized societies, so what's the big deal? Actually, that's largely due to high infant mortality rates caused



OUR BENEFICIAL GUT BACTERIA FEAST ON THE FIBER FOUND IN VEGETABLES.

by infectious disease. Once hunter-gatherers get to be 30 to 40 years old, though, they do pretty well. They don't die so much from things that kill off so many of the rest of us in old age: heart disease, cancer, diabetes, autoimmunity.

"There are very few ecosystems where low species diversity is a good thing, and there's no reason to think our gut is

intake presumably most closely resemble those of our common human ancestors.

The first Hostess CupCake was sold on May 11, 1919. In 1950, its component cake mix and icing were souped up and the signature squiggle added to the top to flag the cupcake's update. By 2011, sales of the cupcake, with its single

## **FAR FROM BEING PARASITIC, THIS COMMUNITY OF MICROBES, MAINLY BACTERIA, GETS ALONG WITH US SO WELL**

### **IT MIGHT BE VIEWED AS AN ADDITIONAL ORGAN.**

any exception," says Erica Sonnenburg, the lead author of the *Nature* study and the co-author with her husband of the book *The Good Gut*, which details what's been going wrong inside of us and do-it-yourself methods to perhaps fix it.

"What has caused this loss of microbial diversity in the industrial Western world?" asks Erica Sonnenburg. "We decided to look at diet. Traditional fiber intake massively eclipses ours. We wondered, might this be the cause of our microbial species loss?"

#### **WONDER BREAD NATION**

Virtually all health experts agree that low-fiber diets are sub-optimal, says Justin Sonnenburg. Probably the chief reason is that fiber, which by definition can't be digested by human enzymes, is the main food source for the commensal bacteria that colonize our colons.

"In essence, our microbiota is like an organ for degrading plant polysaccharides," he says. "Fiber is more than a bulking agent." It's also fuel for microbes. They've got all kinds of enzymes we don't have, which allows them to chop up complex carbohydrates we can't digest on our own. Humans have genes for about a dozen enzymes that help snap apart complex carbohydrates by chewing up chemical links between different combinations of constituent sugar subunits. Our microbiota collectively boasts at least 10,000 such genes.

We don't get much fiber in our diet anymore.

The proliferation of nearly fiber-free, processed convenience foods since the mid-20th century has resulted in average per capita fiber consumption in industrialized societies of about 15 grams per day. That's as little as one-tenth of the intake among the world's dwindling hunter-gatherer and rural agrarian populations, whose living conditions and dietary

gram of fiber, were exceeding 600 million a year.

Wonder Bread, a company birthed in 1921, was in 1930 the first to start shipping pre-sliced bread nationwide, spawning the phrase "the greatest thing since sliced bread." During the late '50s and early '60s, Americans gobbled an average of a pound and a half of white bread per person weekly, deriving 25 to 30 percent of their daily calories from the cloudlike clumps of starch (1 gram of fiber per slice).

The 1950s saw phenomenal growth in sales of processed convenience foods with names like Tang, PopTarts, Velveeta and Kraft Dinner. There were Campbell's condensed soups, and there were Swanson's frozen TV dinners.

Let's not talk about Jell-O.

#### **TRANS-GENERATIONAL CURSE**

There is now some troubling evidence that our dietary decisions can dramatically alter the microbiome we bequeath to our offspring. We pass on not only our genes but our microbes to our children. While we pick up these microscopic passengers in the course of routine exposures throughout our lifetimes, one of the most significant sources of our intestinal bacterial populations is our immediate family, especially our mothers during childbirth and infancy.

In the womb, the gut is largely sterile. Kids pick up mom's microbes in the birth canal, then from close contact such as when breastfeeding, and secondarily from family members, pets and household surfaces.

The January 2016 study spearheaded by the Sonnenburgs showed, in mice, that low-fiber diets not only deplete the complex microbial ecosystems residing in the gut, but can cause an irreversible loss of diversity within those ecosystems in as few as three or four generations.

"Factors including widespread antibiotic use, more-

frequent cesarean sections and less-frequent breastfeeding have been proposed for why we see this depletion in industrialized populations,” says Erica Sonnenburg. “We asked ourselves whether the huge difference in dietary fiber intake between traditional and modern populations could, alone, account for it.”

The Stanford researchers employed several dozen young laboratory mice that had been specially bred and raised in aseptic environments so that, unlike ordinary mice (and ordinary humans), their intestines were devoid of any microbial inhabitants. These “gnotobiotic mice” are a forte of Justin Sonnenburg’s lab. He’s able to perform seminal experiments

The real surprise came after mice had been bred and maintained on low-fiber diets for a few generations. In their experimental confines, these mice were exposed to microbes only through contact with their parents. Each successive generation’s gut-bacterial ecosystem declined in diversity. By generation four, the depletion had reached a point where nearly three-quarters of the bacterial species resident in their great-grandparents’ guts appeared absent in their own. Even after these mice were put back on a high-fiber diet, about two-thirds of the bacterial species identified in the guts of their first-generation ancestors never came back.

## **‘WITHIN A FEW WEEKS WE SAW A MASSIVE CHANGE.**

### **THE LOW-FIBER-INTAKE MICE HARBORED FEWER**

by adding defined combinations of germ species to their guts and then watching how the behavior of one species affects that of the other.

After populating the mice’s guts with microbes from a human donor, the scientists divided them into two groups. They fed one group a diet rich in plant-derived fiber. The other group’s diet, equivalent to the first with respect to protein, fat and calories, was practically devoid of fiber content.

During the experimentation that followed, the researchers analyzed fecal samples from the animals. The two groups’ gut-bacteria profiles were initially indistinguishable but soon diverged. “Within a couple of weeks, we saw a massive change,” says Justin Sonnenburg. “The low-fiber-intake mice harbored fewer bacterial species in their gut.” More than half of these bacterial species’ populations had dropped by over 75 percent, and many species seemed to have disappeared altogether.

After seven weeks, the mice that had consumed a low-fiber diet were switched back to a high-fiber diet for four weeks. The mice’s gut-bacteria profiles partly recovered — probably due to an uptick in abundance of some bacteria whose ranks had declined to undetectable levels during the low-fiber-intake period. Still, this restoration was only partial: One-third of the original species never fully recovered despite the mice’s return to a high-fiber diet.

No such changes were seen in the control mice consistently fed a high-fiber diet.

### **BACTERIAL SPECIES IN THEIR GUT.’**

On the other hand, a somewhat more aggressive measure — fecal transplantation — did enable these lost species to make a comeback. Introducing fecal contents of fourth-generation high-fiber-diet mice into the intestines of fourth-generation low-fiber mice, together with putting them on the high-fiber diet for two weeks, fully restored their bacterial profiles.

Within 10 days of the procedure, the composition and diversity of the bacteria in the intestines of this group were indistinguishable from those of control mice.

#### **WHAT IS TO BE DONE?**

This was a mouse study. Might differences in human versus murine gut environments — say, the sheer length of our digestive tracts compared with theirs — make us less susceptible to the species losses described in the Sonnenburgs’ study?

“There’s no way to perform this generational test on humans,” says Justin Sonnenburg — unless, he jokes, there are families that have the odd tradition of archiving their stool.

“We haven’t found those families yet,” remarks Erica Sonnenburg.

“Mice aren’t people,” says Martin Blaser, MD, the director of the Human Microbiome Program at New York University in New York City, who did not participate in the study but is familiar with its contents. “But these results are very, very clear,” he notes. “There’s a lot of internal consistency. That’s one of the markers of scientific rigor.”

**A**BOUT 15 YEARS AGO, Blaser began advancing a theory he calls the “disappearing microbe hypothesis.” Autism, allergies, asthma, obesity, type-2 diabetes and other chronic diseases have become endemic in industrialized societies over the past 50 years — pretty much the same time frame during which low-fiber diets, births by cesarean section, antibiotics and other practices have been decimating our resident microbial populations. At the time, Blaser suggested that this is more than mere coincidence.

Since then, studies looking at these chronic conditions have indicated almost without exception that the diseased state is associated with less gut-bacterial diversity than the healthy state.

In a 2009 review Blaser co-wrote with Stanford microbiologist Stanley Falkow, PhD, whom Blaser describes as “the most important scientist in our generation in connection with studying bacteria,” the pair expanded that hypothesis, postulating that this microbiota depletion’s health effects might accumulate through generations. Blaser, whose lay-oriented book *Missing Microbes* was published in 2014, says he views the Sonnenburgs’ new study as confirming that hypothesis.

Once a society has lost a big chunk of its ancestral gut-microbe diversity, how do its members regain it?

Simple tweaks in cultural practices — for example, not washing hands after gardening or petting the dog — could be a step in the right direction, and steering away from overuse of antibiotics certainly is, Justin Sonnenburg says.

But the ultimate need is to create an environment within ourselves where the kinds of bugs that have grown accustomed to our gut over hundreds of thousands (maybe millions) of years will feel at home. “It’s now evident that everybody should be eating more dietary fiber,” Justin Sonnenburg offers.

In their everyday life, the Sonnenburgs walk the walk. They eat tons of fiber-rich vegetables grown in their own backyard. They eschew carbonated soda in favor of fiber-filled smoothies whipped up in a blender that’s always easily accessible. They bake their own sourdough, which is leavened with a starter — a fermented flour mixture that picks

up wild yeast and bacteria from the environment. They pack their kids’ lunches rather than rely on the standard low-fiber fare most children will pull off the counters in school cafeterias. They brew their own beer, still brimming with the live yeast cultures whose fermentation skills turned its constituent sugars into alcohol, as well as their own kefir: milk soured by (and teeming with) dozens of species of microbes. They got a family dog, Louis (named after Pasteur), whom they encourage to lick their kids’ faces. They’ve rolled out the red carpet for single-celled soldiers of fortune and the complex carbohydrates that fuel them. As a result, their own gut-microbial diversity has increased significantly.

For those of us who don’t happen to have all the instruments and reagents required to do our own microbe counts, members of the Sonnenburg lab are working on another “homebrew” product: a device for collecting, suspending and analyzing people’s quotidian stool samples and communicating the results to an iPhone app that would interpret the results. This project is in its early stages, but their hope is to develop a prototype of the microbiota monitor that will eventually reside in household toilets, or be deployed for field trials in developing regions of the world.

We can all take at least a few steps in that direction without too much intestinal discomfort, and some of us will be able to tolerate more acute shifts in our dietary trajectories. But what happens if that’s not enough to restore the full palette of beneficial bug buddies? More extreme measures such as mass fecal transplants — which on an individual basis have proven very successful for eradicating life-threatening, colitis-inducing intestinal invasions by pathogens such as *C. difficile* — would require large-scale testing to make sure they are both advisable and safe. (After all, who knows how those hunter-gatherer bacteria might react to a diet of Twinkies

and Velveeta?) In any case, fecal transplants from ... whom? How do you re-expose yourself to essential friendly bacteria if nobody around you is carrying them, either?

“As our modern ways spread around the globe, these traditional peoples are being squeezed into smaller and smaller spaces and rapidly transculturating,” says Erica Sonnenburg. “Our chance to learn from studying them is not going to last forever.”



**THE SONNENBURGS PACK THEIR KIDS’ LUNCHES, RATHER THAN RELY ON LOW-FIBER FARE.**

C O N T I N U E S O N P A G E 4 9

# YOU CAN GO HOME AGAIN

AN ADDICTION SPECIALIST RETURNS TO WEST VIRGINIA TO HELP

My introductory email to state Sen. Dan Foster began, “Greetings from a fellow Stanford Mountaineer.” Like many people who grew up in West Virginia, I retain loyalty to my home state as well as a desire to connect with other members of the hillbilly diaspora. I had learned from a previous issue of this magazine that, after earning his MD at Stanford, Dan went on to become a surgeon and state legislator in West Virginia. I didn’t have to guess which public policy issue consumed most of Dan’s time: addiction. My home state leads the country in tobacco smoking and in fatal drug overdose. Meth labs dot the landscape, heroin traffickers do a thriving business in some cities and, in some impoverished towns, bars and liquor stores are among the few going concerns. The prevalence of addiction makes a mockery of our state motto, “Mountaineers are always free.”

At the time of my email to Dan in 2010, I had just finished a year in the Obama White House as a senior drug policy adviser and had returned to being a psychiatry professor at Stanford and an addiction researcher in the Veterans Affairs Palo Alto Health Care System. I told Dan that what I had learned might be relevant to West Virginia’s addiction crisis. He invited me to the state capitol to speak with lawmakers about some solutions.

West Virginia is distant in many respects from Stanford University. As an academically achieving teenager, I somehow got it into my head that I could apply here, only to receive the painful news from my mother that our family could not afford for me to attend (financial aid was not so generous in those days). Much more recently, I was paging through West Virginia’s latest annual budget and noted that it was less than that of the university. Whereas opportunity was limited most of where I looked in my youth, at Stanford it never seems to end. Such contrasts tend to make us “Stanford Mountaineers” profoundly grateful that we get to partake of all the university has to offer while instilling a desire not to forget where we came from and what we owe to those who are not so fortunate.

**BY KEITH HUMPHREYS**

PHOTOGRAPH BY TIMOTHY ARCHIBALD



KEITH HUMPHREYS HAS WORKED WITH WEST VIRGINIA LEGISLATORS TO INFLUENCE PUBLIC POLICY. AMONG THEIR SUCCESSES: EQUIPPING FIRST RESPONDERS WITH OVERDOSE MEDICATION, MONITORING PRESCRIPTIONS AND BOOSTING TREATMENT PROGRAMS.

**B**EFORE I LEFT for my first trip back to West Virginia, my wife overheard me practicing my speeches to the state legislature and asked why I sounded different — I realized that even imagining speaking to my own people was bringing back my accent. Returning to Charleston, the state capital, was richly nostalgic for me. I hadn't been there since a state math contest in the ninth grade, and I still think of Charleston as “the big city” because it was the only place with more than 100,000 people I'd been to when I was growing up. I was comforted throughout my visit by the mountains all around: When I left West Virginia to pursue a Midwest education, I had been unnerved by the unlimited, empty horizon of the flat states, the absence of mountain mama cradling me in her arms.

Dan escorted me around the capital to hearings at which I testified, meetings with reporters in which I talked about the state's addiction problems, and a briefing for the governor. Everyone in the legislature treated me well, which I suspect was mainly an effect of Dan's halo, but nonetheless meant a good deal to me because it relieved my worry that I might have been gone so long that people no longer saw me as one of their own.

Starting on that first visit, I worked with the legislature on a range of policy options that I had seen be effective in other states. One was to equip first responders such as firefighters and police officers with the overdose rescue drug naloxone, which nonphysicians can safely administer to prevent brain damage or death from lack of oxygen. Another was to return cold medicines containing pseudoephedrine to prescription-only status. Pseudoephedrine is used to make methamphetamine, and states that make it a prescription drug have curtailed the explosions, fires, burns and environmental damage of meth labs.

Because careless (or intentionally inappropriate) opioid prescribing contributes to addiction and overdose, I worked with the legislature on programs that could monitor prescribers without limiting access to pain medication for those who need it. I have also spent time with state as well as city and county officials trying to scratch up some funds for addiction treatment services, which are in short supply in much of the state.

Last but not least, it struck me that West Virginia is an anomaly among states in having very low tobacco taxes despite having virtually no tobacco industry (the usual explanation for low taxes). I consider raising low tobacco taxes valuable even if the resulting revenue were burnt on the Capitol lawn, because higher prices discourage use, particularly among teenagers. But given that higher taxes would bring in revenue, why not use it to provide treatment to addicted people?

Working these issues required me to negotiate a legislative process different from my experience with the U.S. Congress.

Like many states, West Virginia has a part-time legislature, a political arrangement with costs and benefits. On one hand, every session is a mad dash in which many good bills die simply for lack of time (West Virginia's deadline is 60 days). For example, the bill to expand access to naloxone was killed by the legislative clock four times before it was passed in 2015, despite no significant opposition to it. On the positive end, part-time legislators by necessity have real jobs outside of politics, which keeps them in touch with their communities. I often find that when I work with states on mental health or addiction issues, the legislators who have the best sense of what is going on are those whose day job as a nurse or police officer or teacher brings them in touch with afflicted people.

Those of us working for better policies regarding addiction have certainly experienced struggles and disappointments. The cold medicine industry's ferocious lobbying — which one journalist commented inspired envy even from the all-powerful coal industry — narrowly defeated the effort to return pseudoephedrine to prescription-only status. Raising tobacco taxes has been a nonstarter in the past few years. The state legislature also sometimes floats bills with which I don't agree and which I don't think work, such as proposals to drug-test welfare recipients.

But I take comfort in the fact that first responders reversed 3,000 overdoses with naloxone last year, no doubt in many cases saving lives. Addiction treatment has established a beachhead in some parts of the state and has garnered some funding. The state's prescription monitoring program is better resourced and more proactive than ever before. And Gov. Earl Ray Tomblin surprised us (in a good way) by announcing in this year's state of the state address that higher tobacco taxes are now on the table.

At a personal level, reconnecting with my home state has been one of the deepest satisfactions of recent years. With my parents now retired to North Carolina and my siblings and friends having left to pursue educational and career opportunities, I probably would never have visited West Virginia again if not for my newfound legislative collaborations. Each time I see the moon rise over the Appalachians, hear the wind rustling through rhododendron-filled hollows or, most of all, hear a friendly voice say a word like “y'all” or “crick” or “leastaways,” I realize what a profound mistake that would have been. Dan, in his generous way, tells me that my state is grateful to me and continues to need me. But I think the truth is closer to the other way around. **SM**

*Keith Humphreys, PhD, is a professor of psychiatry and behavioral sciences at Stanford Medicine. Contact him at [knb@stanford.edu](mailto:knb@stanford.edu).*

---

**FEATURE**

The puzzle solver

CONTINUED FROM PAGE 15

blood samples are guiding this exploration — his entire genome has been sequenced.

“New technology is allowing us to cast a really big net,” says Mark Davis, PhD, professor of microbiology and immunology at Stanford, who is scanning Dafoe’s infection-fighting T-cells for abnormalities, as well as looking at other aspects of the immune system. “Some would call it a fishing expedition. But fishing expeditions also catch fish.”

The hope is that results from the newly launched trial of 20 severely ill CFS patients from Open Medicine Institute in Mountain View — a medical group practice that conducts research and provides care for patients with chronic illnesses — will increase the size of the net.

“You could say Whitney has been the inspiration for this study,” says Andreas Kogelnik, MD, PhD, an infectious disease specialist and director of the Open Medicine Institute. The study entails going into the homes of the patients to collect biofluid samples — the easily accessible ones like blood, urine, saliva and stool — then comparing them with those of healthy control subjects. This group of CFS patients, who have not been studied before because they are so hard to reach, is likely to show the strongest molecular signals of the disease, Ron Davis says.

Kogelnik, who treats Dafoe and hundreds of other CFS patients, knows firsthand how difficult it is to get research funding for the disease, and how difficult it is to treat patients. Getting someone of Ron Davis’ stature to bring his influence and attention to this disease has made a difference, Kogelnik says. Not only has it helped raise money for this particular study, it’s helped lend

legitimacy to a disease that struggles for acceptance. Davis’ technological inventions that have helped shape the field of genetics over the past 20 years will also make a difference, he says.

“This gene chip was designed in Ron’s lab,” Kogelnik says. He’s in his Mountain View lab, holding a thin, rectangular DNA microarray, or gene chip, between his thumb and forefinger. The gene chip is a collection of microscopic spots of DNA attached to a solid glass surface. It has on it an array of 70,000 different gene components, Kogelnik says, which will allow researchers to test which genes are turned on or off in a specific DNA sample applied to the chip. This technology will be used to test the biofluid samples from the 20 patients in the CFS study. Those results will be shared with CFS researchers. Davis’ inventions have come full circle, returning to help him discover a cure that could save his son.

**ONE RECENT AFTERNOON,** Davis is sitting behind a desk in his office at the Genome Technology Center, preparing to drive home for his afternoon session of caring for Dafoe. He’s dressed in old jeans and sneakers; his gray beard, glasses and kindly demeanor lend him a grandfatherly air. The old, brown hat waits for him on the desk.

But Davis wants to take a moment to tell a story about his childhood. It’s a story of hope. As a boy, Davis used to buy chemicals at the local drugstore to make fuels for the rockets he’d shoot off in the field out back of his house in a rural area of Illinois. Though he had dyslexia, and his teachers and father told him he’d never be college material, he knew his brain could do some pretty cool stuff. At 14, he would sneak into the local college library at night to read chemistry and physics journals, and he’d get his older sister to teach him

the advanced math she was learning in school, partly so he could make better fuel for better rockets, but mostly just for fun.

It was a chronic illness — one that left him bedbound for much of his childhood — that ultimately changed the course of his future, diverting him away from rocket science into medicine. Davis contracted a case of rheumatic fever when he was a year old that never really went away. It recurred maybe 200 times during his childhood in the form of strep throat, bringing with it high fevers, painful swollen joints and inflammation. Trapped in bed, Davis would play mind games to distract himself from the pain and the boredom. He’d dream up new three-dimensional worlds to escape into.

“I’d imagine myself being outside of my body,” he says. “Once I got there, I could go anywhere. It was so real. I could explore the room like an ant. I could slip inside the wall plug and explore the circuits. It must have been some kind of self-hypnosis. It required me to create images in 3-D. I’d rotate things in my brain. Anything spatial was always very easy for me.

“One day, I was absolutely miserable with a high fever. The country doctor came in with his little black bag and said, ‘I have something new.’ That sure made a big impression on me. He injected me with penicillin. Half an hour later, it was just like a miracle. I was completely better.

“I thought, oh my gosh, medicine can do this? And it’s a new technology. It set my course right then.”

**AT 2:30 IN THE AFTERNOON,** Davis arrives back at home, drops his hat on the kitchen counter and walks down the darkened hallway once again to take up his post outside his son’s bedroom door. These shifts provide his wife a much-

needed break in her nearly round-the-clock care of their son. As Dafoe has grown sicker, the boxes of syringes and medicine bottles in the kitchen have multiplied. Nurses and home health-care workers constantly come and go. The acrid smell of antiseptics fills the room. Ashley, an emergency medical technician, cared for her brother full-time for about a year after she graduated from college. She still helps out as much as she can, aids in emergencies, stays over with her mom when her dad travels and brings her parents food.

Janet Dafoe has saved dozens of notecards written by her son from his sickbed when he still had the energy. In January 2015, he tried to explain to his parents what it was like when they entered his room, why it took him time to prepare. He wrote:

*Someone in room feels like wind is blowing THROUGH me pulling me away like I'm made of sand and getting blown away... Draining but it goes deeper than it should. There is no part of me that is safe from it. I think it's just because of how little energy I have. When I'm alone I can ration it and think slow, use less mental energy...*

And so Davis continues to sit in the hallway, waiting for the signal to enter.

"Once you come in the room he just totally doesn't move at all," Davis says. Dafoe wears headphones to block out any sound. He hides his eyes under the bill of his cap. "He doesn't see you but he knows you are there. I don't know what he does to keep from reacting.

"He spent a year in India. He was fascinated with the Buddha. That's what makes me think that possibly he's meditating to manage the pain and isolation," Davis says. Those brightly colored Tibetan prayer flags decorating the porch were brought back from Dafoe's trip to India.

Since Dafoe's ambulance trip to the hospital in December, his parents have

been trying to add nutritional supplements to his diet through a feeding tube implanted in his gut to wean him off the IV and add missing metabolites. So far, his body has rejected most attempts at adding food supplements; they cause unbearable stomach pain and nausea. But his parents remain hopeful.

"Looking at his lab tests, he's unbelievably strong to have all these things wrong with him and still be alive," Davis says.

"I have a lot of respect for him," Davis says. He knows of other severely ill CFS patients who have killed themselves. But Dafoe is committed to doing whatever he can to help find a cure for CFS.

"He's hoping to do this for everyone with CFS," Davis says. Then he pauses. "I told him it would take a while." **SM**

— Contact Tracie White at [traciew@stanford.edu](mailto:traciew@stanford.edu)

---

## FEATURE

Come together

CONTINUED FROM PAGE 19

marshaling immune cells resting in the spleen into the skin and blood to help with wound healing, for example.

"People who are able to mobilize these immune cells quickly and correctly recovered faster, and better, after knee surgery than those whose immune cells responded poorly," says Dhabhar, who published the findings in the *Journal of Bone and Joint Surgery* in 2009. "But the amount of long-term stress an individual is experiencing seems to determine whether or not they can mount the correct protective response. If you increase chronic stress over time, two things happen. One is the baseline number of immune cells that you have to defend yourself decreases. The other is that you are less able to mobilize the cells you do have.

"What we've proposed is the concept of a stress spectrum," says Dhab-

har. "On one end, there's the 'good' stress that can be protective; on the other is the chronic 'bad' stress and disorders such as depression. Ideally we would all find ways to optimize our stress spectrum and avoid the bad stress that is associated with poor immune function and inflammation. One way to do that could be through maintaining adequate social support."

**CAN WE REALLY CONNECT** the dots between the biological effects of stress, depression and anxiety with the role played by our personal relationships and our larger social network? Increasingly, scientists are saying yes.

A 2013 study by researchers at University College London published in the *Proceedings of the National Academy of Sciences* indicated that the risk of death among elderly people was increased in those who were socially isolated, even when other mental and physical factors were taken into account, and multiple previous studies have shown that simple loneliness increases our risk for many types of illnesses, including heart disease and high blood pressure. One analysis of 229 50- to 68-year-old people conducted in 2010 as part of the Chicago Health, Aging and Social Relations Study showed that a higher degree of loneliness at the study's onset was associated with greater increases in systolic blood pressure measurements during the subsequent four-year follow-up period.

Loneliness and social isolation can be hard to define, however. Researchers at the University of North Carolina-Chapel Hill published a study in 2016 in the *Proceedings of the National Academy of Sciences* showing a direct correlation between the size of a person's social network in adolescence and early adulthood and four telling health statistics: body mass index, waist circumference,

blood pressure and the amount of C-reactive protein (a marker of inflammation) in the blood. The researchers found that in adolescents social isolation was as great a contributor to inflammation as physical inactivity; in the elderly it was an even greater risk for high blood pressure than previously known risk factors such as diabetes.

The authors suggest that being aware of and trying to minimize deficits in social relations could be one way to keep people healthy later in life.

Of course, being more connected can also increase the likelihood of unpleasant, stressful interactions. “We’ve found that when women undergo a psychological stress test, which can incite anger, anxiety or fear, their heart rate goes up, their hormone levels change and the amount of interleukin-6, which is associated with inflammatory activity, increases,” says Dhabhar. “The rise in interleukin-6 is proportional in particular to the degree of anger experienced in response to the test. However, this rise is mitigated by the amount of social support the woman expressed having during the preceding week.”

In other words, a good network of support helped the women withstand a flood of anger and anxiety without experiencing a potentially unhealthy increase in interleukin-6 levels.

“A chronic elevation in interleukin-6 levels could contribute to cardiovascular disease and other pro-inflammatory disorders. Therefore, dampening stress-induced increases in interleukin-6 may be one mechanism by which social support buffers against such diseases,” says Dhabhar.

Letting go of anger toward others also appears to be healthy. A small study of 25 people authored by Frederic Luskin, PhD, director of the Stanford Forgiveness Project, published in 2006, showed that those who entered the study with el-

evated scores on a scale designed to measure anger experienced a significant drop in blood pressure after participating in an eight-week forgiveness-training program when compared with peers who did not receive the training.

Even brain scans have shown the effects of friendship. James Coan, PhD, a professor of psychology at the University of Virginia, showed in a series of experiments that the brains of women told to expect an unpleasant electric shock activated regions known to be involved in response to a threat. Holding hands with a friend (but not a stranger), however, dampened this response. Even more interesting, the friend’s brain activity pattern began to mirror that of the person expecting the shock.

During Jennifer MacLeod’s decade in Spiegel’s peer support group, she became familiar with the power of friendship and the difficulty of watching friends suffer. “It’s such a balance,” she says, “between observing, listening and taking to heart what you need for your life, while also being appalled and terrified by what is happening to your friends. The biggest gift you can give someone who is dying, I think, is just to be there. Just walking with them. It’s incredibly important.”

**SO MAYBE WE**, and our physicians, should be tending to our social relationships with the same care that we devote to exercising, eating right and avoiding unhealthy behaviors. Heck, maybe everyone should run out and get married.

After all, a 2013 study in the *Journal of Clinical Oncology* of over 700,000 people with cancer showed that married people are diagnosed earlier and are about 20 percent less likely to die of their disease than are unmarried people. A study published in *Cancer* in April 2016, conducted by Scarlett Lin Gomez, PhD, a consulting associate professor in health

research and policy at Stanford and a researcher at the Cancer Prevention Institute of California, concurred. Gomez and her colleagues found in a study of nearly 800,000 cancer patients in California diagnosed between 2000 and 2009 that those who were married were significantly more likely to survive than those who were unmarried, regardless of whether they had health insurance or of the socioeconomic status of the neighborhoods in which they lived.

Of course, marriage isn’t a panacea. But it’s becoming increasingly clear that relationships with peers, spouses, physicians and caregivers contribute in a meaningful way to health and to our ability to recover from disease and trauma. And health-care providers are taking note. Cheryl Koopman has studied the effect of using videoconferencing technology to conduct peer support groups among women with breast cancer in rural California.

These women bonded through shared experience to help each other through tough times. “Women in small communities can start to feel like they are living in a fishbowl, where everyone knows about their cancer but few people can truly share their experiences,” says Koopman. “We’ve found that breast cancer survivors readily adapt to giving and receiving support through video. This was clear when one woman ‘hugged’ another visually through the monitor. They really were supporting one another.”

MacLeod recalls the vital role the in-person peer support group played in her life and that of her friends.

“One day, after about 10 years, David came in to tell us that the study was ending and the group would not continue. By that time, we’d had a lot of turnover as previous participants died and were replaced with new people, who had also come to rely on the

group. We were horrified. I really think we could have attacked him, we were that angry. ‘You can’t do this. You just can’t,’ we said.”

Together the women agreed that they would each pay out of pocket, if necessary, to keep the group going.

“We’ve worked the bottom-up medical model as hard as we can, learning how to treat acute medical problems like diabetes or a broken leg,” says Spiegel. “But the better we get at that, the more people are left with chronic illnesses like managed cancer or heart disease. Increasingly we’re seeing people having a lot of trouble handling stress and pain and who want nonpharmacological ways of dealing with these issues.

“Social connection, especially in the face of illness, I think is a very powerful ally. It helps us manage our stress responses, it helps our bodies do better and helps us to help one another get through life-threatening situations. It makes complete sense.” **SM**

— *Contact Krista Conger at kristac@stanford.edu*

---

## FEATURE

Overflowing lives

CONTINUED FROM PAGE 31

It won’t be an easy decision. “My biggest fear is that if we take her to a nursing home, they won’t clean her the way we do and she’ll just die of sepsis in a month or two or three.”

### THE SCOPE OF THE PROBLEM

Urinary incontinence is a significant contributor to the cost of health care, on the order of \$76 billion. That includes direct costs such as diagnosis, treatment, incontinence pads and complications as well as indirect costs such as lost wages by patients and caregivers. The adult diaper market alone is about \$1.5 billion per year.

Our demographics are such that a greater and greater proportion of the population will be coping with incontinence in coming decades. “There are suggestions,” says Sokol, “that there won’t be enough physicians trained to take care of this as the population of patients with urinary incontinence grows.” In fact, Stanford has a fellowship program designed to increase the number of urologist and ob-gyn doctors specializing in urinary incontinence and other pelvic floor problems.

An equally serious problem is getting patients to see a doctor who can help, says Sokol, who specializes in pelvic reconstructive surgery. “A lot of patients don’t know what their options are.” They could be candidates for surgical procedures that support or reinforce the urethra and bladder, but getting them to the right specialist is a piece of the puzzle.

“For Mother’s Day,” he says, only half joking, “instead of brunch or a day at a spa, how about getting her an outpatient urethral sling?”

Enemchukwu, a specialist in minimally invasive surgical treatments for incontinence, says that even for older patients like Sam, many treatments are available, ranging from drugs to office-based procedures and outpatient surgeries. But for the elderly, there are special challenges. For example, to make behavioral changes such as cutting back on drinks that can irritate the bladder, going to the bathroom on a schedule or reminding an older person do pelvic floor exercises, you need complete buy-in from all the caretakers, she says.

And that’s often challenging for both patient and caregiver. For caretakers, it can feel like one more source of conflict with the patient, one more thing to coordinate with other caretakers, one more burden. For patients, it’s another step in the relentless loss of autonomy that marks the last years for so many of us. House-

bound and forgetful, a person at least wants to be able to have a cup of coffee.

Enemchukwu also says she avoids medicines that can cause side effects such as confusion in the elderly. Studies suggest an association between long-term use of some incontinence medications and dementia, she says. “In the elderly, confusion may have many causes,” she says. “Is it a medication, dementia, an infection or another illness? You have to be really careful.” For urge incontinence — that “got-to-go” feeling — she recommends advanced therapies that calm the bladder directly — through bladder injections, implanting a pacemaker-like device or similar treatments. “These eliminate the need for daily medications for most patients.”

### AN EXPERIMENT

Finding a doctor who can help requires pushing through that first bit of embarrassment to bring up what’s happening. And it means asking to see a specialist if your doctor doesn’t offer much in the way of help.

When Karen Wood (a pseudonym), a retired nurse who lives in Florida, first sought medical care for her stress incontinence, a Florida gynecologist installed a urethral sling. Unfortunately, it didn’t work. Wood’s case was difficult, as she’d had a hysterectomy and various other surgeries that had left her increasingly incontinent over eight years. She went back and he gave her medications, but those didn’t help either. Finally, her doctor suggested she see a pelvic floor specialist.

“I realized that Medicare would allow me to come to Stanford, and my sister lives here, so three years ago I called and got an appointment with Dr. Sokol,” says Wood.

Sokol, who does research in novel therapies for incontinence and pelvic floor disorders, suggested a gel-like

bulking agent injected into the muscle of her urethral sphincter — a ringlike muscle that holds urine in — and that helped a lot, says Wood. But the cure lasts only 18 to 24 months, after which patients get another injection.

When it was time for her next injection, Sokol mentioned an alternative, a clinical trial that involved injecting thigh muscle cells into the urethral sphincter. Enthusiastically, Wood signed up.

“So in June, they took a bit of tissue from my thigh muscle,” she says. Not long after, Sokol made another injection into her urethral sphincter. It was a blinded study, though, so Wood doesn’t know if she got the experimental muscle-cell treatment or if she was in the control arm of the experiment. At six months, however, she reported an 80 percent improvement in her incontinence. By February, she had stopped wearing pads and reported almost no incontinence.

“I still occasionally have a few drops, but that’s because I go back to my old nursing habits and hold it too long. If I just go to the bathroom when I have to go, I don’t have any leaking problems.” Even sneezing and coughing don’t make her leak. “It’s amazing!” she says. At 69, Wood is delighted to be continent again.

Her advice for others is to get medical help. “Don’t let it affect your life. Get treatment. Get help. And don’t be embarrassed because, you know, it happens to most of us. There are a lot more treatments available now.” **SM**

— *Contact Jennie Dusbeck at [dusbeck@stanford.edu](mailto:dusbeck@stanford.edu)*

---

## FEATURE

Gut bust

CONTINUED FROM PAGE 41

Blaser and Justin Sonnenburg have embarked on a collaborative effort with a half-dozen other investigators to study the Hadza, a remnant of a Tanzanian hunter-

gatherer society with a population of perhaps 300, to better understand the microbiota of people from traditional cultures.

The field researcher who collected the stool samples has also performed, in a personal experiment, a fecal transplant on his apparently perfectly healthy self using material from a Hadza donor. Perhaps it will make sense at some point to harvest and expand libraries of microbial populations from hunter-gatherers for distribution to moderns with recalcitrant germ deficits. But, Erica Sonnenburg says, even if you were to get a fecal transplant from a hunter-gatherer, it’s not clear that those good, rare microbes would stick around if you don’t eat right.

In the future, the Sonnenburgs hope to run a mouse trial in which the initially germ-free mice receive gut microbes from a Hadza donor, to see what kind of diet is necessary to maintain a healthy gut microbiota.

Justin Sonnenburg and David Relman have been named co-directors of Stanford’s Institute of Immunity, Transplantation and Infection’s newly launched Center for Human Microbiome Studies. Among the projects being planned within the new center is a collaboration between Justin Sonnenburg and Christopher Gardner, PhD, a professor of medicine who has focused on diet. Sonnenburg and Gardner intend to initiate a large-scale, long-term, human-diet trial in which people will be fed different diets — for example, high-fiber, plant-rich diets versus more standard Western diets in combination with fiber supplementation — to see if improving the diversity of their microbiota translates to improved health outcomes.

“The hope is to move toward a precision approach to diet: ‘You have microbiota type X, and you are suffering from disease N, so you should eat A and B but not C,’” Justin Sonnenburg says.

Meanwhile, there’s no cause for

### Executive Editor:

PAUL COSTELLO

### Editor:

ROSANNE SPECTOR

### Associate Editor:

KATHY ZONANA

### Art/Design Direction:

DAVID ARMARIO DESIGN

### Director of Print and Web Communication:

SUSAN IPAKTCHIAN

### Writers:

BECKY BACH

KRISTA CONGER

ERIN DIGITALE

JENNIE DUSHECK

BRUCE GOLDMAN

STEVE FYFFE

KRIS NEWBY

RUTHANN RICHTER

TRACIE WHITE

### Copy Editor:

MANDY ERICKSON

### Circulation Manager:

ALISON PETERSON

*Stanford Medicine* is published four times a year by the Stanford University School of Medicine Office of Communication & Public Affairs as part of an ongoing program of public information and education.



© 2016 by Stanford University Board of Trustees. Letters to the editor, subscriptions, address changes and correspondence for permission to copy or reprint should be addressed to *Stanford Medicine* magazine, Office of Communication & Public Affairs, 3172 Porter Drive, Palo Alto, CA 94304. We can be reached by phone at (650) 723-6911, by fax at (650) 723-7172 and by email at [medmag@stanford.edu](mailto:medmag@stanford.edu).

To read the online version of *Stanford Medicine* and to get more news about Stanford University School of Medicine visit <http://med.stanford.edu>. For information from the Stanford University Medical Center Alumni Association visit <http://med.stanford.edu/alumni/>.

despair. “The extremely low-fiber intake in industrialized countries has occurred relatively recently,” he notes. Nor is there room for complacency. “We’re about two generations down the road,” says Erica Sonnenburg. “Is it possible we could have a deep descent if we keep it up?” **SM**

— *Contact Bruce Goldman at [goldmanb@stanford.edu](mailto:goldmanb@stanford.edu)*

# MICROBE MENTORING

**THE RECIPE FOR SUCCESS INCLUDES INDEPENDENCE,  
A GENTLE SHOVE AND A GOOD STIFF DRINK**

To get to associate professor Denise Monack's office, you walk through emeritus professor Stanley Falkow's. "Which I finagled," Monack says. • Not every faculty member would want her lifelong mentor sitting outside her door. But Monack, PhD, and Falkow, PhD, are no ordinary pair. • In 1984, Monack was fresh out of college at UC-Davis when she applied for a technician position in Falkow's lab in the Department of Microbiology and Immunology. "I had no clue how famous he was," she says. The legendary microbe hunter posed two questions: Could she handle profanity? Could she work independently? Yes to both, Monack said.

For the next 14 years, Monack managed Falkow's lab and conducted her own research experiments, developing an animal model for whooping cough and investigating host cells' proclivity to commit suicide rather than be infected with salmonella.

"We had to learn more and more about the biology of animal cells and human cells, and it was a difficult transition but we

made it," says Falkow, the Robert W. and Vivian K. Cahill Professor in Cancer Research, Emeritus. "And in no small measure thanks to her, because she was the common denominator through all these generations of students, and she was the giver of lore to the lab. It got to the point where if you wanted to know something, you asked Denise."

That said, Falkow was concerned about his lab manager's future. "She was able to publish, but she was stuck here and there was no way for her to advance in the system," he says. "She was basically giving away a lot of her knowledge and her skill to other people."

It was time for what Falkow calls a "gentle shove." As Monack remembers it, "He said, 'You know, Denise, I really think you, in the future, would be happiest if you got your PhD. When I go to the big petri dish in the sky, it's going to be hard for you to find another position where you have the freedom that you're used to, and you might be miserable.' And I thought about this, and I realized, he's 100 percent right."

Monack got her PhD at Stanford and was interviewing for positions around the Bay Area when Falkow was diagnosed with a leukemia precursor. She stayed at Stanford to manage his lab as he prepared to retire, and later joined the faculty.

The longtime collaborators distanced themselves until Monack had tenure. Monack worked on *Francisella tularensis*, a pathogen Falkow had never studied; Falkow decided never to publish with Monack again. "I had to stay away and she needed me to stay away," Falkow says.

"Are the rest of the faculty going to think this is really Stanley's lab and Denise is the puppet?" Monack remembers wondering. "It all worked out in the end, but it was not trivial."

As their relationship transitioned from supervisor-employee to adviser-doctoral student to a pair of colleagues, Falkow added one last key ingredient. After Monack gave a presentation at a conference in Cold Spring Harbor, New York, Falkow bought her a congratulatory beverage. "Ever since then, I've become a connoisseur of single-malt whiskeys," says Monack. "And whenever I think I've tried one that he's never tried, I'm wrong. But last week I found out there is one I love and he's never tried it. So I bought him a bottle of that for his birthday." Says Falkow, "She takes care of the old man in my declining years." — KATHY ZONANA



**Stanley Falkow thought his longtime lab manager would be happier if she got her PhD. Denise Monack, now an associate professor, says "he's 100 percent right."**

Stanford University  
School of Medicine  
Office of Communication and Public Affairs  
3172 Porter Drive  
Palo Alto, CA 94304

*Change Service Requested*

# The inner lives of dolphins

MARINE MAMMALS CARRY AN UNEXPECTED MICROBIAL MIX

For more than 50 years, the U.S. Navy has used trained dolphins to find submerged sea mines and detect underwater intruders. Now it appears that the intelligent marine mammals have been hiding some secrets of their own. In a paper published Feb. 3 in *Nature Communications*, Stanford researchers say they discovered a startling variety of previously unknown bacteria living inside the dolphins, and to a lesser degree in U.S. Navy sea lions. • “About three-quarters of the bacterial species we found in the dolphins’ mouths are completely new to us,” says senior author David Relman, MD, professor of medicine and of microbiology and immunology. Lead author Elisabeth Bik, PhD, is a research associate in Relman’s lab.

What they’re learning about the microbial communities within marine mammals is not only a boon for zoology; it could prove useful for monitoring the health of the animals and their habitat, which is under siege from forces such as pollution, warming and overfishing.

Relman started working with the Navy dolphins more than 15 years ago, when he was asked to identify bacteria suspected of causing stomach ulcers in the animals. His efforts to catalog their bacterial communities were prompted by a request for a probiotic strain to keep the dolphins healthy. Navy trainers took regular swabs from the animals’ mouths and rectal areas, as well as obtaining gastric fluid from tubes the dolphins swallowed, samples of air the dolphins exhaled from their blowholes and sea water adjacent to each animal, and shipped them to Stanford for analysis.



Relman’s team also examined oral, gastric and rectal samples from the Navy’s trained sea lions, which revealed an interesting contrast: Even though the sea lions are fed the same fish as the dolphins, and swim in the same water, their bacterial communities are more like those of dogs and cats. The researchers’ next step is to look at samples taken from killer whales, sea otters, gray whales, harbor seals, elephant seals and manatees to understand the general impact of life in the sea on the marine mammal microbiota.

“There’s a lot of concern about the changing conditions of the oceans and what the impact might be on the health of wild marine mammals,” Relman says. “Among other things, we would love to be able to develop a diagnostic test that would tell when the marine mammals are beginning to suffer from the ill effects of a change in their environment.”

— STEVE FYFFE

TO SUBSCRIBE  
TO STANFORD MEDICINE  
email [medmag@stanford.edu](mailto:medmag@stanford.edu)  
or call (650) 723-6911.