

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

Summer 2011

special report

SURVIVING SURVIVAL

BACK TO LIFE

Crashing to Earth

A love story

Kids and cancer
Can I go back
to the
playground, please?

Just do it
On doctor's orders

Khmer Rouge on trial
Is justice a cure for PTSD?

Lucky stroke
Jill Bolte Taylor on inner peace



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THE TROUBLE WITH EARLY BLOOMERS

WHY SO MANY PREEMIES?

David Stevenson, MD, wouldn't mind putting himself out of business. • Over the last 30 years, Stevenson's field, neonatology,

has undergone a giant shift. New inventions such as better treatments for newborn jaundice and for preemies' immature lungs now allow doctors to save many early arrivals who would once have died. • But preemies' stories don't end when they leave the neonatal intensive care unit. Many of these survivors — born between three and 18 weeks early — endure lifelong health problems, such as cerebral palsy, developmental delays and impaired vision and hearing. So Stanford scientists, led by Stevenson, are taking a new approach: attempting to prevent preterm birth altogether. They want to get to the bottom of a dramatic, and largely unexplained, increase in preterm births, which have risen 30 percent in the United States since 1981.

• By helping women carry their pregnancies to term, "We hope to obviate the need for what we've already

invented," says Stevenson, vice dean of the School of Medicine and director of the Johnson Center for Pregnancy and Newborn Services at Lucile Packard Children's Hospital.

One in eight infants is now born early, for a total of a half-million preemies per year. Though some of the increase is explained by other changes — rising maternal age, more maternal obesity and more multiple births due to fertility treatments — about half of preterm deliveries happen for reasons unknown.

"There's a clear need for new research that addresses this challenging public health problem," says Stevenson. He is directing a new center, launched this spring by the March of Dimes Foundation, to understand what triggers preterm birth, predict which women are at risk and translate the new knowledge into strategies to prevent early delivery. The March of Dimes Prematurity Research Center at Stanford University School of Medicine will bring together experts from fields such as obstetrics, sociology, bioinformatics, engineering and public health. The foundation is donating \$2 million per year for 10 years to support their work.

One planned project will examine how infection triggers preterm birth. It's already known that infection in the uterus can cause early labor, but the mechanism is unclear. In addition, it appears that various forms of disturbance in the communities of microbes that normally inhabit

the human body may also lead to early labor. David Relman, MD, professor of medicine and of microbiology and immunology at Stanford, will lead the effort to characterize the microbes that cause these infections and understand how maternal immune responses trigger early labor.

The new center is the first of its kind; March of Dimes may eventually sponsor others as its funding permits. In addition to the broad expertise of its leaders, center research will employ state and national information, including California Perinatal Quality Care Collaborative statistics and the U.S. Standard Certificates of Live Birth data set. These comprehensive resources have the advantage of surveying large populations, giving a more nuanced view than researchers can obtain with small studies at individual hospitals.

The research team ultimately aims to replace high-tech NICU wizardry with methods to stop babies from being born early in the first place.

"As neonatologists, we'll be glad to see this change," Stevenson says. — ERIN DIGITALE

BRIAN CRONIN



S T A N F O R D
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SPECIAL REPORT

Surviving survival

The journey continues

Illness: a great excuse to exercise,
page 18



Between the two of them, they've got one pretty good brain,
page 10



Back to life,
page 8

- 10 The woman who fell to Earth** By Ruthann Richter
A LOVE STORY

- 18 Rxercise** By John Sanford
GET PLENTY OF REST? THAT'S SO RETRO

- 22 A kid again** By Erin Digitale
AFTER CANCER TAKES ITS TOLL

- 26 Her stroke of insight**
JILL BOLTE TAYLOR ON MINDING YOUR BRAIN

- 28 Khmer Rouge on trial** By Tracie White
CAN SERVING JUSTICE CURE PTSD?

PLUS

- 36 The bodyguard** By Bruce Goldman
TAPPING THE IMMUNE SYSTEM'S SECRETS

- 40 Cadaver 2.0** By Tracie White
TESTING A VIRTUAL DISSECTION TABLE FOR TEACHING ANATOMY

DEPARTMENTS

- | | |
|-----------------------|-----------|
| Letter from the dean | 2 |
| Upfront | 3 |
| Letters to the editor | 44 |
| Backstory | 46 |



letter from the dean

IT IS SOMETIMES easy to forget how many individuals are survivors of life-threatening diseases incurred years, or even decades, earlier. This is particularly true for some of the most serious childhood diseases.

When I began my training in pediatrics in the 1970s, most children diagnosed with cancer did not survive. It was rare for children with cystic fibrosis to live beyond their teenage years. Many children with congenital anomalies — especially cardiac defects — were at risk for early mortality. And when HIV/AIDS came on the scene in the early 1980s, early death was the rule. And the list goes on.

Today, the vast majority of children diagnosed with cancer are cured. It is now common for children with cystic fibrosis to live into adulthood, and HIV has become a chronic disease in children and adolescents — just as it has for adults. These successes are the result of basic and clinical science investigation and are exemplars of our translational efforts to turn research into practical health-care advances. I have witnessed these changes personally: Many of the children and adolescents I treated for cancer and AIDS are still living, decades since their diagnosis.

But while this is great news, it has come with a number of price tags. Seemingly curative treatments for catastrophic diseases have sometimes resulted in serious complications later in life. More than 60 percent of childhood cancer survivors have one or more such complication, including cardiac and central nervous system abnormalities. For a number of long-term survivors, these complications rival the primary disease — and they unfold in a slow, inexorable manner. In addition, the years of treatment and uncertainty about the outcome take a huge toll on children and families, leaving psychological and behavioral problems in their wake.

The long-term complications associated with survivorship pose another challenge. As children with pediatric disorders become adults, the expertise to care for them is often limited, making it all too easy for them to become orphans of the medical system. To date, most graduate medical education programs and medical centers have been deficient in considering the care and management of long-term survivors or developing the workforce to care for them. As their numbers grow, they will join the burgeoning ranks of individuals with chronic diseases, and increase health-care costs accordingly. It is thus imperative for academic centers to focus on long-term survivors as an important feature of medical education, research and chronic-care management — including new and improved delivery systems.



Along with seniors, the numbers of patients who are long-term survivors and who need chronic-care management will continue to grow in the years ahead, and thus demand the attention of the leaders in academic medicine.

Sincerely,
Philip A. Pizzo, MD
Dean

Stanford University School of Medicine
Carl and Elizabeth Naumann
Professor, Pediatrics, Microbiology
and Immunology

upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD UNIVERSITY MEDICAL CENTER

Chimp change

Humans are clearly different from chimpanzees. The question is, why? According to researchers at the School of Medicine, it may boil down in part to what we don't have, rather than what we do. The scientists found that the loss of snippets of regulatory DNA could be the reason, for example, humans lack the penile spines found in many other mammals, and why specific regions of our brains are larger than those of our closest relatives.

Understanding these and other differences may help us learn what it means to be human. But it took the recent advent of whole-genome sequencing of several species and an open-minded, combined computational and experimental approach to reveal the particular two-steps-forward, one-step-back evolutionary dance that set us apart from other primates millions of years ago.

"Rather than looking for



species-specific differences in specific genes or genomic regions that exist in humans, we asked, 'Are there functional, highly conserved genetic elements in the chimpanzee genome that are completely missing in humans?' says Gill Bejerano, PhD, assistant professor of developmental biology and of computer science. "We found several hundred locations that, as far as we could see, are absent in our species alone."

Losing small pieces of regulatory DNA rather than the genes they control means that the related changes are likely to be subtle: Although the location or the timing of the expression of the gene within the body may change, the gene product itself remains functional. The distinction causes viable differences among individuals that can eventually lead to the development of new traits and species.

Bejerano and David Kingsley, PhD, professor of developmental biology, are co-senior authors of the research, published March 10 in *Nature*.

The researchers compared the genomes of several species to identify 510 regions that are highly conserved among chimpanzees and other mammals but are missing in humans. They then used a software program developed in Bejerano's laboratory, called the Genomic Regions of Enrichment of Annotations Tool, to see whether these regions preferentially occurred near certain types of

genes. (GREAT is publicly available at <http://great.stanford.edu>.)

The researchers found that one of the missing regions normally drives the expression of the androgen receptor in sensory whiskers and genitalia. Androgen is a sex hormone responsible for growth of sensory hairs, or vibrissae, and surface spines found on the penises of many mammals. The loss of these structures in humans decreases tactile sensitivity and increases the duration of intercourse in humans relative to other species.

Another region was adjacent to a gene that suppresses neural growth in a particular part of the brain. Loss of expression of this inhibitory gene could thus contribute to an expansion of neural production in humans and a larger brain.

The resulting changes may have paved the way for monogamous pair-bonding and the complex social structure necessary to raise our species' relatively helpless infants, the scientists speculate. — KRISTA CONGER

The work was supported by Stanford's Bio-X Program; a Ruth L. Kirschstein National Research Service Award; a National Defense Science and Engineering graduate fellowship; a national science scholarship of the Agency of Science, Technology and Research; the National Institutes of Health; the Edward Mallinckrodt, Jr. Foundation; and the Howard Hughes Medical Institute.

Bladder matters

The bladder is a supple, muscular organ with a well-defined task: Store urine and release it at an appropriate time. Unlike its workhorse neighbor, the intestine, it doesn't need a lot of fussy cell division to get the job done. But when the bladder becomes infected, it launches a massive, scorched-earth attack, sloughing off the innermost layer of cells to keep invading bacteria from latching onto and burrowing into its inner lining.

Now scientists at the School of Medicine have identified the key molecular pathways that form a control circuit involved in kick-starting cell division in the bladder to repair the damage.

"We suspect that this pathway of regeneration might be important in cancer development and metastasis in the bladder and other organs, like the prostate," says developmental biology professor Philip Beachy, PhD, who is the senior author of the research, published online March 9 in *Nature*.

About 10 percent of women each year experience bacterial infections of the bladder that can range in severity from irritating to painfully debilitating. The body's natural defense of shedding at least a portion of the inner lining in which the bacteria hide out works pretty well, but it's not perfect; over one-quarter of women will experience a recurrence within one year, sometimes even when antibiotics are used to treat the infection.

The bladder's inner lining is made up of a tightly connected layer of umbrella cells that protect the underlying cells from toxins and waste in the urine. Under them are intermediate and basal epithelial cells (together these umbrella, intermediate and basal cells make up the urothelium), then a non-epithelial layer of cells called the stroma. The stroma is separated from the urothelium by a thin structure called the basement membrane.

"The bladder is a great system in which to look at this because it's composed of a fairly simple, ordered tissue," says Beachy. "Most of the time, the cells in this tissue undergo little or no cell division, but injury with chemicals or bacterial infection causes rapid proliferation."

In fact, Beachy found that it normally takes about 10 months to replace about half of the cells in the inner lining in the bladders of female laboratory mice. In contrast, in the presence of harmful bacteria, the cells of the bladder begin dividing dramatically, and most turn over within 24 hours.

To conduct the experiments, the researchers used a type of bacteria that causes bladder infections in humans. They introduced the bacteria into the bladders of female mice and watched to see how the cells responded. They found that, after infection, the basal cells in the urothelium and the stromal cells on the other side of the basement membrane "talk" to

one another using a protein involved in the hedgehog signaling pathway, called sonic hedgehog, and at least one other signaling pathway, called Wnt.

The process occurred in what's known as a positive feedback loop: Sonic hedgehog stimulated the stromal cells to produce Wnt, and the Wnt stimulated the epithelial cells and the stromal cells to begin proliferating and make more sonic hedgehog. This loop serves to amplify the signal and encourages the cells of the urothelium to begin dividing quickly.

"Understanding the physiology and the regulation of these regenerative processes might give us a better handle on how to treat bladder cancers and urinary tract infections," says Beachy.

— KRISTA CONGER

The research was supported by the Department of Defense, the National Institutes of Health and the Howard Hughes Medical Institute.

Rejection detection

Heart transplant recipients and their physicians are likely more concerned with the function of the donated organ than with the donor's DNA sequences that tag along in the new, healthy tissue. However, researchers at the School of Medicine have shown that an increase in the amount of the donor's DNA in the recipient's blood is one of the earliest detectable

signs of organ rejection.

The finding implies that a simple blood draw could replace the regular surgical biopsies that are currently used to track the health of the donor heart. Closely tracking the dynamics of this concurrent "genome transplant" might also allow doctors to avoid the high doses of medication required

to combat more advanced cases of rejection.

"Heart transplant recipients undergo at least 12 tissue biopsies during the first year after their transplant and two or three each year for about four additional years," says Hannah Valentine, MD, professor of cardiovascular medicine. "The idea that we might now be able to diagnose

rejection earlier and noninvasively is very, very exciting."

"This approach, which we call genome transplant dynamics, solves a long-standing problem in cardiac transplantation," says bioengineering professor Stephen Quake, PhD, who developed the sequencing technology used in the study. "It's so difficult to find and implant a



donor heart, and then doctors have to remove pieces of it every few months to test for rejection."

Quake and Valentine are co-senior authors of the research, which was published online March 28 in the *Proceedings of the National Academy of Sciences*.

The study involved combining two methods of detecting organ rejection — a blood test Valentine pioneered in 2010 to determine whether the body has launched an attack on the donated organ, and a new technique developed by Quake (called microfluidic digital PCR) to measure levels of donor DNA released when cells in the transplanted heart are damaged, as occurs early in the rejection process.

Past efforts to pick out DNA from a transplanted organ have hinged on one easily identifiable difference — the presence of the male Y chromosome in the blood of female transplant recipients. The team's first step was to confirm that Quake's technique could identify the presence of the Y chromosome in stored blood samples from women who had received, and then rejected, a heart from a male donor.

However, because the pairing of female recipients and male donors accounts for less than one-quarter of organ transplants, the team wanted to determine if the approach could be used on a broader range of patients. As a test, they mixed reference DNA

from two unrelated people in proportions varying from 0 to 7.5 percent, designating one as the donor and one as a recipient. The sequencing approach accurately identified the minute proportions of "donor" DNA in each sample. Following this proof of principle, the researchers applied the technique to three women who had received hearts from male donors, two of whom experienced episodes of rejection and one who did not, as well as four men who received hearts from male donors, who had all experienced rejection.

"In every case we could see an increase in donor DNA in the patient's blood before the biopsy itself showed any sign of rejection," says Valentine. — KRISTA CONGER

The research was supported by the National Institutes of Health and the Howard Hughes Medical Institute. The researchers have filed a patent for use of the technique.

Stem cell PhD

Beginning in the fall of 2012, Stanford will offer what officials believe is the first PhD program devoted solely to stem cell science in the nation and, perhaps, the world. Prospective students can begin applying this fall.

School officials say the creation of a new doctoral program acknowledges the growing importance of stem cell research in biomedical science. They note that Stanford is among a small number of U.S. universities that have

the necessary ingredients to create a program teaching the full range of stem cell science.

In particular, Stanford has received \$192 million during the past five years — more than any other institution in the state — from the California Institute for Regenerative Medicine to advance stem cell research in the face of more-restrictive federal funding policies. The funds have enabled Stanford to build the Lorry I. Lokey Stem Cell Research Building, to develop educational outreach and tissue banking capabilities, and to recruit a number of renowned researchers and trainees from whom the new PhD students can learn both the science and ethics of human stem cell research.

While a few other schools have PhD programs involving stem cell biology, this is the first dedicated solely to stem cell biology and regenerative medicine, an emerging field that aims to repair or replace damaged tissues and organs. One of the program's distinguishing features is that all students will undergo an immersive clinical rotation in which they will shadow attending surgeons, physicians, residents or fellows.

"Stem cell biology is a distinct discipline that requires unique skills and includes a scope of knowledge and a skill set that is not covered by other disciplines," says Renee Reijo Pera, PhD, professor of obstetrics and gynecology and the new program's director.

Theo Palmer, PhD, associate professor of neurosurgery and co-director of the doctoral program, says students helped spur its creation after voicing frustration that existing programs lacked the breadth of cross-disciplinary training needed for a successful career in regenerative medicine. "The new program not only engages subjects taught within the School of Medicine, it crosses the Stanford schools to capture fundamental principles in engineering, law, business and society," Palmer says.

— CHRISTOPHER VAUGHAN

Embryo imbroglia

It's a waste. People who have completed in vitro fertilization procedures usually have leftover embryos, and they usually discard them. Meanwhile, scientists studying human development or stem cells would love to use those embryos for research.

These fertility clinic patients can choose to have them stored, disposed or donated for research, but the methods clinics use to ask their preferences vary. In general, clinics take a hands-off approach to avoid unethically influencing patients.

A new process developed by researchers at the School of Medicine and used by Stanford's biobank allows these people to make this decision at home — without any interaction with clinic personnel or scientists who might benefit from the research — yet offers an easy route



to more information about donation if they're interested.

"There is concern that conflicts of interest and influence by researchers and clinicians may play a role in donor choice," says bioethicist and senior author of a study of the method, Christopher

Scott, who directs Stanford's Program on Stem Cells in Society. "The Stanford biobank process allows people time to make the primary decision to donate on their own, when it's right for them. It also allowed us to ask whether donors have preferences as to the

type of research they will allow on their embryos."

In the two-part procedure, described in the April 8 issue of *Cell Stem Cell*, the information about donation for research is included in the normal embryo-storage bill from the clinic. "At that

point," Scott says, "the recipients are free to throw the information away or put it on the coffee table to consider and talk about." Only after the couple has made the initial decision to donate do they interact with Stanford biobank staff members.

People who indicated that they would like to donate were sent an informed-consent packet outlining the types of research that could be done with the embryos, such as creating embryonic stem cell lines or studying human development.

Once the potential donors had time to review the material, they took part in a phone interview with Stanford biobank staff members who were unconnected with either the original in vitro fertilization clinic or the researchers who might use the embryos. The staff members followed a script to confirm the donors' preferences and make sure they understood their options.

The researchers found that donors were equally likely to give consent for their use in the creation of embryonic stem cell lines (30 percent of the eligible respondents) as for the study of human development (32 percent). Thirty-eight percent gave consent for their embryos to be used for either type of research.

— KRISTA CONGER

The research was funded by the California Institute for Regenerative Medicine and Stanford University.

BACK TO LIFE

ILLUSTRATION BY JEFFREY DECOSTER

“Am I going to make it?”
That’s the question at the back of your mind,
if not the front, when you’re
facing a health crisis.

Today, the answer is mostly yes.

As a result of medical advances over the past few decades,
you can face down demons such as AIDS, diabetes, heart disease and many types of cancer.

You can come back from severe injuries — widespread burns, for instance —
that used to be insurmountable.

And so you survive. You breathe a huge sigh of relief,
throw open a window and get back to living.

Yet for many, there’s no returning to normal.

Physical changes get in the way. You’re weak. You’re tired.
Your body no longer moves the way it used to.

Your thoughts are foggy. And then there is the emotional dimension —
the joy at surviving, the urgency to live each day to its fullest,

the memories of pain and fear, all of which can radically change your outlook on life.

The medical profession is not especially practiced at helping survivors live among the well again,
but it’s making strides. For decades, rehabilitation programs have been a standard
part of treatment for those emerging from heart attack, stroke and traumatic brain injury.

More recently, survivor support groups — both online and in the real world —
have emerged as important sources of emotional sustenance. And in the past decade
cancer centers throughout the country have opened clinics specifically for adult survivors.
These supports are crucial for America today, where one in 20 adults has survived cancer, one in 45
has survived a stroke, and every year hundreds of thousands survive a heart attack.
We’re a nation of survivors.



THE

WOMAN

WHO

S U R V I V I N G S U R V I V A L

FELL

TO

EARTH

A love story

By Ruthann Richter

Photography

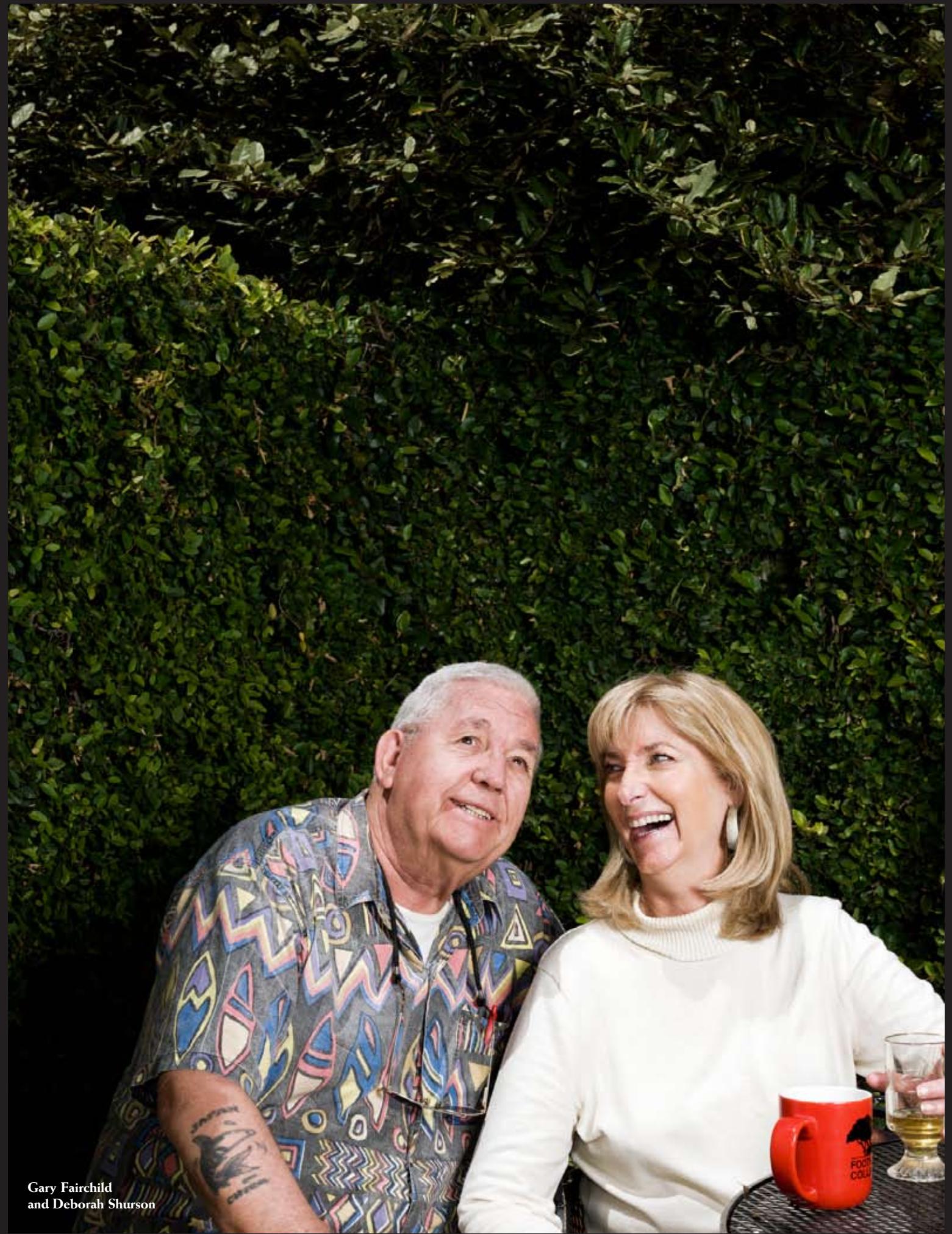
by

Misha Gravenor

The April morning dawned clear,
with the winds
relatively calm and the air
freshened by weeks of heavy rains.

Thirty-year-old
Deborah Shurson, tall, blonde
and willowy, strapped
nearly 100 pounds
of gear on her 118-pound
frame and stepped into
the Cessna 206 on that day
in 1982 when she; her husband,
Randy; and two other friends
would be carried

2,600 feet into the air. • Randy was first in line to jump,
and he prepared by dangling his legs over the edge of the
aircraft. He then leapt into the void, his arms
spread-eagled and his back arced, the wind full force
in his face. • “See you below,” he yelled to Deborah as he flew
through the air. Five seconds into his fall, the static line
engaged his chute, which opened above. Randy clutched
the handles around his shoulders, terror in his
throat, resolving never to skydive again. • He landed in the drop
zone at the Antioch, Calif., airfield with a thud **when he**
heard screams and turned to see Deborah,
her partially opened white chute wrapped around her like
a shroud as she streaked toward the ground. Her main chute had
never opened, and she was frantically clawing her way to
her reserve chute. • Deborah’s parents, who had brought a picnic
lunch, stood paralyzed as they watched her in freefall at 125
miles per hour, then saw her disappear behind a hill
in a little mushroom cloud — her reserve
chute opening too late.



Gary Fairchild
and Deborah Shurson

Randy, a trained paramedic, ripped off his pack and raced to Deborah, pausing briefly to pray since he knew she was gone. "Please God, accept her," he said under his breath.

He arrived to find Deborah unconscious, her breath labored, like a primal gasp one takes before giving up on life.

Snowball in hell

As the doors flew open to the emergency room at John Muir Medical Center in Walnut Creek, Calif., neurosurgeon Paul Chodroff, MD, kicked aside a crash cart to clear a path for the gurney bearing Deborah's shattered body.

She had already been resuscitated twice at Antioch's Delta Memorial Hospital, and the scans there showed a staggering array of injuries: a punctured, collapsed lung that was leaking blood, a bruised heart, 14 or 15 broken ribs, a broken breastbone and ruptured spleen.

Her pelvis was fractured, as were both of her legs, and her right ankle had split off altogether. Her right shinbone had penetrated 12 inches into the earth. Most worrisome, Deborah was in a coma, with diffuse injuries to her brain and signs of contusion to her brain stem. Some of these injuries alone were life-threatening; taken together, they presented a grim prognosis.

Chodroff, her lead doctor, later likened her odds of survival to a "snowball in hell." He told Deborah's family that he could keep her alive for the next three or four *minutes* but couldn't promise anything after that.

"He took us all aside and said, 'Don't expect her to be alive tomorrow,'" recalls Deborah's father, Dave McCahon, choking back tears. "He said, 'If she does live, she will be a vegetable. She will not walk or talk.'"

Clinging to life

In the intensive care unit, Chodroff, a thin, intense man with glasses, stood at the foot of her bed like a traffic cop directing the myriad medical specialists and nurses who had been called in to try to save her life.

Without oxygen, Deborah's brain would survive only minutes, so his first job was to keep her breathing despite critical damage to her lungs and chest. Artificial breathing support — a respirator and chest tubes — had been installed and he turned up the

pressure. Miraculously, Deborah lasted through the night.

For weeks, her condition remained precarious, her life suspended in a limbolike state. Randy slept at the hospital, and with Deborah's parents, brother, sister and sister-in-law kept a vigil at her side, enlisting church friends throughout the world to pray for her, playing tapes of favorite pop songs, reading letters from friends and keeping up a regular chatter in hopes of reviving her dormant brain. The nurses braided her long, blonde hair and placed it on her head like a crown, giving Deborah the aura of a sleeping princess.

"She looked beautiful, and we thought, she's just going to wake up any moment," recalls her sister-in-law, Robin McCahon.

Against all odds

Deborah wasn't awake but, incredibly, she was still alive.

"When you hear these amazing stories of survival, they suggest that, among other things, these may be individuals who mounted an optimal fight-or-flight response during life-threatening stressors," says Firdaus Dhabhar, PhD, an associate professor of psychiatry at Stanford who studies human resilience in the face of stress.

He speculates that while Deborah was zooming to Earth, her stress physiology and immune system were actively priming her for the fight ahead.

In an optimal stress response, the body initially releases a flood of immune cells into the blood, which subsequently lodge in the skin and other sentinel areas to defend against wounds or infection, he says. If there is an injury, this response enables larger numbers of immune cells to travel to the damaged area to help promote healing. In Dhabhar's studies with surgery patients, he has found that those who effectively launch this short-term physiologic response have significantly better recoveries than those who don't. But a primed immune system could do only so much.

Deborah's condition deteriorated during those first weeks. Despite a tube-delivered daily diet of 6,000 calories — about triple her ordinary intake — she was wasting away. Suspecting a hidden infection, orthopedist Doug Lange, MD, took her into the operating room in week three, opened up the cast on her right leg and found jammed inside her shin bone several inches of dirt and clay from her crash landing. He also found a massive infection. He carefully cleaned and pinned the wound.

From that day on, Deborah grew stronger. About a week after the leg wound was cleaned, a friend was massaging her feet and promising her chocolate chip cookies when Deborah's eyes flew open and she seemed to hold her gaze. She

was awake, showing the first signs of consciousness, vaguely alert to movements around her.

On day 51 at the hospital, Deborah hit her biggest milestone. Perched in a hallway in a wheelchair, she looked up at Chodroff and said: "Hi, Doctor." She could speak. Randy gleefully lifted up the doctor and swung him around as they both laughed and cried. Over the next weeks, Deborah began to speak more but she was far from recovered. She couldn't follow commands and had forgotten basic things, like how to chew her food, which padded her cheeks. She did not recognize Randy, her husband of six years.

Her dramatic story and her determination to live resonated through the halls. Deborah had become a star patient, and word of her revival quickly spread. Her final days at the hospital were filled with celebration. The staff threw a party with cake, an honorary nurse's cap for Randy and a diamond bracelet for Deborah. Still, when she left the hospital, three months after the accident, she was in a wheelchair, both legs in a cast, unable to take a step. Her speech was limited to a few dozen words. She was childlike in her behavior, smiling but unable to understand why there was so much fuss around her.

She had survived, in part a result of excellent medical care, and in part because of her fantastic luck — and the mud.

"Had the winds blown her just 50 feet to the left, she would have landed on an asphalt road. Had she blown another 50 feet to the right, she would have landed in a lake and drowned. By the grace of God, we'd had 10 weeks of solid rain, and the ground was saturated. She went 12 inches into the mud," recalls her mother, Doris McCahon, who refers to Deborah as "our miracle girl."

Her gender also may have been on her side. Studies suggest that the high progesterone levels women experience during certain days of the menstrual cycle protect their brains during trauma.

And there was another factor, one that can't be quantified: Deborah's determination.

"A lot has to do with the person — their underlying drive in life and how much of that drive is preserved after the injury," says Jeffrey Englander, MD, chair of physical medicine and rehabilitation at Santa Clara Valley Medical Center in San Jose, Calif.

Deborah certainly was bent on regaining her independence. "I remember one of the doctors saying to me if I ever walked again, it would be years down the road," Deborah recalls. "I remember the doctor looking me in the eye and I said something like, 'Watch me.' He threw up his hands and said, 'I give up.' I just grinned. That's me — I'm a fighter from the word go."

But it was not a fight Deborah could wage alone, and she would find help from an unexpected source.

"I REMEMBER ONE

OF THE

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IF I EVER WALKED

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"WATCH ME."

The long journey begins

When Deborah arrived at the brain injury rehabilitation unit at Santa Clara Valley Medical Center, her legs still in casts, she was able to stand only with help on both sides, her shoulders stooped over her slender frame.

But brain damage was what most incapacitated her. She spent her next three months at the San Jose hospital relearning the basic gestures of daily life. There she devoted six hours a day to therapy, practicing baby steps in the gym and regaining the skills needed to care for herself — how to wash her face and button her blouse, how to lift a spoon to her mouth and swallow her food, slowly repeating the motions to get them right. At first, her speech was so poor that she communicated mostly with her hands or by nodding. In therapy, she began to recapture lost words and phrases. Her caregivers taught her to hold a pen and form letters on a page. Her short-term memory was impaired, so she obsessively wrote things down in a barely legible scrawl, her notepad always at her side. Eventually they taught her what it meant to write a check, though her understanding of financial matters was elusive and remained that way for years. She didn't remember conversations or who had visited her moments before. But she was resolved to get better.

For patients, "This is probably the most devastating injury of their life," says Englander, whose unit is one of 16 nationwide designated by the National Institute on Disability and Rehabilitation Research as model facilities. "They have to say, 'I'm a differently capable person now and I choose to make the best of where I am and work on that.' And that's a big step for people to realize that."

"They're beginning their journey, and the journey takes years," he adds. "It's a tough journey — it really is."

The extent to which brain-injured patients recover depends on their type of injury, such as a stroke, tumor or



trauma; the depth of the injury; and whether it affects both sides of the brain, says Thao Duong, MD, the unit chief and vice chair of physical medicine and rehabilitation at Valley Medical. If a patient with traumatic brain injury is in a coma of longer than four weeks, the likelihood for a good recovery decreases significantly, she says. By all these measures, Deborah's prognosis was poor.

Brain-injured patients typically show the most progress in the first year or two; after that their progress is typically slower, though there is still the possibility of some improvement, Englander says. "People can take something very important to work on, whether it is walking or communication or performing a favorite activity, and they can learn not only from professionals but from peers," he says.

"TBI patients are very motivated," says Odette Harris, MD, MPH, director of the polytrauma unit at the Veterans Affairs Palo Alto Health Care System and associate professor of neurosurgery at Stanford. "What binds them all is that those who do survive tend to be very driven."

Home

After three months, Deborah left Valley Medical, returning with Randy to her Los Altos home and an enthusiastic greeting from her golden retriever, Charlie.

She continued physical therapy: Within months she had discarded her walker and crutches and was tottering around unaided, determined to be independent. But her cognitive abilities were limited and she had the emotional maturity of a child.

"The doctor told us she would go back to infancy and we would have to teach her everything along the way," says her mother. "That, for Debbie, was extremely frustrating."

At home, she was depressed and withdrawn, sometimes lashing out. Her speech was slurred and her voice hoarse, damaged by the tubes in her throat. "She could sit down and have two eggs on a plate and eat them, and if you asked her what she had eaten, she couldn't tell you," Randy says.

Asked about this time in her life, Deborah recalls little, other than her occasional walks with Charlie and her feeble attempts to tidy up the house. "I felt like I was in a fog. I would keep blinking and thinking it would get clear, but it never got clear," she says.

Her transformation into a dependent person was a challenge for all those around her.

Deborah and Randy, who had met as college students at

Chico State, had been leading fast-track lives. Deborah, a synchronized swimmer and former "Miss Congeniality" at San Carlos High School, had been an up-and-coming commercial interior designer. Randy was acting captain in the Menlo Park Fire Department. Both fitness buffs, they had taken a trip to Lake Tahoe just before the accident, hitting the difficult black-diamond ski runs. They were at the top of their game, with plans to remodel their three-bedroom home and start a family.

But now Randy was confronted with a strange new person in his life, the change in Deborah like a "Dr. Jekyll and Mr. Hyde," he says.

Six years after the accident he and Deborah divorced, an unfortunately common side effect of brain injury, experts say. "To this day, it still hurts me," Randy said years after the accident. "I still have a lot of grief. I avoid Deb because of the grief I have over the loss of her."

The couple sold their home, and Deborah moved to an apartment with a roommate whom she found through her church, "a motherly type" who helped keep an eye on her. She wasn't able to work in interior design, and her old friends, seeing a different person, abandoned her.

Deborah's parents, who were in the nursery business, helped her find a job at a local floral shop, where Deborah used her skills as a designer to make floral arrangements. Later she got jobs at a health food store and at Safeway, where she worked as a bagger until the pain of standing on her right leg made it impossible to continue. She was struggling.

Ten years after the fall

At Foothill College in Los Altos Hills, Deborah at 40 was hunched over a computer in a class for disabled students, trying to make sense of a game called Find the Keys, which challenges a player's organizational skills.

She had already taken every class for the disabled at De Anza

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College, in Cupertino, and had just started at Foothill, still not quite having mastered the basics. To all appearances she was physically recovered but she still read one word at a time rather than full phrases, and her writing looked like chicken scratches, she says, embarrassed to see it today. She signed up for what she calls the "bonehead" classes.

"The teachers would lecture, and some of it would go over my head, and it was hard for me to write things down. I would get bits and pieces. It was hard. It didn't come easily," she says.

One day, she looked up to seek help from the instructor, and saw standing there a tall, burly man with wide glasses and a stutter. Actually, he was a classmate, 53-year-old Gary Fairchild, who was only too happy to help the attractive blonde. He and Deborah, it turned out, had much in common.

Gary had been a successful real estate developer when, while sitting in his office, he felt his head begin to ache. As he reached for an aspirin, he shook uncontrollably and felt as if his head were exploding. His son-in-law rushed him to Kaiser Permanente Medical Center in Redwood City, Calif., where he was diagnosed with a relatively uncommon congenital defect known as an arteriovenous malformation.

AVMs are a tangle of thin-walled vessels that can pop at any time, causing significant bleeding and stroke. In a 10-hour surgery, doctors removed the affected area of Gary's brain, a lemon-sized section of his parietal lobe.

Gary woke up in the hospital after three weeks. A week later, he returned to his \$2 million home in Los Altos Hills a changed man.

Once the fast-talking life of the party, his speech was garbled. His vision was impaired, and he walked into walls. He couldn't find his way beyond his own driveway. He threw things and raged in frustration. He suffered such frequent seizures — a common side effect of his condition — that the local paramedics came to know him by his first name. At Foothill, he sat on a bench every day in the green

expanse of the quadrangle, head in hands, and cried.

"I was heartbroken," Gary says. "I had just built this beautiful house. My business was going well. I was in a good part of my life. I had sailboats and the fancy cars, and one day it's all over, and you can't get it back. Once the brain goes, it goes. If I hadn't had all the mentors — all the people who helped me — I would have killed myself."

In Deborah he found a kindred spirit. "She was lost emotionally. She didn't fit in and she knew she didn't fit in," he says, as Deborah nods assent.

The two began meeting for lunch on campus as they sat in the quad, gazing at the shapes of the clouds, imagining golden retrievers in the sky. Deborah was bewildered by the Foothill campus, where all the red-tiled, Mission-style buildings looked alike, so Gary taught her some tricks he'd learned: follow the path to the yellow fire hydrant and turn right to find Building L, where their speech classes were held.

They went out on their first official date, riding their bikes to a deli at the Stanford Shopping Center. There Gary confessed that he still loved his wife. "OK, we'll keep it cool," Deborah told him.

But Gary's wife had had enough. She was no longer able to cope with Gary's erratic moods and outbursts, dependency and daily seizures. One morning at 7:30, she called Deborah to ask if she would be willing to rent Gary a room in her apartment. Gary was devastated, as he realized his marriage of 31 years was over.

He moved in with Deborah, and they soon discovered they had remarkably complementary abilities.

"I like to joke that between the two of us, we have one brain," Gary says.

Gary had lost the vision on his left side, so Deborah protected his left flank. He also had a severe spatial-visual defect and easily lost his way, so Deborah stepped in to try to help navigate. When Gary was at a loss for words, Deborah helped complete the sentence. But when Gary's speech returned, Deborah, herself mildly speech-impaired, often would turn the conversation over to him.

"What he didn't know, I did, and vice versa," Deborah says.

Both had short-term memory problems that hampered their ability to read books or watch movies, but that disability proved to be an asset in the relationship.

"Both of us forget things, so when we get into an argument, sometimes we just forget what we're arguing about," Gary says.

Together Deborah and Gary began reaching out to others with brain injuries, participating in a peer support group at Valley Medical for patients and families struggling through the early recovery phase. "Many people told us we were an

inspiration to them — it gave them the hope and the drive to go on,” Deborah says. Deborah also got a job at Foothill College as a teaching assistant in the disabled students program, while Gary volunteered to help students in the pool during rehabilitation therapy.

“It made my heart feel good to know I could help,” Deborah says of the Foothill job, recently felled by budget cuts. “I was once in their shoes. I had been there and done that.”

Lucky in love

The injuries that had kept Deborah and Gary so isolated from others became a source of comfort and renewal.

“What alienates you from some people can be a bond with someone who has shared losses. I see this time and time again,” says David Spiegel, MD, professor of psychiatry and behavioral sciences at Stanford. “When you are injured, you automatically feel excluded from the rest of the world. But the wonderful thing about this kind of mutual support is you’re now among people with the same problem, and you feel accepted and appreciated. You have this instant sense of feeling oddly normal. So something genuinely good has come out of a bad situation. You have learned how to cope and you can use that knowledge to help other people with similar problems.”

And social support can not only be psychologically but also physically beneficial. Spiegel demonstrated the physical value of social support in a widely cited 1989 paper in the *Lancet* that showed women with advanced breast cancer randomly assigned to group therapy lived 18 months longer than those who had standard medical care alone. This finding was reaffirmed recently in two major studies, one in the journal *Cancer* and another in the *New England Journal of Medicine*. Both found that social support prolonged the lives of patients with breast and lung cancer, and while these studies were restricted to cancer patients, there’s reason to believe they could apply to others as well, Spiegel says: “Social support is good for your health.”

Now 18 years together, Deborah and Gary are inseparable. They love to travel — though they need a third person to come along to help them find their way. They love to socialize, especially when food is involved. They love staying fit. And they even enjoy the daily work to improve their cognitive skills. Gary begins his day seated at the computer in the living room of their Los Altos condominium, located in a turreted, red-brick building they call “the castle.” He tracks flashing figures on a screen to improve his vision, completes reading comprehension exercises, and plays a counting game — rooting through a jumble of numbers to pick out one through 50 in order.

HERE'S HELP

Brainline

A comprehensive website with information on prevention and treatment, as well as management of day-to-day issues for those living with brain injury.
<http://www.brainline.org>

Brain Injury Association of America

The largest U.S. brain-injury advocacy organization, this group lobbies for greater resources and research, and disseminates a wide range of information on symptoms, treatment and other issues related to brain injury. <http://www.biausa.org>

The Center of Excellence for Medical Multimedia

Developed by the Defense and Veterans Brain Injury Center, this includes a guide for family caregivers.
<http://www.traumaticbraininjuryatoz.org>

“I do it before I drive because it gives me confidence that my brain is engaged,” he says. But he still never drives without Deborah at his side. “She’s like having another set of eyes in the car, although she doesn’t always remember the points of navigation either.”

“Between the two of us, we figure it out,” Deborah says, laughing that their adventures are sometimes “like the blind leading the blind.”

They serve as a constant source of support for each other. “Deborah has been my angel. She’s been there for me when I’m down and when I’m up,” Gary says. Deborah calls Gary “my rock of Gibraltar.”

“We love in such a special way — it may not always be romantic, but it has a lot of ...,” he stops, searching for the right word. “Empathy,” Deborah says. “Compassion,” Gary adds. “And meaning,” she says.

Now approaching her 60th birthday, Deborah is radiant, with no physical signs of her staggering injuries other than a gouge in her right shin. She has a lift in her right shoe to compensate for the bone loss, and walks 5,000 steps every day around her neighborhood to maintain her mobility. She is ever upbeat, cherishes her time and calls her life fantastic.

“I often ask myself, ‘Why did I live?’ They gave me less than a 2 percent chance, and I proved them all wrong,” she says. “I’m stubborn. It wasn’t my time yet. I have a lot of people to see and meet. I have too much living to do.” **SM**

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RX

S U R V I V I N G S U R V I V A L

EXERCISE GET PLENTY OF REST? THAT'S SO RETRO

By John Sanford

PHOTOGRAPHY BY MISHA GRAVENOR

In 1966, Walter Bortz, MD, was downhill skiing with his family in Stowe, Vt. — “absent-mindedly tooling along,” he recalls — when one of his ski tips stuck in the snow and he fell, tearing his right Achilles tendon. After surgery, doctors put a cast on his leg. Six weeks later, the cast came off, but his leg looked as though it had aged 40 years.

• “It was purple, weak and withered,” he says. • Bortz, now an adjunct clinical associate professor emeritus of medicine at the Stanford School of Medicine, speculates that the surgery was not to blame for the decrepit state of his limb. The problem, he believes, was that he had not used it for a month and a half. A search of the medical literature supported this hypothesis: Immobility appeared to produce the same effects on the body as aging. • Bortz later coined the term “disuse syndrome” to describe the profusion of physiological changes — cardiovascular vulnerability, musculoskeletal fragility, immunologic susceptibility, premature aging and frailty, among others — that occur when someone is in a state of forced inactivity, such as prolonged bed rest. “The lesson is, ‘Use it or lose it,’ ” he says. • Of course, it’s not as though people have only recently discovered the benefits of exercise. “Lack of activity destroys the good condition of every human being, while movement and methodical physical exercise save it and preserve it,” Plato observed more than 2,300 years ago. • Slower to take hold, however, has been the evidence that exercise can help people recover from illnesses and injuries. “The science on this is solid, but it is still not well-recognized in medicine,” Bortz says. “What I learned in medical school — that if it hurts, lie down — still largely rules.” • The familiar doctor’s advice to rest and get plenty of fluids still makes sense for many short-term injuries and illnesses. But bed rest for more than a few weeks? Not so much — even for transplant recipients, kidney failure patients and cancer survivors. Bed rest, as well as just general inactivity, is being challenged as study after study shows that it is often counterproductive to the healing process, prolonging the time to recovery and increasing the risk of other complications.

“THERE’S PRACTICALLY NOTHING that exercise isn’t good for,” says Michael Fredericson, MD, director of the Physical Medicine & Rehabilitation Sports Medicine Clinic at Stanford and a professor of orthopaedic surgery. “It helps with every single health parameter, from lowering cholesterol to improving heart function and preventing atherosclerosis, obesity and Alzheimer’s.” • The past few decades have brought a boom in research on the health benefits of exercise, including its role in recovery. How does it help? At the cellular level, exercise, especially weight training, first actually damages muscle fibers, causing satellite cells — a type of progenitor cell, like a stem cell — to proliferate and form

FOR ANABEL STENZEL (L) AND ISABEL STENZEL BYRNES, living with cystic fibrosis and a lung transplant (or two) is no excuse to take it easy. In fact, the twins believe exercise will help extend their lives.



myoblasts that fuse to the site of the damage. The myoblasts donate their nuclei to the muscle cells, each of which can hold lots of nuclei, allowing the cells to synthesize more protein and grow bigger. Thus, muscles grow stronger. Similarly, aerobic exercise strengthens the heart muscle, improving its pumping efficiency. It also increases the number of red blood cells in the body and fuels the growth of microvascular networks in muscle tissue, all of which increase endurance. Exercise also boosts collagen synthesis to strengthen ligaments and tendons, and it releases neurotransmitters and endorphins to fight depression and anxiety.

On the flip side, the negative effects of inactivity have been thoroughly cataloged, perhaps nowhere more starkly than in a famous 1966 study in which researchers recruited five 20-year-old men to spend nearly three weeks in bed. Of course, the men's heart health declined; what was surprising was how much. By the 20th day in bed, their cardiac output, the amount of blood pumped each minute by the heart, had dropped 15 percent. Their bodies' ability to transport and use oxygen during exercise — a common measure of physical fitness — had fallen nearly 28 percent. A 30-year follow-up study concluded that the 20 days the young men spent in bed "had a more profound impact on physical work capacity than did three decades of aging." Yet these men were all able to regain — and in some cases exceed — their initial aerobic strength after an eight-week training program.

Fredericson cautions, though, that exercise is no panacea and that not all types are good medicine. Seriously ill individuals should get the go-ahead from their doctor before launching a regimen. Some people really are simply too sick to exercise. But that's not as common a scenario as you might think.

HAD BORTZ INJURED his leg in 1990 as opposed to a quarter of a century earlier, he likely would have benefited from a growing trend in medicine called accelerated rehabilitation, a clear corollary to the use-it-or-lose-it school of thought. This concept began to gain ground in the late 1980s after doctors observed that patients recovering from muscle and ligament injuries, or surgical repairs to those injuries, fared better the sooner they started exercising the afflicted body part. For example, orthopedic surgeons found that patients recovering from the surgical reconstruction of their anterior cruciate ligaments who neglected doctors' orders — that is, they put weight on their knees and moved them around more than they were supposed to — "regained strength much faster and performed better and with more confidence in the later stages of rehabilitation" than those who adhered to the prescribed rehabilitation protocol, according to a 1992 study in the *Journal of Orthopaedic & Sports Physical Therapy*.

The same study found significantly better outcomes among patients who followed a more intense rehabilitation regime — one that had them putting weight on their leg and performing range-of-motion exercises just two to three days following surgery. Recently, a *Wall Street Journal* article focused on how doctors are increasingly prescribing exercise for patients suffering

from osteoarthritis, a degenerative joint disease, as opposed to the traditional advice of taking it easy to protect the joints.

In many cases, exercise cannot specifically target an injury or disorder (think of kidney disease or cancer). But it can improve a patient's functional capacity — that is, the ability to do everyday kinds of work, from picking up a dropped pen to carrying a box of books up a flight of stairs.

Improving dialysis patients' functional capacity is often overlooked, says Patricia Painter, PhD, an expert on kidney patients' physical function and an associate professor of nursing at the University of Minnesota. Painter, a former Stanford research scientist, says nephrology has been slow to promote exercise. "It's frustrating. There's plenty of research that says exercise is good for patients with kidney disease and on dialysis. But nothing is being done about it," she says. "Most nephrologists are not pushing exercise. Medicare covers dialysis but not exercise."

Among patients ages 40 to 50 on dialysis, close to half are classified as frail, she says. "They're basically functioning like very old people, and that can be prevented and corrected with exercise," she says. "What's the point of going through all this dialysis treatment if you can't do things for yourself? If your quality of life is going to be so poor?"

"WE WERE ALWAYS TOLD that you have to exert twice the effort for half the reward," says Anabel Stenzel, 39, who received lung transplants in 2004 and again 2007, as she walks to and fro, hands on her head, warming down after a 100-meter sprint on Stanford's Cobb Track. Organ recipients have to work harder than people in the general population to gain muscle and the aerobic benefits of exercise because the steroids, immunosuppressants and other drugs they take impair muscle and bone health.

Stenzel and her identical twin sister, Isabel Stenzel Byrnes, who received a lung transplant in 2004, both have cystic fibrosis. Inspired by workouts they attended while training for the 2008 U.S. Transplant Games, they started the Transplant Boot Camp, a weekly workout for organ recipients at Stanford.

"It's really about camaraderie," Anabel Stenzel says. "There are people who join us with only 45 or 55 percent lung capacity, and they can do only so much. But we're all in this together. We're here to do our best."

A 2010 literature review in the *Journal of Heart and Lung Transplantation* found evidence that exercise improves skeletal muscle strength and lumbar bone mineral density, as well as functional capacity, among lung-transplant patients.

Stenzel believes exercise can extend transplant patients' lives. "Everyone I know who has lived 10 years post-transplant is an active exerciser," she says. "It improves well-being, but maybe more importantly helps decrease the side effects of the medication. I believe exercise is as important as immunosuppression and is not stressed enough by transplant doctors."

Patients fighting cancer also face serious side effects, including weakened muscle, bone and immune function, from



**RUNNING FOR THEIR LIVES
AND FOR THE FUN OF IT** at the weekly transplant boot camp
at Stanford's Cobb Track.

the powerful drugs they take to treat the disease. In addition, the drugs cause nausea and overall physical and mental fatigue. It's hard enough to motivate people to go to the gym when they are not dealing with such discomfort and pain, says Joyce Hanna, MA, MS, associate director of the Stanford Health Improvement Program. She has tackled this head on with a program called Living Strong Living Well. It invites adult cancer patients to participate in a free, 12-week exercise program now running at many YMCAs. Classes include weight and cardiovascular training and take place twice weekly for 85 minutes.

Instructors urge participants to show up regularly — even if that means just making it through the door of the gym. Says Hanna, "When I give them a presentation on the first day, I say, 'You're going to wake up one day and not want to come. I can promise you that. You're just not going to feel like it. But we want you to come anyway, and we'll just adapt the program for you.'"

Research shows that physical activity helps counteract the effects of chemotherapy and improve overall quality of life among cancer patients. Exercise also has been shown to help fight the depression and anxiety cancer patients can feel as a result of the disease and arduous treatment regimen. Other research suggests that exercise may actually decrease the recurrence of certain types

of cancers and increase the longevity of cancer patients.

A little more than a decade ago, however, advising cancer patients to exercise would have raised eyebrows.

"People in the health field were saying you should not exercise cancer patients," Hanna says. "They felt that since cancer wore down the immune system, exercise would wear it down even more. They also questioned why you would exercise someone who was already fatigued. Wouldn't that make them even more fatigued? But this was kind of a myth. Now research suggests that moderate exercise, not rest — with some exceptions, of course — is just what cancer patients need."

On a Wednesday last March at the El Camino YMCA in Mountain View, Calif., a half-dozen women were led through a series of stretches by Julie Grosvenor, the Y's Active Older Adults Program coordinator. "The first couple of weeks I think are the hardest," Grosvenor says of the program. "Some patients are feeling scared about what they've gone through, and they're all feeling pretty weak because of chemo."

One participant, Laura Toby, 55, says that she had always done aerobic exercise. But treatment for multiple myeloma took a big toll on her muscles. "After I got a stem cell transplant, my whole body just went thbfffft," she says, making a deflating sound. "So I was really interested in lifting weights and having someone work with me, and this program has been great for that. I always seem to injure myself when I try to do weights on my own. I definitely feel now that I've got better body toning."

Another participant, Emily Williams, 61, says she, too, has always been an avid exerciser. She is living with terminal ovarian cancer. "Working out is always something I've enjoyed. But for the last two years that I've been going through chemotherapy, I've also realized that it gives me some control over what's happening to me," she says. "Not only do I feel better physically, but I don't feel as much under the control of my cancer and all the stuff that surrounds it — all the blood tests and infusions. Taking this class has given me a lot of confidence to continue. So I guess not only has it been physically good, it's been emotionally good for me. It's the highlight of my week." **SM**

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H E R E ' S H E L P

American College of Sports Medicine

offers exercise guides for a wide range of health conditions:

<http://exerciseismedicine.org/YourPrescription.htm>

Living Strong Living Well

is an exercise program for cancer patients and survivors:

<http://lslw.stanford.edu>

U.S. Department of Health and Human Services

has physical activity guidelines, sample exercises and tips to get moving: <http://health.gov/paguidelines>; (800) 336-4797



A

Isabelle's parents were worried. Their toddler was vomiting every morning and regressing developmentally—forgetting words she'd known days before.

So Heather and Derek Wagner convinced their pediatrician to investigate. • When an MRI revealed a malignant, golf-ball-sized tumor at the base of Isabelle's brain, "we started living life in segments of time," Derek says of the unforgettable period in 2006. Even in the two days after the MRI she declined further, crying in pain and needing to be held continuously. "Things changed by the minute."

Derek and Heather soon learned that the tumor was a medulloblastoma, which meant Isabelle had relatively good odds for surviving. More than half of the 350 U.S. patients diagnosed each year are cured.

Isabelle was immediately scheduled for surgery with Michael Edwards, MD, chief of pediatric neurosurgery at Lucile Packard Children's Hospital. He operated two days after her diagnosis and was able to remove all the visible tumor.

"Instantly she was in better shape," Derek says.

"In the hospital, she cracked a joke

LEFT: ISABELLE'S CANCER IS GONE.
Five years after her treatment, her health is great. But her parents know it might not stay that way.

kid again

After cancer takes its toll

By Erin Digitale
Photography by Misha Gravenor

for the first time ever," Heather says, recalling her amazement. Before surgery, she had thought Isabelle was introverted. "She's not; she's really outgoing."

In tears, Heather pauses.

"She couldn't be herself. She had this *thing* in her head."

ON FEB. 10, 2011, Isabelle passed the five-year anniversary of her surgery. It's a significant milestone in a journey that included 14 months of chemotherapy and radiation.

SURVIVING SURVIVAL

"It's fantastic," says Derek. "And yet there's a bit of holding back, the feeling that this isn't over."

The Wagners' mixed feelings reflect a larger truth about pediatric cancer. Today, nearly 80 percent of childhood malignancies are cured. But reaching the five-year landmark—when doctors first use the word "cure"—does not mean a child's medical journey is over.

Isabelle, like most cancer survivors, faces lifelong risks for side effects from her treatment. Complicating risk assessment further, the available research findings on childhood cancer survivors don't always apply to newly cured kids like Isabelle. A generation ago her diagnosis was almost always fatal, and the few who survived to be studied as adults received therapies that are now outmoded.

The only large-scale study on young people treated for a variety of childhood malignancies has shown that the first pediatric cancer cures came at a significant cost. Patients treated in the 1970s and early '80s suffered blows to their long-term physical and emotional health and social functioning.

However, pediatric oncologists are working to minimize the harm the therapies cause and help patients manage long-term challenges of survival. And the original survivorship studies will soon be updated with findings from recently cured children, which should give new patients a better sense of what to expect.

Still, no one can be certain what the future holds for a 7-year-old who is five years past what was at the time a new therapy. So, as they try to help Isabelle enjoy her childhood and live with the aftereffects of cancer treatment, the Waggers are stepping into the unknown.

THE FIRST BIG effort to study pediatric cancer survivors began around the same time as the 1989 premiere of *Doogie Howser, MD*,

a hit TV show whose teenage-doctor protagonist was a leukemia survivor. In the preceding 30 years, childhood cancer had gone from being almost universally fatal to having cure rates that exceeded 50 percent. But no one knew what life was like for the growing population of survivors, and physicians worried that as these young adults lost touch with their childhood oncologists, their experiences and concerns were being lost, too.

"We decided that to really understand long-term effects, we had to go directly to survivors themselves," says Les Robison, PhD, who started the Childhood Cancer Survivor Study, a wide-ranging research project funded primarily by the National Cancer Institute. In the late 1980s, Robison, an epidemiologist now at St. Jude Children's Research Hospital in Memphis, Tenn., called on North American pediatric oncology programs to enroll their survivors in the new study.

"We said, we need to ask what's bothering them and find out what they're experiencing," says Sarah Donaldson, MD, a Stanford professor of radiation oncology who helped design the study.

Since it launched, CCSS has produced more than 140 peer-reviewed publications on 20,000 pediatric cancer survivors treated between 1970 and 1986. Data on participants' diagnoses and treatments have been paired with extensive surveys about their physical health, emotional well-being and social functioning. The study, which uses 4,000 cancer survivors' siblings as its control group, has documented everything from participants' struggles to obtain health insurance to their rate of second malignancies.

"The thing that's most surprising is the true magnitude of the negative health consequences" experienced by cancer survivors, says Robison.

MAJOR BRAIN surgery is a risky operation — and the younger the child or bigger the tumor, the higher the risk.

But physicians can quickly ascertain the neurocognitive effects of surgery. And its payoff for patients like Isabelle, who came through without significant neurologic deficits, is quick and dramatic.

"Every day she had five new words," Heather says of the first month after Isabelle's surgery.

In contrast, aftereffects of chemo-

therapy and radiation can crop up decades after treatment, sometimes long after the recurrence risk for the original cancer has dropped to nil. That's the situation Isabelle is in now, Edwards explains. If medulloblastoma is going to reappear, it usually comes back within a period equal to the patient's age at diagnosis plus nine months. For Isabelle, diagnosed at 20 months, the risky period was the first 29 months after her surgery, and a return of her tumor now, more than five years later, is "very, very unlikely," Edwards says.

But she still faces potential late effects of chemotherapy and radiation, which vary depending on treatment doses, the specific drugs, the physical site of radiotherapy and the age of the patient.

For the CCSS patients treated in the 1970s and '80s, the long-term damage was often severe.

One major CCSS paper, published in 2006, found chronic ailments in 62 percent of survivors versus 37 percent of siblings. Survivors were eight times more likely than siblings to have a severe or life-threatening condition such as blindness, deafness, a second malignancy, congestive heart failure or stroke. These problems appeared before the survivors reached middle age — survivors were, on average, 27 years old at the time of the study and 17 years past their original cancer diagnosis.

Equally worrying, the majority of adults who survived pediatric cancer had not received adequate follow-up. A 2008 CCSS paper shows less than one-third get "survivor-focused care" that addresses specific health problems arising from cancer treatment.

While, at first blush, these numbers are depressing, oncologists see reasons for hope. The study has led to new recommendations for maintaining survivors' health and to less-risky cancer treatments. For instance, girls who receive chest radiation are now cautioned to be extra-vigilant about breast cancer

screening — they need annual mammograms or MRIs starting at age 25.

And, with cure rates high, many cancer researchers can now focus on fine-tuning established cures to reduce their late effects.

ISABELLE BENEFITED directly from one such fine-tuning.

After her surgery, she was part of the first group of young medulloblastoma patients in the world to receive radiation only at the site of the tumor, as opposed to the standard procedure — irradiating the whole brain and spinal column. The radiation therapy was augmented by four chemotherapy drugs, which she received in intervals over a 14-month period following her surgery.

"We wanted to tailor her treatment such that we could cure her but also not devastate her," says Isabelle's oncologist, Paul Fisher, MD, chief of neurology at Packard Children's.

The new therapy appears to have spared Isabelle's brain function. Young children who receive radiation to the entire brain and spinal cord inevitably experience significant developmental delays. Isabelle, in contrast, is now a creative, outgoing little girl who recently completed first grade in a regular classroom.

"Isabelle really is in the vanguard of lesser treatment to create better long-term outcomes," Fisher says, noting that the treatment she received is now widely used.

But being in the vanguard isn't simple. "It is a very different world once you're in it," Heather says. Because so few patients make it as far as Isabelle, the family feels they are in "uncharted territory," she says.

To help future childhood cancer patients get a better sense of what lies ahead, the Childhood Cancer Survivor Study team is focusing on a new cohort of survivors. The researchers are recruiting 14,000 childhood cancer survivors treated between 1986 and 1999,

plus 4,000 of their siblings; they expect to begin studying the new group in 2012. About 400 of the survivors in the new cohort will be former Stanford or Packard Children's patients, says Neyssa Marina, MD, the pediatric oncologist who is the principal investigator for the Stanford arm of the study.

Marina expects the new cohort will demonstrate, on a large scale, the benefit of the lowered radiation exposure that helped Isabelle. Smaller radiation fields and doses have been adopted not just for brain tumors but also for many other diagnoses, she points out. "And we think a lot more about which patients get radiation."

With its focus on survivors, the

the CCSS research.

Each HAT clinic visit lasts 90 minutes to two hours. Arun Rangaswami, MD, and nurse practitioner Verna Mitchell question patients about all aspects of their lives.

"We tell them that the clinic's purpose is not just to point out potential late effects," Mitchell says. "It's to say, you have your life, your health. Make the best of it that you can."

After years of being in battle mode against cancer, this is a significant shift of view for many patients.

Nutrition and exercise are a focus at the clinic — many survivors received drugs that raise obesity and heart disease risk, or were left with sedentary

"Isabelle really is in the vanguard of lesser treatment to create better long-term outcomes."

CCSS gathers no data on the newest therapies, but it still makes a huge contribution to treating new childhood cancer patients, Robison says. Pediatric oncologists can now tell their patients that most will be cured, and work from day one to educate them about long-term health effects.

"When a patient is first diagnosed," says Robison, "we start talking about the future."

NOW THAT Isabelle has graduated to survivorship, she receives annual monitoring with Fisher's comprehensive neuro-oncology team.

Packard Children's cancer survivors who had non-brain-tumor diagnoses get similar care at the hospital's Health After Therapy clinic, which educates people who have lived through pediatric cancer. Such clinics exist across the country, another indirect outcome of

habits after long hospitalizations. The team also ensures patients are checked for specific physical problems linked to their treatments: for instance, cisplatin, a drug given to Isabelle, may cause deafness. (Fortunately for Isabelle, her hearing is normal.) They educate patients about possible side effects that may be years away, such as early strokes, impaired fertility and secondary cancers.

Mitchell also questions closely about psychological and school performance issues: information-processing problems, poor attention span and focus, difficulties with reading and math. Are patients sleeping enough? Do they experience anxiety?

"We don't accept, 'I'm doing well in school,'" Mitchell says. The HAT clinic team wants to hear the fine details so they can refer the patients properly for additional treatment. The team also points patients to resources that can help

CONTINUES ON PAGE 44



Her stroke of insight

JILL BOLTE TAYLOR ON MINDING YOUR BRAIN

When Jill Bolte Taylor tells you about her stroke, she takes you on an *Alice in Wonderland*-like journey, watching herself sort of inside out. In her book, *My Stroke of Insight: A Brain Scientist's Personal Journey*, Taylor, a PhD specializing in neuroanatomy, describes in sharp detail the collapse of her motor skills as her brain fragmented, and tells of being "strangely elated" as her grip on reality melted. "In the wisdom of my dementia, I understood that my body was, by the magnificence of its biological design, a precious and fragile gift."

Five years ago she wrote the memoir about the trauma to her brain and the long road of recovery. "Every brain has a story and this is mine. Ten years ago I was at Harvard Medical School performing research and teaching young professionals about the human brain. But on Dec. 10, 1996, I was given a lesson of my own." Her story has been optioned as a major feature film.

She says the stroke was a "blessing and revelation" that has brought her a new sense of inner peace. It took her eight years to recover and learn how to talk, walk and read again. These days, she lectures widely, is working on a game for neurological rehabilitation and creating a nonprofit organization dedicated to the health of the brain. She spoke about all of this and why she "chose to survive" with Paul Costello, the School of Medicine's chief communications officer.

Costello: *Most people would think that having a stroke is a bad thing, but in the end you clearly don't see it that way.*

Taylor: Well, my particular stroke was definitely a devastating neurological trauma to the brain, but I happened to be the right person in the right place at the right time to have the kind of stroke that I had and then the ability to recover from that. So I do not see my stroke as a terrible thing.

Costello: *During your recovery you relearned basic skills and you changed your outlook on life. Can you talk about that? Is there some sadness about some of the things you left behind?*

Taylor: The biggest thing I lost was my emotional baggage from the first 37 years of my life. I have to say that to be set free from the emotional pain of attachment to things in my past has been extremely liberating. It's really nice waking up in the morning not knowing if you're mad at anybody.

Costello: *That would be great.*

I think most people would take that experience. But has that complicated your life?

Taylor: Well, I've had to start over with my relationships. So, for example, my mother came to me immediately following the stroke as my primary caregiver. I did not know what a mother was much less who my mother was. What that meant was my mother no longer had the power of the mother that she had had for 37 years of my life. So she and I had to re-navigate a new relationship. It was complicated, the fact that we had to begin again, but at the same time it was a gift because it gave us the opportunity to get rid of the garbage.

Costello: *Are there some key ingredients to successful recovery?*

What really matters?

Taylor: Well, for us I'd say the first thing that mattered was sleep. We really had to honor the healing power of sleep. The brain is processing literally billions and billions of bits of data moment by moment and when there's trauma to the cells, by definition, the cells are not communicating with one another as they normally would. So information comes in confused and somewhat chaotic. Sleep allowed me to close out new, incoming stimulation and to process and file information that had come in to try to make some sense of it.

My mother was very good at pushing me as far as I could go, and then backing off and allowing me to go to sleep. And that's the biggest difference between what we did and what traditional rehabilitation does.

Costello: *It struck me that the energy people brought into the room really impacted you while you were first recovering.*

Taylor: Without a left brain capable of communicating with language or breaking information down into differences and boundaries and edges, my right brain looked at everything as on a continuum — a continuum of flowing particles, of energy. So when people came into my presence I couldn't understand a word they said, but I could certainly experience their affect and the intonation of their voice and their body language. Is it turned toward me or away from me? Are people happy to be there or were they preoccupied? Those were the kinds of subtle messages that I was receiving.

Costello: *Your mother was an important watchdog in that matter; which seems to indicate to me that everyone needs a cop standing near them, standing in the room, standing at their bedside as this recovery occurs.*

Taylor: Well, I certainly did. I needed someone to watch out for me and prioritize the use of my energy because life, just living life in a normal day, takes so much energy, and in my level of trauma I had hardly any energy whatsoever, so the question was, what am I going to use that for? Am I going to put my mind into trying to make some sense of the world or am I going to have that energy pulled away from me by a well-intentioned visitor?

Costello: *What do you do these days to take care of your brain?*

Taylor: I'm very good at giving my

brain downtime. I love to walk through nature, I love to do art, I love to sing and play my guitar. I allow myself the time that really allows me to shift away from my predominantly left-brain detail base into the bigger picture.

Costello: *What about the brain still baffles you?*

Taylor: Well, I have to say, the power of hate really, really, really confuses me. That's something that I struggle with. How do we help people realize that hate, whatever it is that you are projecting at the object of hate, is really a painful, personally destructive thing to yourself and not necessarily to the object that you're projecting the hate to.

Costello: *You write now that your life is, as you said, a perfect life.*

It's extraordinary for anyone to say that they have a perfect life.

Tell me why your life is so good.

Taylor: Well, I think life is so good because I celebrate that I have the capacity to have the life that I have. I wake up in the morning with gratitude in my heart. I thank my cells that allow me to wake up in the morning. It's a specific group of cells in my brain stem. Throughout my day I'm appreciative of the people I interact with, I'm appreciative of my dogs, I'm appreciative of my environment. I really live a life filled with gratitude, and I find that when I run the gratitude circuit like that, I just say thank you. Thank you for another great day.

This interview was condensed and edited by Rosanne Spector.



K H M E R
R O U G E
T R I A L
ON

Can
serving justice
cure
PTSD?

By Tracie White

Photography by Misha Gravenor

It was 1976, a year into the Khmer Rouge's reign of terror in Cambodia. Sophany Bay and her two young children struggled moment by moment to survive. Each day, the small family ate a cup of rice soup, or nothing at all, growing weaker and thinner. Each night, they slept in a cagelike hovel built of bamboo stalks and leaves. At gunpoint, Bay spent 12- to 14-hour days in a rock quarry, swinging a hammer and loading the broken pieces into baskets that she carried on a pole across her back, barely able to stand. While she worked, the children were forced to stay behind where they were repeatedly interrogated and beaten by soldiers. • "One day, my son, he cried that he want to go with me," Bay recalls. She speaks in halting English, occasionally falling into her native Khmer. "The soldier said my son is not Cambodian. He is American or French. He put a gun in my son's mouth and told him to stop cry-

At left: Sophany Bay, a mental health counselor and Khmer Rouge survivor, inside Wat Khemera Rangsey Buddhist temple.

ing. My son couldn't stop because he was so scared. He cried harder. The soldier used a scarf to bound my son's hands. He put him in water up to his waist. He was just 6 years old. He kept crying. Two soldiers put a gun behind me. 'Go to work!' they said, or they would kill my son. From that time on, he became sick. His body swelled. There was no medication."

The three and a half years of the Pol Pot regime's rule, from 1975 to 1979, left between 1.7 million and 2 million people — about a quarter of the population — dead from starvation, torture, sickness, bullets. All city dwellers in Cambodia were forced to live and work in the country as laborers in squalid, inhumane conditions. Schools, hospitals, banks, businesses were closed. Religion was banned. The entire population was overworked, starved and denied medical care. Anyone associated with the Cambodian military or the intellectual elite was shot. Thousands more died from preventable diseases.

"My daughter grew sick too," Bay says. Diarrhea left her daughter emaciated. Her son grew sicker and sicker. The soldiers hit her children every day.

"The soldiers would ask my children about their parents. 'Where is your father?' My kids did not say anything. I told them every night before sleep, close to their ear, 'If anybody asks you about your father don't say anything. If they know he's a soldier in the [Cambodian] military, they'll kill you and kill me too.' They never told. They saved my life.

"My son went two days with no food. At nighttime, he slept in my embrace. In the morning, his body was so cold. He just quietly died. One month later, my daughter died also. The soldiers beat her and bound her hands for eating the soldiers' table scraps. She was only 5 years old. I held her close to my breast. 'Mom,' she said, 'take me to the clinic! I want to live.' She asked when her father was going to return. Then she closed her eyes and died. I become so depressed. I did not talk to anyone. Because I wanted to die too."

BAY, A SAN JOSE, CALIF., MENTAL
health counselor, is telling her story 36 years later, talking with me while seated at a table in the Wat Khemera Rangsey Buddhist temple in East San Jose. She's a small woman, dressed professionally in slacks and a blazer, her hands folded primly before her. Like many of the 5 million survivors of the killing fields, she's struggled for years with symptoms of post-traumatic stress disorder, reliving those horrific times in her dreams. She's managed to rebuild her life, working to help those like herself recover from psychological scarring, but even now the nightmares won't stop. Occasionally, she still wakes screaming, heart pounding.

"My son went two days with no food. At nighttime, he slept in my embrace. In the morning, his body was so cold. He just quietly died. One month later, my daughter died also."

"The pictures stick in my memory. It sticks in there," she says. "I still remember my children's voices, their faces." Her stories are unspeakable, she knows this well. But she refuses to cry as she tells them. She speaks loudly and forcefully, with the determination of someone who has suffered for years, and wants the suffering to stop. She wants the world to hear her story. And finally, after all this time, a chance to make this happen is within her grasp.

In a history-making move, the United Nations-backed tribunal trying Khmer Rouge war criminals — the Extraordinary Chambers in the Courts of Cambodia — is including victims in the proceedings to an unprecedented degree. As a result, thousands of survivors have submitted their testimonies to the tribunal. Bay is among them. The first of a series of trials concluded last year. The second began this summer, in June.

The survivors are looking to the tribunal for justice after decades of suffering in silence, but many have an additional motive. Hopes are high that by participating in the international criminal justice system, by telling their stories to the world, they will find some degree of healing for the psychological trauma that haunts them still.

Whether such lofty goals can be achieved remains to be seen. There's concern that reliving some of the worst horrors of the 20th century will cause even more psychological damage.

"These witnesses often have horrible symptoms — and they're testifying," says Daryn Reicherter, MD, clinical assistant professor of psychiatry at Stanford, who has been providing support and treatment for survivors of the Cambodia genocide who now live in San Jose. "They're in front of the people who tortured them. They're facing their tormentors."

Human-rights activists complain that the court has been slow moving, that its costs — over \$100 million so far — are too high, that it's under the thumb of Cambodia's current government, which is pressuring it to fold early, leaving many unpunished. But they've praised the court for its attention to the mental health of its witnesses. During the first proceedings, which tried an infamous prison director for murder and torture, a counselor sat next to each of the 13 survivors who testified.

This summer's trial judging four higher-ranking Khmer Rouge leaders will include many more survivors. Half of the more than 4,000 who applied have been accepted as civil parties, with the number set to testify as yet undetermined. The Cambodian court is attempting to surpass previous tribunals' levels of victim participation, in keeping with a worldwide trend among international tribunals toward more inclusiveness. Victims with civil party status are allowed to sit in court with their lawyers and to ask questions of witnesses. Civil parties also have the right to reparations, and to be consulted on what those reparations might be if the defendants are found guilty.

These reparations will be collective and primarily symbolic — such as museums or memorials or monuments. Many victims are pushing for reparations to include improvements in mental health facilities in Cambodia. Reparations made to the civil parties of the first trial included copies of an apology from the defendant.

But for survivors like Bay, telling their stories in an international court of law before the crimes' perpetrators is the reparation they seek. They're willing to risk the possibility of re-traumatization for the hope of something closer to a cure for the wounds of the past.

The tribunal is not only a chance for the world to hear and acknowledge her suffering and the suffering of her community, says Bay, but it's a chance to help end her nightmares as well.

"I want to ask them why. Why you do this? Why you kill even babies?"

BAY WAS A SCHOOLTEACHER AND
the wife of an anti-communist military officer when the Khmer Rouge invaded Phnom Penh on April 17, 1975. She and her children were at home the day the Communist guerilla troops marched down the boulevards wielding guns and threatening to kill anyone who didn't evacuate the city. By mid-afternoon, hundreds of thousands of city dwellers were on the move. Thousands were already dead.

"I heard the guns in the morning," says Bay, eyes wide behind large, gold-rimmed glasses. Soldiers were shouting, shooting guns in the air, forcing everyone to leave their homes immediately and start walking into the forests, into the fields. They had to leave everything behind.

"Dead people lined the road — pregnant women, children. It was too, too crowded. Some people the soldiers would shoot, if he or she was in the military, old people. Nobody knew why. Still, we don't know why."

"They told us the Americans are bombing the city, and

we could return in three days. They lied to us," says Bay, who was 29 at the time. "The streets, they were so crowded. Thousands of people were walking away. I carried my baby, and left with my two kids at my knees. I couldn't bring anything but a bottle of milk for my baby. I was so scared."

Bay and her children — Paul, 6; Pine, 5; and 6-month-old Pomme — walked for days into the forests. When the rains came, they had no shelter and the baby became sick with fever and diarrhea.

"My baby was so, so sick," Bay says. "There was no clinic." Bay begged a Khmer Rouge soldier for help, handing him her small baby. He injected a needle into the baby's head and, immediately, Pomme died. "They kill my baby," Bay says. "We cry together, my two kids and me, because my baby was so beautiful."

THOUSANDS, PERHAPS MILLIONS,
of Cambodians struggle with the psychological wounds of genocide. Cambodian refugees in San Jose tell of the anguish of losing spouses, children, parents, siblings — the depression, sleeplessness, panic, flashbacks, fear. They recount nightmares that won't go away.

The defining diagnosis is post-traumatic stress syndrome, a severe anxiety disorder that entered public awareness in the 1970s when large numbers of Vietnam War troops returned home unable to function in society. The diagnosis eventually made its way into psychiatric diagnostic manuals under the current term in 1980. But the disorder has a history of documentation stretching back to symptoms seen in survivors of the eruption of Mt. Vesuvius in AD 79 that buried Pompeii. Army physicians diagnosed Civil War troops with something called "soldier's heart," and "shell-shocked" World War II veterans returned home with symptoms that lasted a lifetime.

Most commonly linked with combat troops, PTSD is marked by emotional numbness, withdrawal and an almost daily reliving of frightening images. Relationships fall apart. Flashbacks torment them: A Vietnam War veteran pumping gas smells napalm.

"For the survivors of Pol Pot's genocide in Cambodia, the 30-year-old psychological scars are often more fresh than one might think," says Reicherter, who is co-editing a book on the mental health damage to those survivors. "And the memories of horror from that epoch are at the forefront of many Khmer-American's minds on a day-to-day basis." He hopes the book he is co-editing with Beth van Schaack and Youk Chhang, *Cambodia's Hidden Scars: Trauma Psychology in the Wake of the Khmer Rouge*, will sway the court to include treatment for mental health trauma among the reparations.

The book, to be published this summer, is an outgrowth of work by Chhang's Documentation Center of Cambodia, which amassed more than 600,000 pages of documents detailing the activities of the Khmer Rouge regime, providing the evidence that led to the creation of the tribunal. During the collection of this evidence, the ubiquity of mental health trauma in post-genocide Cambodia became apparent, compelling the center to include trauma-related mental suffering as a category in its documentation.

"After countless interviews with survivors, the same patterns of psychological trauma presented again and again," Reicherter writes in the introduction to the book. "These hidden scars would open again and again to reveal a profound suffering that is known well to the field of psychology, but is also intrinsic to the documentation of genocide."

Studies show that the prevalence of PTSD in the adult population in Cambodia is around 15 percent, more than five times the rate among U.S. adults, based on the National Comorbidity Survey. A much higher proportion has been measured among the 157,500 Cambodians, mostly refugees, who resettled in the United States. The rate hovers around 65 percent among the largest U.S. community of Cambodian refugees in Long Beach, Calif., according to a recent National Institutes of Health study — not surprising considering the severity of the trauma experienced, says Amit Etkin, MD, PhD, an assistant professor of psychiatry and behavioral science at Stanford and a researcher at the Veterans Affairs Palo Alto Health Care System.

Holocaust survivors have been found to suffer from PTSD at similarly high rates, says Etkin. While a wide array of traumatic experiences can trigger PTSD — from a car accident, to rape, to the death of a child — the more severe the trauma, the more severe the symptoms: obsessive thoughts, a heightened startle response, hypervigilance in response to uncontrollable fears. For a population that experienced multiple traumas including the deaths of entire extended families, years of starvation, torture and the destruction of their society, the disorder is often so severe that repeated attempts at treatment simply fail.

PTSD is unique among other anxiety disorders in that the medial prefrontal cortex, the front part of the brain that is involved with regulating emotion and fear, has been shown to be smaller and less responsive than in healthy brains, Etkin says. In essence, the brain's chemistry has been altered, creating a different person. Whether this is reversible is uncertain.

Bay, now 65, has learned to manage most of her symptoms. A university graduate in Cambodia, she studied psychology at Evergreen Community College in San Jose to learn how to help refugees like herself. Today she works as a mental health counselor for low-income Cambodians at the

Gardner Family Health Network in San Jose.

Yet at night, Bay's dreams always take her back to those years of torture by the Khmer Rouge. "I'm seeing a man who wants to use a knife to kill me," Bay says. "A Khmer Rouge soldier trying to hit me or beat me or catch me. When I wake up, I talk to myself. 'Go back to sleep, go back to sleep,' I tell myself. 'It will all be there to deal with tomorrow.'"

The nightmares are so difficult to treat, Etkin says. Often they just never go away.

ON A SUNNY SATURDAY MORNING

this February, about 50 members have gathered at the Wat Khemera Rangsey temple for an update from the lawyers and human-rights activists working to bring their stories of injustice to the international tribunal. The proceedings will be broadcast in Phnom Penh. The Buddhist temple, a remodeled residential home in a working-class neighborhood, doubles as a place of worship and as a community center for San Jose's roughly 10,000 Cambodian Americans. Cambodian and American flags fly out front. Inside, the walls are painted with murals of Buddhist monks at prayer.

The crowd, primarily refugees, is looking for justice. The meeting organizer made time for a few survivors to tell their stories for the benefit of close to a dozen reporters and college students studying human rights. In halting voices, weakened by age, they speak of husbands led away in handcuffs to executions, entire extended families wiped out, schools turned into torture chambers, a homeland destroyed. They ask why the accused have rights, while theirs were taken away.

The meeting is one of many that have been held across the country in cities with large populations of Cambodians — from Long Beach, Calif., to Portland, Ore., to Arlington, Va. — organized by Cambodian-American Leakhena Nou, PhD, a medical sociologist at California State University-Long Beach. "We're here to help survivors write their own history, not the Khmer Rouge. Your stories will live on even after the court is over," Nou tells the crowd. "The court did accept your applications. Now we're going to need the best minds in the world to fight for you in the courts of international law."

Nou began traveling across the United States to collect the stories of the genocide survivors in 2009 after she heard that Cambodian Americans, like their countrymen, could offer testimony and have legal representation at the tribunal proceedings. "When I heard about the trials, I thought, maybe this would be a chance for their voices to be heard," Nou says. "Despite being resettled here and having access to mental health services, the survivors were not getting healthier. I thought, 'What if they were given the chance to

give their testimonies? Maybe it will directly or indirectly help with their mental health status.” In 2002, she founded a nonprofit to provide support for Cambodian refugees in America — the Applied Social Research Institute of Cambodia, or ASRIC, which is now supporting survivors hoping to participate in the tribunal.

Nou's own story is deeply entwined with the survivors. Her family escaped from Cambodia just prior to the invasion. Her mother and Sophany Bay were childhood friends. The two grew up together swimming in a lake in a village called Touk in the province Battambang. Her aunts and uncles and cousins were killed by the Khmer Rouge.

Nou collected oral histories from 170 survivors. Forty-one of these survivors submitted testimonies to the tribunal for acceptance as civil parties. Then, she recruited the Center for Justice and Accountability, an organization of international human-rights lawyers in San Francisco, to represent them. Thirty of those survivors who submitted testimonies have been accepted as civil parties, Bay among them. “We feel strongly that at least some of the people from the diaspora should be allowed to testify,” says Andrea Evans, legal director of the center. “We’re hoping that they choose some of our clients, but we can only advocate. We are going to fight to have Ms. Bay testify.”

Bay has brought a photo of her baby to share at the temple. It’s a copy of the only photo of any of her children to survive the killing fields. She had sent the original to her husband just a week before the Khmer Rouge invasion. He was in Fort Benning, Ga., where he had gone for military training one year earlier, with the intention of returning to support the anti-Communist government. While he was there, the government of President Lon Nol was overthrown by the Khmer Rouge, who cut off communication with the rest of the world. No one was allowed in or out of the country. The only people who knew of the horrors that were taking place were their perpetrators and victims isolated inside Cambodia’s borders.

At first her husband, Sarit Bay, heard no news at all. Then as the years passed he heard rumors that his entire family had been killed. He kept searching, asking anyone he knew with ties to Cambodia if they had heard anything. Eventually, he moved to Birmingham, Ala., where he worked as a medical technician at University Hospitals.

Sophany Bay has enlarged the photo of their baby and

“These hidden scars would open again and again,” writes psychiatrist Daryn Reicherter, at right.



had it framed. In the photo, the baby is resting on her belly, proudly pushing up her head with her arms, staring out with curiosity at the camera. Dressed only in a diaper, she radiates health and happiness.

At the February meeting at the temple, Bay — wearing a black jacket and black slacks, with a white scarf draped over one shoulder — told her story to the crowd, pointing to the photo held up by a human-rights lawyer. Her husband sat in the audience holding a tissue to his eyes. Dry-eyed, Sophany told her story one more time:

“They said leave Phnom Penh now. I left my home immediately. I had no food for my baby except a bottle of milk. . .”

DARYN REICHERTER SITS CROSS-

legged on the floor of the San Jose Cambodian temple at the February meeting. The survivors seated around him, some of them his patients, have been asked to bring photographs of loved ones who died. A few have photos, many don’t. The others list names on a piece of paper and the monks seated at a table at the front of the room light a small flame and burn the list. They chant and pray together with the crowd. They bless the survivors and their departed loved ones.

Reicherter has worked with survivors of some of the worst conflicts of the 20th century — asylum seekers from Darfur,

Congo, the Middle East; political refugees from Central and South America, Vietnam War veterans. But the survivors of the Cambodia genocide are among the most traumatized he's seen and among the most difficult to treat. Much of the treatment for PTSD sufferers has been left up to individual practitioners, experimenting with a variety of methods to bring patients relief. Few studies have shown benefits from the traditional medication or psychotherapy that often helps with depression, Etkin says.

For seven years, Reicherter has moonlighted at the Gardner mental health clinic, where Bay works. He's trying to find treatments that will help — medication, talk therapy. In frustration, he traveled to Cambodia for the first time in 2006 to research what works for survivors there. Back home, with Bay's help and understanding of the Cambodian culture, he began a program that linked patients with meditation therapy at the temple.

"I visited some of the mental health clinics in Cambodia and asked, 'Where do these patients go when they have symptoms?' Usually, they would go to a monk. The monk does a blessing or a meditation. The breathing taught in meditation helps with panic attacks or helps bring sleep.

"I thought maybe I could take some of these ideas to the temple in San Jose. So phany took me to the temple's monk. He said, 'Are you Buddhist? Do you meditate?'" When Reicherter said no, the monk asked him to come back and learn to meditate, then he would help. Reicherter came back almost every Friday for three years. The result has been a liaison between the Gardner clinic and the San Jose temple. Currently, a monk comes to the clinic and teaches a 12-week course with a co-therapist on mindfulness meditation for PTSD. It's taught in Khmer and tailored toward concepts intrinsic to Khmer Buddhism.

One of the few available PTSD treatments that appears effective according to research, says Etkin, is a form of psychotherapy known as "exposure therapy" or "trauma-focused therapy."

"Patients retell and try to master the trauma," Etkin says. "Even Vietnam vets with PTSD for more than 40 years responded dramatically to this form of psychotherapy: the retelling of the story — carefully, so that it's not re-trauma-

tizing. They create a narrative, create a story out of what happened in the past. That way they're not in the past anymore. They're not in Vietnam anymore. Having that narrative somehow ties the trauma into long-term memory. It becomes a memory that you can control."

There is also a body of evidence that "reparative justice" can help the healing process. Yael Danieli, PhD, a clinical psychologist specializing in traumatic stress and healing and director of the Group Project for Holocaust Survivors and Their Children, in New York, claims justice is, in fact, one of the essential elements to the healing of genocide victims.

"Reparative justice insists that every step throughout the justice experience — from the first moment of the court's encounter with a potential witness, to the follow-up of witnesses after their return home, to the aftermath of the completion of the case — presents an opportunity for redress and healing," Danieli wrote in a 2009 article in the *Journal of Traumatic Stress*. "Conversely, this experience may present a risk of missing opportunities for healing and reintegrating victims into their societies, or, worse, re-victimizing and re-traumatizing them."

Victims played a minimal role in the Nuremberg World War II war criminal tribunal, according to Danieli, leading her to call it a missed opportunity for healing the victims' psychological trauma.

Researcher and epidemiologist Jeffrey Sonis, MD, sees the Cambodian tribunal as a historic opportunity to test whether the international tribunal can provide mental health healing. Sonis, an assistant professor of medicine at the University of North Carolina-Chapel Hill, is conducting a series of studies on the attitudes of a cross section of all adult Cambodians toward the trials. The first of the studies, published in the *Journal of the American Medical Association* in 2009, found that 75 percent of Cambodians believed the trials will provide justice and promote reconciliation. At the same time, more than 87 percent of those old enough to remember the Khmer Rouge era said the trials will rekindle "painful memories." The study also found a direct relationship between the desire for revenge and PTSD before the trial had taken place.

"This does raise the possibility that mechanisms that promote justice may have a positive impact on mental health," Sonis says. "One theory is that you might decrease PTSD symptoms by decreasing the desire for revenge. Then again, you might increase symptoms by having people re-experience the stories. We just don't know yet."

Sonis is compiling data from a not-yet-published study of interviews that compare the mental health status of native Cambodians from both before and after the first trial.

Several of Reicherter's patients submitted written testimony to the court to participate in the second trial, and he's

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been careful to provide extra care and support through the process. "My clients who testified, initially they had a worsening of symptoms," says Reicherter. "They had more nightmares, more anxiety, panic. Maybe a month later...things improved to better than before. We kept checking in. They had a rough patch and then some relief. I have not heard one say they regret it."

"The trial is not meant to be a therapeutic mechanism," says Sonis. "The goal of the trial is to seek justice. But let's just suppose it may also be a mechanism for improving mental health. Cambodia is a country with fewer than 40 psychiatrists, much the same as other Third World countries in post-conflict settings. Wouldn't it be wonderful if the trial did succeed in promoting mental health? Wouldn't it be the coolest thing in the world? Now we just have to wait and see."

IN 1979, VIETNAM INVADED CAMBODIA

and deposed the Khmer Rouge regime. In the months that followed, tens of thousands of refugees, ill and emaciated, surged toward Thailand. They hiked hundreds of miles through jungles to sanctuary in refugee camps with nothing to eat.

Bay fled with a few other refugees after searching for her parents and siblings and finally hearing that they were all killed by Khmer Rouge soldiers.

"I escaped from Cambodia, running in the jungle for days with just a few others," Bay says. "We had no food, no drink, no shoes. I ate leaves from the trees. We just ran and ran through the jungle. One day, I felt so tired I let the other people go ahead. I laid down on the grass trying to eat it, but I could not eat. I remembered a French proverb: 'Life is a struggle,' so I tried to run again. I was captured by soldiers on the border, but escaped. Finally, I reach a refugee camp in Thailand."

For years, she lived in the Khao I Dang refugee camp where she used her French to become a relief worker.

During those same years, her husband's efforts to find any news of his wife failed until he became acquainted in this country with former residents of the Khao I Dang camp. The former refugees still had friends in the camp, and eventually Sarit Bay heard the news that Sophany had been seen alive at the camp.

Sarit Bay, still living and working in Alabama, appealed to Sen. Howell Heflin, D-Ala., who contacted the U.S. Embassy in Bangkok. There were delays. The first came because Sophany was at the Thai camp illegally and the government didn't have any records of her being there. After the Thai

HERE'S HELP

Crisis lifeline:

National Suicide Prevention Lifeline's free, 24-hour hotline for those in emotional distress: (800) 273-8255

The National Center for PTSD:

Explanations and information about treatments, from the Department of Veterans Affairs. <http://www.ptsd.va.gov/public>

Trauma Intervention Program:

Trained volunteers provide emotional aid and practical support to victims of traumatic events and their families. <http://www.tipnational.org>

The National Institute of Mental Health:

An overview of the latest research on PTSD: <http://stan.md/1oLgbc>

government finally recognized Sophany as legal, the U.S. Embassy in Bangkok wanted proof of the marriage, but the certificate had been destroyed during the Khmer Rouge invasion. Eventually, embassy officials got a witness to the wedding to testify and, after years of corresponding by mail, in 1983, Sarit succeeded in getting his wife flown out of Thailand into America.

On a Saturday night in 1983, holding a broken long-stemmed rose in his shaking hands, Sarit awaited his wife's arrival in front of United Airlines Gate C10 at the Birmingham Municipal Airport. His eyes stayed riveted to the gateway. It had been nine years since he'd seen her last.

Sophany arrived in blue jeans with a scarf around her hair. She was so thin, he barely recognized her. A photo in the Nov. 5, 1983, *Birmingham Post-Herald* shows them embracing.

SOPHANY BAY IS READY TO TRAVEL

to Cambodia to testify before the court, in front of the perpetrators of these crimes. She's not afraid.

"For more than three decades, I waited to see justice," her statement says. "When I and other victims can see justice has [been] done, we will be able to calm our sufferings, to have less depression and fewer nightmares. We are getting old. We want to see justice before we die." **SM**

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the bodyguard

TAPPING THE IMMUNE SYSTEM'S SECRETS

By Bruce Goldman • ILLUSTRATION BY BRIAN CRONIN

So, how's your immune system doing?

It's not a question you've likely heard before. Give it about five years, though, and that will all change, if a forward-looking pack of Stanford immunologists have their way.

These scientists are out to generate a simple battery of tests, performed on blood obtained from a single needle-stick in a doctor's office, to let you know what shape your immune system is in. Not just whether it's acting up, or idling too slow, but specifics you and your doctor could use to guide your next medical move. You've got the sniffles: Is it an allergy, or an infection? You're getting older: Do you need a bigger dose of the annual flu shot, or is the standard one going to work just fine? You feel great: Are you cruising asymptotically toward an autoimmune disease that will flare up five years hence, and if so, how can you prevent it? • For now, from the standpoint of the practicing clinician the immune system remains a black box, says Garry Fathman, MD, a professor of immunology and rheumatology and associate director of the Institute for Immunology, Transplantation and Infection. • "If a patient were to ask me, 'How's my immune system doing today?' I would have no idea how to answer that, and I'm an immunologist. *None* of us can answer that. Right now we're still doing the same tests I did when I was a medical student in the late 1960s," he says. • "What we need is a scorecard: a routine, standardized, easily interpreted blood test you take *before* you get sick — analogous to the ones you get for cholesterol or glucose levels," says Mark Davis, PhD, the director of the institute. "This would let you and your doctor know how well your immune system is functioning in general — and, if it's malfunctioning, how, and with what consequences." • Sounds reasonable. We've got blood tests for cholesterol, blood tests for liver function, blood tests for pregnancy. So, why not blood tests for the state of our blood — or more precisely, the state of that all-important blood- and lymph-borne network of circulating sentinels, soldiers and signals that compose our immune system? • Alas, that's easier said than done. In the last few decades a huge amount has been learned about the basic mechanisms of immune response — a super-smart system of sensors, cells and secretions that has evolved to guard us from invasion by pathogens or betrayal by our



CRO
NIN

own tumor-prone tissues. It's staggeringly complex, comprising at least 15 different interacting cell types that spew dozens of different molecules into the blood to communicate with one another and to do battle. Within each of those cells sit tens of thousands of genes whose activity can be altered by age, exercise, infection, vaccination status, diet, stress, you name it.

"That's an awful lot of moving parts. And we don't really know what the vast majority of them do, or should be doing," says Davis, the Bert and Marion Avery Family Professor in the Department of Microbiology and Immunology. "We can't even be sure how to tell when the immune system's not working right, let alone *why* not, because we don't have good metrics of what a healthy human immune system looks like." Despite billions spent on immune stimulants in supermarkets and drugstores last year, we don't know what — if anything — those really do, or what "immune stimulant" even means.

So Davis, Fathman and a cohort of their fellow Stanford scientists have launched a far-reaching effort to create the first-ever program capable of characterizing the human immune system under normal conditions — and thus identifying the multitude of minute changes it undergoes when we get sick, or successfully vaccinated, or old. To fund the endeavor, Davis has received over \$40 million in public and private funding, and Fathman, \$3 million.

Pulling off such an ambitious undertaking requires a shift in the way immunological research is conducted. In classical laboratory science, a researcher asks a question, then selects a simplified "model system" (such as a lab mouse) to help track down the answer. The researcher keeps everything as close to the same as possible, messing with only a single variable to see what happens when it's tweaked. What happens isn't always so good for the mouse. Maybe not such a great idea to try these tweaks on people. Besides, huge environmental and species differences render the mouse results less than perfectly applicable to us.

But Davis, Fathman and their colleagues think there's a way around that. The marriage between new or improved analytic instrumentation (much of it pioneered at Stanford) and the latest computing technology, they believe, will let them find needles in a haystack.

"Suppose you've got a very complicated system, with a lot of moving parts," Davis says. "You don't know how those parts talk to one another. You don't even know where to start. So instead, you keep your eye on the whole thing, and you watch what happens to the parts when you hit it with a hammer. Some of the parts move together. Some move one after another. Then, you hit it with something else — a bucket of ice water, maybe — and see what moves this time, and when, and how much."

"We can perturb the immune system all kinds of different ways, measure the levels of hundreds or thousands of differ-

ent things in response to that, and figure out which ones go up or down with different states of health or non-health," Davis says. "Anything that might affect the system — a vaccine, a disease, a drug — can tell you something."

To get answers, Stanford has created the Human Immune Monitoring Center, consisting of a couple of clusters of world-class instruments and expertise. The HIMC operates according to a principle Davis only half-jokingly refers to as "ignorance-driven research." The more formal name is systems biology, an information-technology-rich approach to unraveling complex systems of intensely interacting components.

With systems biology, you don't have to know what you're looking for until you find it — some extremely high or low level of something (a cell count, a secreted immune protein, expression of a gene) that turns out to correlate with a disease or a vulnerability to it. You call that a "biomarker." In a human blood sample, there's an embarrassment of potential biomarkers to pick from, and the HIMC is bringing new sophistication to the task.

The idea is to make that huge haystack, human blood, smaller by fishing out a few, or a few dozen, biomarkers that by themselves may not be so great but that, taken together, correlate with various states of health, disease, vulnerability and resistance, or are highly predictive of immune response to particular challenges. With standardized assays, improved methods and increasing efficiency, these markers could someday be measured simultaneously via a simple blood test a patient can get in a clinical lab or doctor's office.

In the past decade, scientists have steadily advanced the technologies capable of pinpointing such biomarkers of immune status. These technologies can capture the tens of thousands of changes that might be induced by a vaccine, a disease or aging. The changes might be in immune cells' activity or numbers, in the amounts and types of molecules they secrete, or in which of their genes are idling or running in overdrive. Among the new techniques the HIMC employs:

Tetramer profiling: This technique, pioneered by Davis, detects attractions between members of a class of immune cells and the foreign or altered biochemical entities they target. For instance, it can measure the presence, or changes in the number, of specialized immune cells targeting a particular entity such as a viral or bacterial component — changes that could signal a state of immune readiness or sluggishness.

Mass-spectrometry of single cells: This was developed in large part in the lab of Garry Nolan, PhD, professor of microbiology and immunology. It involves an instrument — one of five in the world — that busts a single cell's contents into tiny pieces and, effectively, flings them at a wall; different metal tags attached to as many as 30 or more chosen proteins enable researchers to track levels of those proteins in

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individual blood cells. Knowing in such sensitive detail how individual cells' protein contents are altered by challenges with drugs or disease may allow the detection of important events, such as the onset of illness or response to therapy, well before they become obvious.

Luminex panel: This method uses beads carrying fluorescent barcodes to quickly determine, for almost 100 different blood samples at a crack, which and how much of 51 different important immune-signaling molecules called cytokines reside in each sample. Viral infection, bacterial infection, cancer, immune deficiency, age and traumatic injury, to name a few "perturbations" life visits on us, all result in different "cytokine signatures": characteristic patterns of these molecules' presence and activity in our blood. These signatures could be used to quickly map a person's immune health.

IF YOU'RE COLLECTING ABOUT 40,000 DATA POINTS PER BLOOD SAMPLE, FROM HUNDREDS OF PATIENTS PER YEAR, you're going to pile up a staggering amount of raw data. So, taking the systems-biology tack, you hand the entire database to the computer guys and let them sift through it, asking questions like: What's different between samples from, say, older versus younger people or people whose flu shots worked versus those who got sick anyway? Which differences appear to be medically important? Which are the most reproducible? Which could be used in a diagnostic test?

Having started life in 2005 as a bootstrap operation, the HIMC now employs 12 people and works on dozens of projects. Director Holden Maecker, PhD, regularly meets with investigators to help them plan studies, determine their needs (what samples to take, how to bank those samples and which assays to use) and interpret their data. "For them, it's like going to the best restaurant," Maecker says. "Everything's on the menu."

The center's resources are good for much more than simply characterizing the immune system under normal conditions. Researchers and clinicians from more than a dozen departments and divisions within the medical center have teamed up with the HIMC to study everything from anesthesia's impact on wound healing, to opioids' effects on immune function, to potential biomarkers of depression. The search is on for immune biomarkers of aging, Alzheimer's, autoimmune disease, cancer, chronic pain, rejection in organ transplantation and

viral infection — both acute (influenza) and chronic (HIV).

Investigators from around the world send samples to be assayed for their own experiments. In fact, the center is one of the medical school's biggest money-makers, with a good half of its \$1.2 million annual budget last year generated internally as a service center for both internal and external laboratories.

University of Washington immunology professor Jerry Nepom, MD, PhD, is providing the HIMC with samples in the hope of identifying biomarkers of immune status. "We don't have any standard, clinically validated test to do that," says Nepom, past president of the Federation of Clinical Immunology Societies, a 40,000-member organization of clinical immunologists Fathman founded almost a decade ago. "What they're doing at Stanford is unique — developing the tools that will get us there."

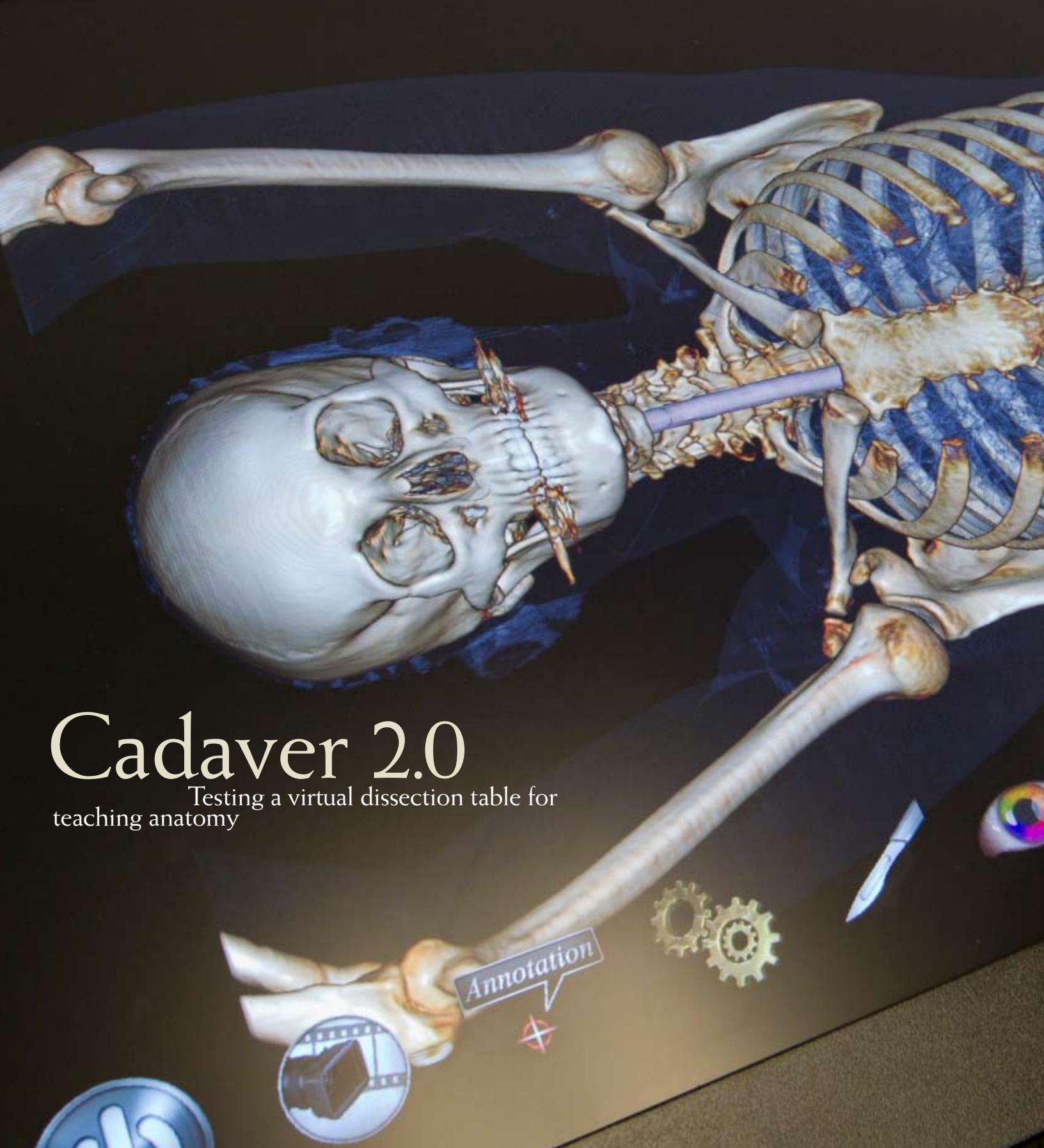
Regardless of its origin or fate, every blood sample — and the data that comes from testing it — becomes part of the center's database. That growing pool of data, combined with clinical comparisons of patient's health status (diseased versus healthy, old versus young, male versus female), promises to reveal solutions to medical riddles that for obvious reasons can't be solved by subjecting humans to the kind of experimentation that immunologists have been using on mice.

The mice themselves may have already told us much of what they can about the human immune system, Davis says. While he's quick to acknowledge the value of mouse studies in puzzling out details of the immune system's interactions, he thinks we're bumping up against an evolutionary limit. Having diverged from a common ancestor 60 million years ago, mice and people are — how to say this gently? — *different*. They've got four legs, we've got two. Their hearts beat 500 times a minute, ours 60. And their immune systems are different, too.

"We've cured cancer and autoimmune disease in mice many times over," muses Davis. He says a colleague of his often starts his talks with the salutation: "For the mice in the audience, I have *wonderful news!*"

Your immune system is there to save your life. Will Stanford's new systems-biology approach speed the day when this 24/7 lifeguard's signals are accurately interpreted in real time, on a patient-by-patient basis, in a clinician's office? That would be wonderful news for the rest of us. **SM**

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Cadaver 2.0

Testing a virtual dissection table for
teaching anatomy



SO HOW DOES THIS WORK, EXACTLY?

The dissectionist's usual scalpels, forceps and probes won't do the job here. Instead students peel away layers of imaged flesh and bone by tapping and swiping the touchscreen tabletop.

BY TRACIE WHITE

Photography by
Norbert von der Groeben

"You make the diagnosis," says the anatomy instructor, looking up expectantly at his students.

The handful of undergraduates gather around the newest anatomy teaching aid, a life-sized, iPad-like dissection table with an image of a young woman's injured shoulder.

Peering intently at the screen, the students can't resist touching it. With a swipe of the forefinger, they zoom in on the image. Then zoom out. One touch, and the virtual shoulder rotates. Another touch, and the muscles disappear, leaving just the bones. One more touch and the bones dissolve, leaving the circulatory system behind.

"I've never seen anything like it," says Meghan Bowler, 21, a junior bioengineering student from Boston.

Only an hour or so earlier in a nearby classroom, the instructor, Sakti Srivastava, MD, associate professor of surgery and division chief of clinical anatomy, had presented a lecture on the anatomy of the upper limb using visual aids—illustrations and diagrams—and then led the group to the lab for hands-on education using cadavers, some

3-D dissection photos and the new technology, essentially a virtual dissection table.

With the table, Silicon Valley engineers have now joined a long list of doctors, artists, photographers and other technology innovators seeking the best way to explore and learn about the anatomy of the human body.

The new virtual dissection table takes advantage of 20th-century technological advancements in imaging, such as X-rays, ultrasound and MRIs, and combines them for use in a 7-foot-by-2.5-foot screen. At Stanford, the table is being tested as a way to further enhance that age-old teaching method — the dissection of human cadavers.

"The virtual isn't the same as the real," says David Gaba, MD, associate dean for immersive and simulation-based learning. "What we want to do is leverage the best of both. It's not really, 'Is one better than the other?' Rather it's, 'What can we do with the two combined?'"

Its creators refer to it as something of a reusable cadaver, with the added benefit of allowing users to easily explore hard-to-reach parts of the human body.

The table, which made its debut on campus in April, is on loan from Anatomage, a San Jose-based medical technology firm, to the anatomy division at the medical school. Faculty are experimenting with its use as a possible teaching aid for everyone from undergraduate anatomy students to medical students, residents and even patients.

"We want to see what the educational value of this resource, this tool, might be," Srivastava says. "Does it complement the cadaveric work of our students?"

The \$60,000 device is part of a new wave of technology that makes possible interactive displays of the body using real-life images. The touch screen — created by placing two LCD screens together horizontally — allows users to investigate a realistic visualization of 3-D human anatomy and to delve inside the human body. CT scan images are augmented with 3-D modeling and annotation explaining what the viewers are viewing. (One body-sized LCD screen would have had to be custom-made, and thus prohibitively expensive.)

The images morph from soft tissue to hard tissue. The tissue can be sliced much like actual tissue on cadavers in the dissection lab next door, but no knife is needed — just a single slide of a finger will do. Then, with the press of a button, the entire body is restored instantly.

"The idea is you can build the body part by part," says Paul

"We want to see what the educational value of this resource, this tool, might be."

Brown, DDS, consulting associate professor of anatomy.

The concept for the table sprang to life about a year ago during an informal conversation between Brown and Jack Choi, PhD, the CEO of Anatomage. Choi happened to be visiting Stanford to provide a tutorial on software in use by the medical school. Brown mentioned that he'd been researching and working on the idea of bringing such a table to Stanford for teaching purposes but had failed to find a way to have one made that would be affordable.

For about two years, Brown had scoured the globe for hardware and software vendors to build such a table. His search led him from the University of Illinois, where engineers were working on a prototype of a life-sized digital video screen, to Sweden where a company has built a virtual



autopsy table. But neither was quite right for the classroom use he envisioned.

After listening to Brown's idea, Choi said, "Oh, I can build one of those," Brown recalls. So Choi put several engineers to work on developing the table.

"Finally, it's ready for prime time," Brown says. The Anatomage table is designed to be used for teaching anatomy on various levels of complexity.

"Each image brought up will have a reason for being there. It's not meant to be just pretty, but extremely useful as a teaching tool," says Brown. "There are so many different normal variations in human anatomy and then there are all the different pathologies."

Four faculty in radiology and anatomy are building a searchable library of digital anatomical images based on CT scans, MRI and ultrasounds of the human body that could be used with the table as well as other educational technologies. The Stanford researchers know of no resource comparable to what they're shooting for.

With access to such a library, a virtual dissection table could include many anatomical variations and pathologies — from tumors to fractures to cystic fibrosis. Anatomy profes-

sors at Stanford and other schools could use the image library to develop a wide variety of lesson plans.

Srivastava and the three others who are working on the imaging library — called the Searchable Digital Anatomical Library — hope to have it licensed through Stanford's Office of Technology Licensing. Their goal is to make it available to other educational institutions, nonprofits and companies such as Anatomage. Any financial proceeds from the library would be divided among Stanford, the faculty and their departments as is typical for technology transfers by universities.

The first students to work with the table were in the new undergraduate bioengineering anatomy course taught by Srivastava. The day's instruction began with a tra-

"The humerus is out of the socket," Bowler answers.

"Right, it's a complete dislocation," Srivastava says. "Now, rotate the image a little bit. You can see there are smaller, fractured sections. You can predict the direction of the force that caused the dislocation. This is a rare variety. The patient comes in like this," he says, holding his arm straight up in the air.

Then, he reiterates the anatomy that he described in the lecture hall: "This is the brachial artery. It divides into two."

On to the elbow. "I want you to see this little piece of bone, the medial epicondyle. See that groove there? The ulnar nerve — that's the funny bone — that's where that sits. See the ulnar artery?"

Later, Srivastava says his experiences with the table are encouraging. "The virtual dissecting table affords new ways to



ditional lecture focused on the anatomy of the shoulder and the arm: the veins, arteries, nerves, bones, muscles. Then students walked over to the lab.

In one room was the traditional dissection lab. It was filled with rows of the medical students' cadavers, each covered by a blue tarp. Two were uncovered: human arms were on display. With gloved hands, teaching assistants picked up and pointed out the ulnar artery, the brachioradialis muscle — each anatomical piece described and illustrated previously in the lecture hall.

"What artery is this?" asks a teaching assistant, separating one vessel from the other.

"The ulnar," the group says.

"And this?"

"The radial."

When they were finished, the students moved to the room next door to view 3-D images of the shoulder and chest from the world-renowned Bassett photographic collection of human dissection. And then on to a third lab room where the virtual dissection table was open for class.

At the virtual dissection table, Srivastava asks the students for a diagnosis of the shoulder problem.



DIGITIZED CORPSES CAN'T SUBSTITUTE FOR REAL ONES, but they have some advantages. Students using a virtual cadaver can remove entire organ systems with a finger tap.

Above right: Viewing 3-D photos of real dissections.

see and interact with the same anatomy, as well as providing access to a collection of normal variations and abnormal pathologies," he says. But it will take some time to determine how widely it will be used on campus in the long run, if at all.

After working with the table for a few weeks in anatomy lab, bioengineering student Bowler is still impressed. "As a modeling tool and a tool for teaching diagnosis, I think the table holds great potential. It possesses the unique ability to allow us to look at the same body at different layers, with different features present and missing," Bowler says. "But I have personally found the cadavers most helpful in lab because they allow me to inspect the muscles and bones of a real specimen — nothing is approximated."

For her at least, the cadaver is still the best learning tool, because, well, it's the real thing. **SM**

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FEATURE

A kid again

CONTINUED FROM PAGE 25

them navigate situations in which they might face discrimination. For instance, early CCSS research showed that many pediatric cancer survivors had problems obtaining health insurance once they grew too old to be covered by their parents' insurance.

"That story came back over and over again," Donaldson says. "And boys who wanted to enlist in the military wouldn't be accepted because they had previously had cancer ... it went on and on and on."

Though most patients are grateful for the HAT team's efforts, Mitchell says, some never come back after the first visit.

"It's hard for them," she adds. "Across the board, these families have been affected for the rest of their lives. Some don't want to face it again."

FOR DEREK and Heather Wagner, life may never be back to normal, but it is good. Though their old family photos show

a tiny bald girl with a feeding tube, the newer pictures are happier: the family at Disneyland; Isabelle and her little brother, Ryan, dressed in red, white and blue for the Fourth of July; Isabelle with a snowman that she and her grandmother built at Lake Tahoe.

"Our measurements of time are stretching out," Derek says.

For Isabelle, who has no memories of her diagnosis, surgery, chemotherapy or radiation, her illness is abstract. At home with her mom, she describes what she knows about her illness: Follow-up MRIs are notable mostly for the cherry-flavored anesthetic gas she inhales beforehand; going under the anesthetic makes it feel like things around her are vibrating; Fisher is a good audience for the pictures she draws when she's sitting in his waiting room.

Discussing family photos of an early hospitalization, Isabelle sounds momentarily upset as she asks Heather, "Why did I have to go in the *baby* crib?"

"You were a baby," Heather says, calm and matter-of-fact.

And that's that. Isabelle is quickly on to more important 7-year-old concerns: showing off a skinned knee; telling an

animated story about her music teacher ("He's super funny!"); describing plans for her upcoming birthday party.

The family is keeping a close eye on Isabelle's school progress, as they want to address any cognitive problems as soon as possible. She struggles a bit with speed-based math quizzes, which hints that she may have deficits in processing speed.

"There are a few things we're concerned about, but clearly, relative to what she had and to what other patients go through, she's phenomenally well," Derek says. "We're really grateful for that."

And Isabelle's stubborn streak is serving her well in school, Heather adds. "She's determined. She keeps trying."

Most important, Isabelle has the support system she needs to make sure that complications can be caught early and treated aggressively.

The weight of the CCSS results has helped make it easier for childhood cancer survivors to obtain services under the Americans with Disabilities Act, such as individualized education plans that are part of special education programs. Isabelle benefited from this change when she was enrolled in a preschool pro-

LETTERS TO THE EDITOR

Responses to last issue's Q&A with Paul Gelsinger, whose son died during a flawed clinical trial:

GIVEN THE EXCEPTIONALLY RAW emotions that the loss of a child evokes, Paul Gelsinger put a face on the very real risks of clinical trials, and in particular, this tragedy has been used to focus attention on researcher conflicts of interest. Spurred into action by Gelsinger's heartbreak, the political and regulatory domains of government together drove a wholesale revamping of IRB processes, resulting in the creation of a thicket of regulation around the issue of physician conflict of interest. Fearful of running afoul of these new rules, and possibly jeopardizing the largesse emanating from their NIH overlords, leading medical schools responded by placing even more strin-

gent (than the government) restrictions on the financial activities of clinical faculty involved in patient research. In calming the public furor that accompanied allegations of investigator conflict of interest, medical academia seemed to give only slight regard to the delicate balance needed for innovation and translational research to occur.

For physicians in the research trenches, the flip side of Jesse Gelsinger's tragic death has been the skyrocketing challenges to performing novel clinical studies inside U.S. academia; while seeking to eliminate perverse financial incentives, medical schools have eliminated important incentives for clinical faculty to innovate. Can altruism, by

itself, motivate many academic physicians to take out a second mortgage on their home to fund the development of critical technology, as I once did? In today's overly regulated environment, I am quite certain that the clinical research I did in the 1990s and which created the field of image-guided radiation would not be possible at Stanford today. Meanwhile leading-edge medical device companies, for example right next door in Silicon Valley, no longer even consider performing the critical and most creative phase-1 studies inside U.S. medical schools. More-permissive regional hospitals have largely usurped this traditional role of American academia, while growing numbers of clinical trials are being "off-shored" to medical schools in less-regulated countries. Both trends serve to reinforce the growing irrelevance of U.S. academia to the development of medi-

gram that included physical therapy for her floppy feet, a common side effect of vincristine, one of her chemotherapy drugs. And she will receive extensive cognitive testing this summer.

Meanwhile, Derek and Heather are still feeling their way forward.

"We wonder if we have to worry about leukemia—it's one of the more common side effects of the treatment Isabelle got," Heather says. She and Derek don't want to focus too heavily on a bad outcome, but they want to be well-informed about all the possibilities.

"You have to really become the advocate for your child," Derek says, adding that such advocacy requires not just fact-finding but also a "defensive posture"—the ability to step in and protect Isabelle from the scariest information about her medical situation until she is ready to handle it.

"I just want her to be able to feel like there isn't anything she can't do," says Heather.

The family got an unexpected boost to their outlook at a July 2009 follow-up visit at Packard Children's. Fisher was absent, so the Wagners saw neuro-oncologist Sonia Partap, MD. After answering

a long list of questions, Heather recalls, Partap said, "I hope you're not worrying about all this stuff. You are in a really special category of people; there are not a lot of people where you are."

They'd known this, of course, but until this conversation with an outside observer it hadn't sunk in, Heather says.

"That's when we realized that Isabelle is one of the lucky ones." **SM**

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HERE'S HELP

Children's Oncology Group

This worldwide clinical trial group for studying childhood cancer offers long-term follow-up guidelines on its website:

<http://childrensoncologygroup.org>

The Childhood Cancer Survivor Study

The National Cancer Institute's overview of the study's findings so far:

<http://stan.md/epatqR>

cal devices. Is this really what we as a society want? Do the moral demands of human subject research and conflict of interest really make the current situation inevitable?

Thanks in large part to the generosity of the American public, the basic research enterprise inside U.S. medical schools remains robust. However, after once dominating the world in cutting-edge clinical innovation, these institutions have simply given away their historic role in technology development. As a consequence, countless patients with incurable diseases can at present no longer expect American medical schools to produce the clinical advances they so desperately seek. Who speaks for these faceless millions? Jesse Gelsinger has been used repeatedly to justify much of the new clinical research environment. If Jesse, the heroic young man who gave his life in an effort to

advance medical innovation, were alive today, what would he say about the current balance of regulation and pace of medical innovation?

JOHN ADLER, MD

Stanford professor of neurosurgery

THE PERSPECTIVE AND FEELINGS of Mr. Gelsinger are understandable. Such occurrences should never happen. Unfortunately, we know they happen even with the most stringent regulations. It is impossible to regulate all things. Occasions of bad judgment, dishonesty, inappropriate assumption and unbridled enthusiasm in an attempt to make things better will continue to occur regardless of regulation.

Yet there are unintended consequences to rules and regulation made because of situations like Gelsinger. At present, many hospitals and clinicians

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Stanford Medicine is published three 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.

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are reticent to enter into any clinical trial because of bad press and conflict-of-interest issues. Conflicts of interest are real. Conflicts can be managed in many ways. Any proposal that deters the best institutions from being involved in clinical research is not in the best interest of patients or students.

The problems brought to light in the Gelsinger case would most likely not have happened if full disclosure were made during the entire clinical study. Rules and regulations are in place that address most of these difficulties. More regulation is not always better.

TOM FOGARTY, MD

*Stanford adjunct clinical professor
Fogarty Institute for Innovation, Founder*

HOLY INSULIN SHOCK, BATMAN!

A DYNAMIC DUO TACKLES DIABETES

Shawn Winer wanted to be Spiderman. Actually, scratch that. He still does. His identical twin brother, Dan, however, prefers Batman. • “At least Batman’s still human,”

Dan says, inciting a spirited discussion about spider bites, the Batmobile and Marvel Comics. • It’s not all comic books and online video games, though. The brothers also want to build a time machine. Obviously. • Oh, and they’re 35 years old. • “We’ve always been science geeks,” says Dan, “and we like to think outside the box. We don’t go for dogma.” Rather, Dan and Shawn look for hidden ideas or patterns that may have escaped other people — particularly in human biology and health. • Their most recent discoveries set the world of diabetes care on its head by suggesting that type-2 diabetes, largely believed to be a malfunction of the chemical processes we use to regulate blood sugar, may actually be fueled by a defined autoimmune response. This idea opens the door to new therapies and may even lead to a vaccine to prevent the disorder, which in the United States affects nearly 24 million people.



DANIEL WINER
(LEFT) AND
SHAWN WINER
COLLABORATED ON
RESEARCH SHOW-
ING THAT TYPE-2
DIABETES MIGHT BE
AN AUTOIMMUNE
DISEASE.

This tendency to look beyond accepted ideas has served the Canadian brothers well. After graduating at the top of their high school class, the two went to the same college and majored in immunology. Shawn then went on to complete an MD/PhD, studying type-1 diabetes at the University of Toronto, while Dan went to medical school at the University of Ottawa and then to Stanford for research with pathology professor Edgar Engleman, MD. Through it all, the brothers never stopped talking about science and biology.

“We’ve always kept in touch,” says Dan. “We’d play video games online late at night and exchange messages about our research through *World of Warcraft*.” It was during one of these online gaming sessions that the brothers started wondering whether type-2 diabetes might be influenced by the immune system.

“We both feel that the immune system probably plays a role in almost every disease,” says Shawn. “Think about it. The immune cells in your blood have access to nearly every tissue in your body, and there is no reason to think they don’t influence heavily genetic diseases like Huntington’s or other conditions like type-2 diabetes.”

The brothers’ brainstorm led to two groundbreaking papers in *Nature Medicine* that have fundamentally changed the idea of how type-2 diabetes develops. One, published in 2009, proved for the first time that an immune cell called a T cell kicks off insulin resistance, the precursor to full-blown diabetes. The other, published in April, showed that another immune cell, called a B cell (and the antibodies it produces), is also involved, probably by attacking the body’s own tissues in a way that impairs the ability of cells to respond to insulin.

Now the brothers are back together, both in the pathology department at Toronto General Hospital — Dan as a new staff member and Shawn as a resident.

“We have almost the same training now,” says Dan. “We each specialized in immunology and pathology. I guess it probably does look like we copied each other. But I don’t think either one of us ever wanted to do anything different.”

Well, that is, except for maybe one thing. Because Shawn devoted extra training time to complete both an MD and a PhD, Dan is now Shawn’s supervisor. And while there’s no proof that Shawn’s looking into that time machine, Dan might want to be cautious. — KRISTA CONGER

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Weak links

TIES BETWEEN BIOMARKERS AND DISEASE ARE OFTEN OVERSTATED

MORE THAN HALF OF 35 OF THE MOST WIDELY CITED STUDIES linking genes, proteins or other "biomarkers" to specific diseases vastly overstate the association, according to new research. As a result, clinicians may have been giving patients some bad advice. • What's behind the faulty biomarker-disease connections? At least in part, they're the result of statistical vagaries. But human nature and the competitive nature of scientific publication also play roles, says John Ioannidis, MD, DSc, chief of the Stanford Prevention Research Center, in a paper published June 1 in the *Journal of the American Medical Association*. • "No research finding has no uncertainty; there are always fluctuations," he says. "This is not fraud or poor study design, it's just statistical expectation. Some results will be stronger, some will be weaker. But scientific journals and researchers like to publish big associations." • Once published, the perception of a strong link between a marker and a disease often persists. As subsequent studies repeatedly reference the landmark findings, they become accepted as incontrovertible even in the face of later, larger studies reporting less-spectacular or even statistically negligible associations. • Among the links that now look weaker based on larger follow-up studies include one tying the BRCA1 mutation to colon cancer, another that associates elevated C-reactive protein in the blood with cardiovascular disease and one that connects high homocysteine levels to vascular disease.

"We found that a large majority of these highly cited papers suggested substantially stronger effects than that found in the largest study of the same markers and outcomes," says Ioannidis.



He notes that studies with greater numbers of patients or studies called meta-analyses, which compile the results of several independent studies, are more likely to be accurate than smaller studies. To use the example of flipping a coin, you might not be surprised to come up with two, three or even four heads in a row, but over the course of hundreds of flips you will approach a ratio of 50:50.

In addition to statistical aberrations, you also have the potential for superimposed bias, Ioannidis says. "Researchers tend to play with their data sets, and to analyze them in creative ways. We're certainly not pointing out any one investigator with this study; it's just the societal norm of science to operate in that fashion. But we need to follow the scientific method through to the end and demand replication and verification of results before accepting them as fact." — KRISTA CONGER

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