

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

Summer 2014

special report

INSIDE JOB
SURGEONS AT WORK

The cutting edge
The world of surgery evolves

Sanjay Gupta
CNN's surgeon journalist

In the joint
Focusing on the gristle

Healing wounds
New techniques to repair the skin

Losing consciousness
What does it mean to go under?

Funky hats and
rock 'n' roll
My, how the OR has changed

plus

An excerpt
from the book
Surgeon General's Warning



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RODIN'S VIRTUAL HANDS

ART AND MEDICINE

MEET IN AUGMENTED REALITY

While James Chang, MD, was doing his surgery residency at Stanford, he took to playing a game of sorts with the campus Rodin sculptures: He'd come up with specific medical conditions based on the appearance of their hands. He had plenty of hands to choose from as Stanford's Cantor Arts Center holds one of the world's largest Auguste Rodin collections, with 200 of his sculptures, including *The Thinker* and *The Gates of Hell*.

"I began to notice that most of the hands looked like the conditions I was treating, from fractures to malformations to tumorous growths," Chang says.

Rodin's *Large Left Hand* appeared to have some broken metacarpals. He speculated that *Large Clenched Hand*, a sculpture frozen in a painfully exaggerated and abnormal posture, had Charcot-Marie-Tooth disease, an inherited neurological disorder. From sculpture to sculpture, hand to hand, the surgeon proceeded to identify a ganglion cyst, a thumb amputation, a stiff joint and other conditions.



WITH THE HELP of an iPad at the Stanford exhibit, you can see virtual blood vessels, nerves and bones within Rodin's *Left Hand of Eustache de St. Pierre*.

When he became a surgery professor at Stanford, his hobby turned into a teaching tool, which he incorporated into the undergraduate course *Surgical Anatomy of the Hand: From Rodin to Reconstruction*.

Now Chang's diagnoses are part of the inspiration behind an exhibit at the art center, *Inside Rodin's Hands: Art, Technology, and Surgery*, celebrating the connection between Rodin's fascination with the human form and medicine's fascination with human anatomy. The center's program includes a "virtual operation" to fix the perceived broken fingers on the *Large Left Hand* and a 3-D, augmented-reality model showing how the statue would look post-surgery. The exhibit runs through Aug. 3.

"Art is informing medicine in the exhibit, and medicine is informing art," says the museum's director, Connie Wolf. "It's unlike anything we've ever done before."

Stanford has a history of scientists using art to inform their teaching and learning, stretching back at least to the early 1990s, when surgery professor Robert Chase, MD, and Rodin authority Albert Elsen, PhD, challenged medical students to find clues of medical conditions in the Rodin sculpture garden — located conveniently near the medical school.

The new exhibit builds upon this history, says Paul Brown, DDS, consulting associate professor of anatomy. Brown, together with exhibit production manager Matt Hasel and medical artist Sarah Hegmann, used CT scans from Stanford hand clinic patients to create virtual sculptures showing the hands' supposed internal anatomies.

Rodin studied anatomy like other art students of his day, and he spent time at the Musée Dupuytren in Paris (a museum of anatomical items illustrating diseases and malformations), says Rodin expert Bernard Barryte, the exhibit's curator. So were Rodin's hand sculptures based on living models or did they grow from his imagination? According to Barryte, no one knows for certain. — TRACIE WHITE

WEB EXTRA

See a video about the exhibit at <http://stan.md/1nxKrv9>

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

SPECIAL REPORT

Inside job

SURGEONS AT WORK



Inside the mind
of a surgeon
page 14

- 6 **Opening up** *By Ruthann Richter*
THE EVOLVING WORLD OF SURGERY
- 14 **Her left hand** *By Tracie White*
A SURGEON'S JOURNEY BACK
- 22 **Medical coverage**
A CONVERSATION WITH CNN'S SANJAY GUPTA, MD
- 24 **Incredible cartilage** *By Sara Wykes*
FOCUSING ON GRISTLE IN THE EFFORT TO IMPROVE JOINT REPLACEMENTS
- 28 **Sculpting bones** *By Julie Greicius*
A TECHNIQUE THAT REQUIRES PRECISION, ARTISTRY AND, FROM THE PATIENT, TRUE GRIT
- 32 **Healing wounds** *By Elizabeth Devitt*
CLOSING THE GAP
- 36 **Going under** *By Sarah C.P. Williams*
RESEARCH INTO CONSCIOUSNESS CROSSES FROM PHILOSOPHY TO SCIENCE
- 40 **In the groove** *By M.A. Malone*
BEHIND THE SCENES IN THE OR

Bones and bravery
page 28



PLUS

- 42 **Rethinking Alzheimer's** *By Bruce Goldman*
LOOKING TO ITS ORIGINS FOR A TREATMENT
- 46 **The demise of the surgeon general** *By Mike Stobbe*
AMERICA'S DOCTOR FADING AWAY

When being insured
buys worse care
page 4



DEPARTMENTS

- Letter from the dean 2
- Upfront 3
- Backstory 54

It was an office visit nearly 20 years ago, yet I remember the April 1995 day as if it were yesterday. My patient was a 50-year-old man with a strange problem: Whenever he whistled or hummed loudly, objects seemed to him to move around “like on a clock face.”

As an otolaryngologist, I was used to patients who found their symptoms perplexing. The vestibular system, my area of focus, controls balance and eye movements, and when it malfunctions strange things happen. But this man’s condition had me perplexed as well.

Over the next months some other patients reported similarly odd symptoms. One man told me he got dizzy when he sang in the shower. Another patient said she could hear the sound of her own eyes moving. Some patients assumed the problem was psychological until their psychiatrist referred them to me.

What was the culprit? My hunch was that it had something to do with the small, curved tubes in the inner ear that help us sense motion — the semicircular canals. I first tested my theory by observing these patients’ eye movements in response to loud noises — a technique used over a century ago for defining the relationship between each of the three semicircular canals and the eye movements that result from their activation. I found that a canal was indeed involved in causing this bizarre constellation of symptoms and signs: the superior semicircular canal.

When I explored further using the advanced imaging techniques of the day, I discovered the patients had tiny holes in the bone overlying this canal. The openings allowed changes in intracranial pressure or sound transmitted through the inner ear to cause motion of fluid in the superior canal and that in turn led to the symptoms and the eye movements. I labeled the openings with the word dehiscence and thus “superior canal dehiscence syndrome” entered the medical vocabulary.

I was glad to have discovered the cause and manifestations of the syndrome, but what mattered most to me, and certainly to my patients as well, was figuring out how to treat it. So I was extremely pleased that the surgical procedure I devised alleviated my patients’ symptoms — and could be used to reduce the suffering of hundreds of others.

In operating rooms today, patients benefit from spectacular innovation. Perhaps the most revolutionary change during my lifetime has been a shift toward minimally invasive surgery. Instead of traditional approaches, which often require large incisions and extensive manipulation of tissues and organs, many surgeries are now accomplished through tiny entry portals. This low-impact approach to surgery usually results in less risk of infection, less pain, less damage to tissues and faster recovery. Instead of a week in the hospital for gall bladder removal, most patients can be back home the next day.

At Stanford Medicine, innovation is part of our culture, so it’s no surprise that we’re a hotbed for new techniques and technologies that improve surgery results. Among recent advances: brain surgeries that bypass easily damaged healthy tissue by using the nostril as an access route, tools for minimally invasive surgeries sized to treat children, a retraction device that protects against wound infection and a post-surgical dressing that reduces scarring.

The power of innovation in surgery continues to amaze me. It inspires me to push ahead with our initiatives to transform the science and practice of medicine for a healthier world. It fills me with gratitude for the patients who enable innovation to move forward. And it explains why I’m so proud of Stanford Medicine, where innovation flows freely.



Sincerely,
LLOYD B. MINOR, MD
Carl and Elizabeth Naumann Dean of the School of Medicine
Professor of Otolaryngology-Head & Neck Surgery

upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD MEDICINE

Garbage strike

Normally, the body is extremely efficient at taking out the garbage. Two hundred billion cells die every day in our bodies, and most get cleared out within a matter of seconds. But when this process breaks down and garbage, in the form of dead cells, starts building up in the walls of blood vessels, it's not a good thing.

Researchers led by Nicholas Leeper, MD, assistant professor of cardiovascular medicine and of vascular surgery, now have evidence that faulty garbage disposal explains why variation in one particular stretch of chromosome 9 increases risk for a wide range of cardiovascular diseases, including stroke, heart attacks and aneurysms.

Their research, published in the *Journal of Clinical Investigation*, shows that disturbing the usual genetic sequence at chromosome location 9p21 leads old cells and debris to build up in the walls of blood vessels.

In studies with mice with atherosclerosis, the researchers showed that this genetic variation leads to impaired "efferocytosis" — from the Latin for "take to the grave" — the process by which dead



or necrotic cells are removed. Mice with this genetic variation showed an increase in buildup of these dead cells, further advancing their atherosclerosis.

"If you were born with genetic variation at the 9p21 locus, your risk of heart disease is elevated, though we haven't understood why," Leeper says. "This research gets at that hidden risk. You can be a nonsmoker, be thin, have low blood pressure and still be at risk for a heart attack if you were born with this variant. This work may help explain that inherited risk factor, and more importantly help develop a new therapy to prevent the heritable component of cardiovascular disease." — TRACIE WHITE

15%
is the portion of U.S. foreign aid spent to support health. More at <http://stanford.edu/1ieLGdU>.

From smartphone to "eyephone" "THINK INSTAGRAM FOR THE EYES," says assistant professor of ophthalmology Robert Chang, MD. His team has created inexpensive adapters that make it easy to use a smartphone to capture high-quality images of the eye — one for the front surface of the eye, another for the inside view.

It matters because the usual eye-imaging instruments are expensive and hard to use, and even ophthalmologists who have the equipment and know-how find capturing and sharing the images slow going.

Physicians who'd like to test the adapters can e-mail the team at eyegotech@gmail.com. — ROSANNE SPECTOR

Mysterious paralysis

SOFIA JARVIS WAS ONLY 2 YEARS OLD WHEN, AS SHE REACHED FOR A TOY, her left arm abruptly stopped working. An MRI showed a spinal cord lesion, and an evaluation at Lucile Packard Children's Hospital Stanford confirmed that she is among 16 children in California who have developed sudden-onset, permanent paralysis similar to polio.

"Although poliovirus has been eradicated from most of the globe, other viruses can also injure the spine, leading to a polio-like syndrome," says pediatric neurologist Keith Van Haren, MD, who diagnosed Sofia.

Doctors at the California Department of Public Health suspect enterovirus-68, a member of the poliovirus family, in cases like Sofia's, though they're also considering non-infectious causes. The group of cases, which began in mid-2012 and apparently ended in late 2013, is similar to recent outbreaks of paralysis from another virus, enterovirus-71, in Asia and Australia.

"Fortunately, this is not exceptionally virulent," Van Haren says. "It's just happening in the very unlucky few."

But public health officials are keeping a close watch on the situation.

Meanwhile, Sofia, now 4, is generally healthy, but her arm is still paralyzed. "We really want to know what caused this," says her mother, Jessica Tomei. — ERIN DIGITALE

Insult to injury

Have insurance, will get proper care? Maybe not, according to a School of Medicine study. • In this study of cases of severe injuries, patients with insurance are more likely to get poor trauma care than those without. Apparently, more insured patients are held back at non-trauma hospitals instead of being sent to centers specializing in trauma, the *JAMA Surgery* study reveals. • The findings of the study — one of the first such population-wide analyses — are concerning, the authors say. • Perhaps emergency doctors fail to follow guidelines or recognize conditions that need extra care, suggests lead author Kit Delgado, MD. Or maybe, more disturbingly, non-trauma hospitals hold insured patients back so they can get reimbursed. • To curb such practices, these hospitals could better monitor emergency room encounters and split transfer costs with trauma centers, the authors say. Previous studies show that trauma-center care reduces the chances of a severely injured patient dying by 25 percent. • Senior author Nancy Wang, MD, earlier found such insurance-based disparities in trauma care access for children and seniors in California. "Researchers and the community should understand this trend," she says, "so that it can be changed." • The authors analyzed over 4,500 nationwide reported trauma cases for the study. Next they hope to figure out if and how patients' preferences and knowledge of options affect trauma transfer decisions. • Wang is an associate professor of surgery. Delgado is a former Stanford emergency medicine instructor, now at the University of Pennsylvania. — RANJINI RAGHUNATH



AUTISM: VIDEO DIAGNOSIS

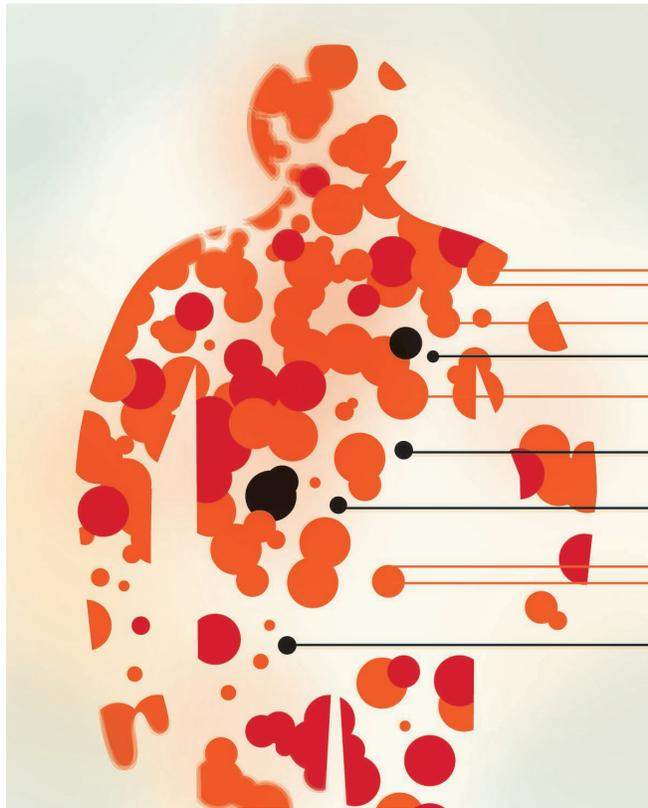
Short home videos may be a powerful tool for diagnosing autism, according to new findings from associate professor Dennis Wall, PhD, and colleagues. Wall's team scored the level of autistic-type behaviors in brief YouTube videos of 100 children. The method, described April 16 in *PLOS ONE*, identified autism with 97 percent accuracy. Though video-based diagnosis won't likely replace traditional assessments, it could speed the now-sluggish diagnostic process. "We could use this system for clinical triage, as a way to channel traffic so that children can get the kind of attention they need as early as possible," Wall says. Children who clearly have autism might be diagnosed with videos and started on therapy, freeing clinicians to spend more time evaluating kids whose condition is less clear cut.

— ERIN DIGITALE

Samples'

side effects

There's no such thing as a free lunch. Or, for that matter, a free drug sample. Oh, sure, your doctor might hand you a medication to try before writing a prescription, and you could walk out the door without forking over any cash. But a recent study in *JAMA Dermatology* by Stanford dermatologist Alfred Lane, MD, indicates that when doctors with access to free samples do write prescriptions, they tend to be for more-expensive medications — an average retail cost of \$465 versus about \$200 for a diagnosis of adult acne. Dermatologists without access to samples (Stanford for example, bars doctors from receiving drug samples) are more likely to use cheaper, generic medications. Lane's not suggesting your doctor's in cahoots with pharmaceutical companies — the increased expense is likely unintentional. What he's found is evidence of the power of marketing. And the fact that your mother is always right. — KRISTA CONGER



Detection without radiation

One whole-body PET-CT scan exposes you to as much ionizing radiation as 700 chest X-rays.

After learning they have cancer, lymphoma patients usually get scans to locate tumors throughout their bodies. But the standard imaging method, whole-body PET-CT, has a big drawback: One scan exposes the patient to as much ionizing radiation as 700 chest X-rays. • This is especially risky for children and teenagers, who are particularly vulnerable to radiation because they are growing. They are also more likely than adults to live long enough afterward to develop a secondary cancer. • That's why researchers at the School of Medicine and Lucile Packard Children's Hospital Stanford developed an imaging technique that uses no radiation at all. The method, described in *The Lancet Oncology*, is a modification of magnetic resonance imaging that employs a novel contrast agent. • The new agent consists of injected nanoparticles of iron, which are already FDA-approved to treat anemia. On MRIs, they cause blood vessels to appear brighter, providing anatomic landmarks. The nanoparticles also cause healthy tissues such as bone marrow, lymph nodes, liver and spleen to appear darker, making tumors stand out. • The nanoparticle-enhanced scans had similar levels of sensitivity, specificity and diagnostic accuracy to whole-body PET-CT. Although more evidence of the technique's efficacy is needed before it will be adopted, there are no technologic hurdles to its use. • "It's really exciting that this will soon be clinically applicable," says radiologist Heike Daldrop-Link, MD, who led the research. — ERIN DIGITALE

The gene team

Stanford's hospitals have launched a new testing service for their patients that deciphers their DNA. The clinical genomic service will help doctors at Stanford Hospital & Clinics and Lucile Packard Children's Hospital Stanford diagnose and treat genetic conditions. With this, Stanford joins a small group of medical centers — about 15 — that provide genome sequencing.

During its pilot phase, testing will be limited to patients with inherited cardiovascular or neurological disease, hereditary cancer risk, unexplained drug reactions or an illness that has defied diagnosis. Its directors are Euan Ashley, MCRP, DPhil, associate professor of medicine and of genetics, and Jason Merker, MD, PhD, assistant professor of pathology.

In 2010, Ashley and bioengineering professor Stephen Quake, PhD, were the first in the world to use a healthy person's genome sequence to predict disease and anticipate reaction to several common medications. These new genomic services are the first wave to test this new knowledge. — SARA WYKES

O P E N I N G

U P

THE EVOLVING WORLD
OF SURGERY

SEPIDEH GHOLAMI STOOD AT THE SURGEON'S ELBOW, USING A METAL PRONG TO EXPOSE THE DARK, TENNIS BALL OF A TUMOR IN THE YOUNG PATIENT'S COLON. IT WAS HER THIRD YEAR AT STANFORD MEDICAL SCHOOL, AND SHE'D BEEN A RELUCTANT STUDENT OF SURGERY, AS THE OPERATING ROOM SEEMED LIKE AN ALIEN, FOREBODING PLACE. But in her first week at Kaiser Permanente Santa Clara Medical Center, she was taken in by the artistry of the process — the ritual passing of the instruments and the deft movements of the surgeon's hands as he carefully cut out the cancer. There was a rhythm to it. It felt like dancing, one of her passions. • The surgeon moved quickly, and in short order life would change for the patient. Gholami felt a connection with him, a Mexican man in his 30s who had come to the hospital surrounded by a very large family. • "I remember going to the family afterward, saying that we were able to get it all out and seeing the glow in their faces," she recalls. "That feeling stuck with me." • It rekindled a childhood memory: the glow on her own mother's face when she learned the cancer had been extracted from her breast. • "I thought, 'This is what happened to my mom,' who is now disease-free. This is how she must have felt." • And so Gholami, 32, became seduced by the practice of surgery, ultimately setting her sights on a career as a surgical oncologist. • Now finishing her sixth year as a surgical resident at Stanford Hospital, Gholami, MD, is being raised in an era of burgeoning surgical technologies, changing training practices and a more collaborative culture that is opening its gates to women. She must master a breathtaking array of new surgical tools, all designed to minimize the impact of the surgeon's knife. With these tools, procedures that once produced a foot-long scar on a patient's abdomen have been reduced to operations that

By Ruthann Richter

PHOTOGRAPHY BY MAX AGUILERA-HELLWEG

**Sepideh Gholami is finishing her sixth year
of training to become a surgeon.**



'WHEN I WAS A MEDICAL STUDENT, I REMEMBER A

SENIOR SURGEON SAYING, "BIG HOLE, BIG SURGEON."
THAT, OF COURSE, HAS CHANGED.'

leave a few pencil-thin marks. And surgeons are pushing the boundaries with operations that need no incision at all, such as tumor removal through the nose, the ear or the mouth.

"When I was a medical student, I remember a senior surgeon saying, 'Big hole, big surgeon,'" recalls Tom Krummel, MD, the Emile Holman Professor and chair of the Department of Surgery. "That, of course, has changed. We do the same big operation. We just don't make a big hole."

Now surgeons commonly carry out big procedures through small incisions. They slide in a tiny video camera, called an endoscope, which transmits the view of the surgical site to a monitor in the operating room. Through additional small incisions or through the tube-shaped endoscope itself they slide in other surgical tools — maneuvering them with handles that extend outside the body. "The collateral damage of an incision is no longer the badge of what I can do," says Krummel. "It's harder to work with chopsticks, which is essentially what we're doing."

The benefits of surgery's advances have been enormous for patients, who now undergo some 50 million surgical procedures a year in the United States alone.

THE PROFESSION GHOLAMI IS ENTERING TODAY IS A FAR CRY FROM THE SURGERY OF THE EARLY 1800s, when modern practices had their beginnings, notes surgeon Atul Gawande, MD, in a 2012 *New England Journal of Medicine* article. Back then, a Boston surgeon performed the first reported cataract removal using a cornea knife to successfully excise the thickened capsule from the eye of an unanesthetized patient, who regained his sight. Other surgical techniques soon followed, including extraction of kidney stones and treatment of arterial aneurysms and gunshot wounds. But these procedures could be brutally painful and were limited in part by the threat of infection and the lack of anesthesia, whose introduction in the mid-1800s revolutionized the field, says Gawande.

More than 125 years later, the second revolution in surgery came with the advent of endoscopy and other tech-

niques to minimize the intrusion of the surgeon's knife. Less-invasive surgeries cause less pain and blood loss, reduce the risk of infection and lead to quicker recoveries, as many procedures that once required long hospitalizations can be done without an overnight stay.

A striking example is surgery for patients with an aortic aneurysm, a bubble in the aorta that can rupture and cause death. Patients used to undergo a massive, risky procedure in which surgeons made a foot-long opening in the abdomen to remove the damaged part of the artery and then sewed a Dacron tube in its place. Now it's done with two small holes in the groin, as surgeons snake a catheter up into the aorta and repair the aneurysm with a stent graft — a procedure pioneered at Stanford. Most patients now go home the next day, whereas in the past they would typically spend seven days in the hospital, including two in the intensive care unit.

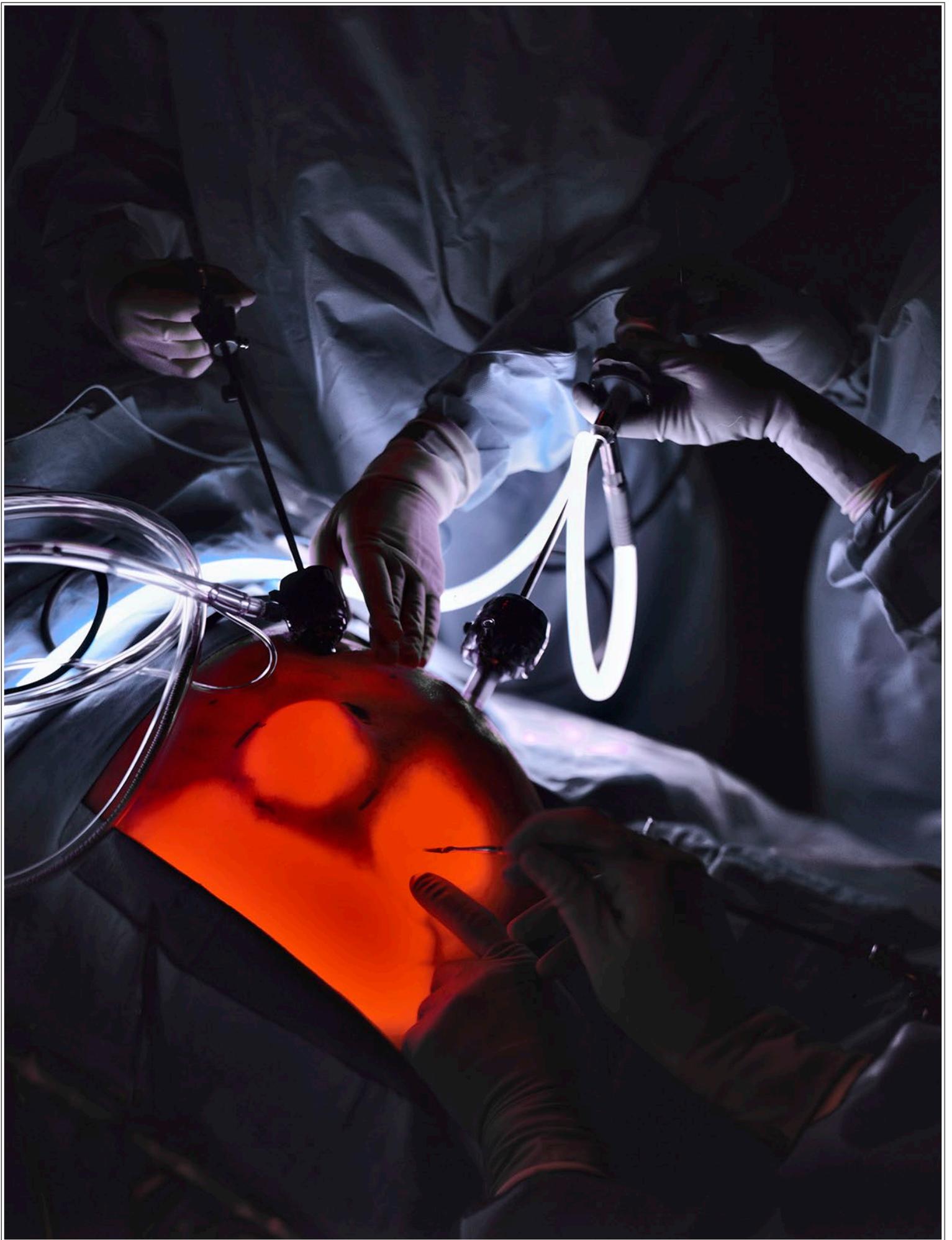
"The transition to less-invasive, image-guided therapy has revolutionized vascular surgery and requires us all to continue to learn new skills and innovate, all for improved patient care," says Jason Lee, MD, director of endovascular surgery at Stanford and a principal investigator on several trials of devices to make it easier for patients to recover from surgery.

With the shift to minimalist procedures, "Surgeons have had to change mentality," says David Spain, MD, chief of trauma and critical care surgery. "If you're doing a procedure with small incisions, are you less of a surgeon? It's kind of an identity crisis for surgeons," he says, especially for those like him who trained in the 1970s and 1980s, when big, open surgeries were the bread and butter of the practice.

On the other hand, there is the satisfaction of fixing a patient's life-threatening problem with a few tiny cuts and a quick hospital stay. "You're doing the same big surgery on the inside," says colorectal surgeon Natalie Kirilcuk, MD, one of a younger generation of surgeons. "I feel a sense of accomplishment when I do it with as little external impact as possible. You can take out an entire colon with a few poke holes and a small incision."

New imaging and navigation tools also play a key role in modern surgery, exposing previously hidden structures in the body to help guide surgeons to minute targets with-

Fiber-optic light casts a red glow as Gholami and David Spain repair a hernia laparoscopically.



Gholami thought she'd grow up to be a mechanic. Now she can't imagine being anything but a surgeon.

out harming critical structures.

For instance, with advanced brain imaging, neurosurgeons can visualize structures deep within the skull in three dimensions, enabling them to extract malformed vessels through a 5-millimeter (a fifth of an inch) opening or to successfully remove a tumor near the brain stem, a previously impossible feat, says Gary Steinberg, MD, PhD, the Bernard and Ronni Lacroute-William Randolph Hearst Professor in neurosurgery.

"We couldn't get there without devastating the patient," says Steinberg, chair of the Department of Neurosurgery. "With current imaging, we can view the brain with a precision of 1 to 2 millimeters," or less than a tenth of an inch.

The development of surgical robots, a form of computer-assisted surgery, has added another dimension to the field. With robots, a surgeon sitting at a console in the operating room can manipulate robotic tools inside the body through a single incision.

Surgeons love working with their hands, and surgical robots are helping bring back the "feel" of traditional surgery as the surgeon uses dexterous hand and wrist movements to guide the robotic arms, which serve as a natural extension of the human hand. "It restores the attributes of open surgery without making a big hole," says Krummel, a robotics expert who came to Stanford in 1998 in part to expand the university's robotics program by bringing together surgery and engineering. Robots have been used in more than 1.5 million procedures nationwide and are now the tool of choice in prostate surgery, gynecologic surgery and some other procedures.

With the exponential growth in new tools, even highly experienced hands like those of Jeffrey Norton, MD, the Robert L. and Mary Ellenburg Professor in Surgery and chief of general surgery, have had to relearn some aspects of the trade. "You have to learn to do new things. It's like starting over," says Norton, who is widely recognized for his skills as a surgical oncologist.

At times, Gholami says she has found herself in the operating room with mentors who themselves are acclimating to some new piece of technology. "They are still in their own



learning curve," she says. "So when you are scrubbing, it may be with an attending who hasn't done it many times. So he or she may be more cautious."

As surgical technology has soared, so has patient demand, along with the number of skilled practitioners. By 2008, nearly one in every five active physicians in the United States was a surgeon, according to the American College of Surgeons. These master technicians now have some 2,500 procedures at their disposal, Gawande notes in his article.

And because of greater ease and safety, these procedures are performed far more often. At the current rate, projects Gawande, the

average person in the United States will have seven surgical procedures in his or her lifetime.

"The technological refinement of our abilities to manipulate the human body has been nothing short of miraculous," Gawande writes.

FOR GHOLAMI, IT WAS A LONG, HARD ROAD INTO THE OPERATING ROOM, WHICH WAS FAR FROM HER CONSCIOUSNESS AS A YOUNGSTER IN HER NATIVE IRAN. At the age of 5, she fled the Iranian revolution with her family in the early 1980s and grew up in a hostel for asylum seekers in Germany. Her father, an auto mechanic, inspired her to use her hands to fix things. As a child, she remembers repeatedly taking apart the videocassette recorder to clean and put back together, all out of sheer delight over the workings of the device. She envisioned herself as a mechanic one day, though it was hardly a vision of herself as a skilled mechanic of the human torso.

Her life as an immigrant in Germany was hard, so she jumped at the chance to visit an uncle in Northern California whom she barely knew. There happened to be some fine universities nearby, and she was fortunate to attend the University of California-Davis and, later, Stanford medical school, from which she graduated in 2008.

Even in medical school, surgery was far from her mind.

She chose it as her first rotation “just to get it out of the way,” she says.

But she quickly became seduced by the exhilarating tempo in the OR and the gratification that comes from immediately fixing a problem and restoring someone to life.

“Surgery is very fast-paced. It is so fast-paced that a lot of people get lost and think it’s too much for them — you have to keep 500 things in your head,” she says.

There is a very quick turnaround: “You round on your patients in the morning, then do the operations and in between cases or after see patients again. It’s not like other fields of medicine — it’s a very different type of lifestyle. ... I don’t think it’s for everyone, but if you do love it, as I do, you will feed off it. There may be days when I go without sleep and am still going. But when I get out of the OR, it doesn’t matter if I slept last night or not — it is so gratifying. There is nothing else I could envision myself doing.”

The demands are evident on a recent morning, as Gholami works alongside Spain to repair a hernia — a weakness in the abdominal wall that showed up as a large lump on the patient’s midsection. They take turns controlling a slim, tubular endoscope, known as a laparoscope, and other tools — periodically alternating places at the operating table in a quick do-si-do. “See, surgery is like a dance,” says Gholami, her dark oval eyes framed by her surgical mask and cap. “Sometimes you have a good partner,” responds Spain. “Other times you have to lead them around.”

After estimating the size of the surgical site, Spain cuts out a circular mesh shield — “arts and crafts,” he calls it — to restrain the gaping hernia. Gholami folds the mesh, inserts it through the laparoscopic tube and positions it inside the body. She and Spain then work in tandem over the patient’s midsection, which glows in the laparoscopic light, their hands weaving in and out as they stitch down the mesh and staple it in place. “So pretty,” Gholami says of their handiwork. “Yes, pretty,” says Spain. “I hope it works.”

Gholami is then off at a run to the emergency room to examine a young car accident victim, to review scans and order surgery for a man with a perforated bowel, and check lab results for a gallbladder patient.

“This is the challenge, you see. Everything happens so fast,”

she says as she jogs back to the OR for another hernia fix.

Surgeons are, by nature, nimble practitioners, quick to move and act. They have to be, for while a patient’s internal organs are exposed, open to possible infection, there’s no time for long debates about what to do next.

They also feel a special connection to their patients, who put their full faith in the clinician while anesthetized on the operating table, often in an undignified pose. “The patients are completely incapacitated, so when you are in the OR, you have to do the right thing — make the right decision,” says Kirilcuk, a clinical instructor of surgery. “I think surgeons have a lot of passion for their patients because of the trust that patients put in us.”

GHOLAMI BEGAN HER TRAINING AT A TIME WHEN THE TEACHING OF SURGERY WAS AT A CROSSROADS. In 2003, the Accreditation Council for Graduate Medical Education, the national accrediting group for medical and surgical training programs, imposed the first of a new set of work rules that included a strict, 80-hour work week limit for residents. These regulations have caused much consternation among medical educators, particularly in the surgical community. Surgeons in their 50s, like Spain, remember their training days when they virtually lived in the hospital, spending 100 hours a week or more there, on call every other night and consoling patients at the bedside for long stretches of time.

It was dog-eat-dog in the surgical world those days, with interns angling to seize every opportunity to be in the operating room so they could beat the competition and survive the program, he says. With trainees today limited to working 80 hours, “they have 20 percent fewer opportunities to see stuff,” says Spain, who is the Ned and Carol Spieker Endowed Professor of Surgery. “A lot of people from my generation, who grew up in the competitive era, think those rules are killing surgery. Though I don’t agree.”

Many argue that surgical trainees back then were so tired that they were prone to mistakes and weren’t really able to soak up what they were learning — the rationale behind the work limits, which were strengthened in 2011. Krummel, the

**‘A LOT OF PEOPLE FROM MY
GENERATION, WHO GREW UP IN THE
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SURGERY. THOUGH I DON’T AGREE.’**

department chair, remembers falling asleep at the wheel after being on call for 36 hours as a resident in Richmond, Va., in 1982. “I could have killed someone,” he says. “I woke up real fast when I hit the guardrail.” Luckily, no one was injured.

He also questions whether patients benefited from having tired trainees leaning over the operating table. “We all know patients for whom we didn’t exactly deliver what was needed,” he says. “We blundered along. It was learning on the job. We might have been having trouble getting the appendix out. We could have used some gray hair in the operating room, but it was a sign of weakness to call for help. Our trainees today are much better — they don’t worry about calling for help.”

James Chang, MD, professor and chief of plastic and reconstructive surgery, says when he was a medical student at Yale in the 1990s, surgery residents routinely slept through lectures. He saw them as tired, hungry and unhappy. “They couldn’t see the end of the tunnel in their education.” Today, he says, “As a result of getting good sleep and having an outside life, residents are happier people. They’re awake and engaged.”

Stanford has adapted to the new work rules by developing a more structured curriculum, including time in simulation, to help residents master the vast body of knowledge and the bewildering array of technologies and procedures they are likely to encounter in their practices.

Medical simulation, says Krummel, is crucial. “Simulation allows you to develop a curriculum in a more thoughtful, organized way,” rather than have residents scrub in for whatever patient happens to come in that day.

He founded the Goodman Simulation Center at Stanford Hospital & Clinics in 2007 and helped develop the Roy B. Cohn Bioskills Laboratories, a rare type of facility where surgical trainees use cadavers to hone their skills. Simulation allows trainees to practice procedures over and over before they even see a patient, says Lee, an associate professor of surgery. With simulation, a trainee can face a console resembling a video game and manipulate wires and catheters inside a box, rehearsing what it’s like to do an angiogram, say, or install a stent.

“We entrust our lives to pilots and they train by working on simulators,” Lee says. “We entrust our lives to surgeons and yet we have no metric to measure performance other than they have practiced alongside someone for five years. What if pilots didn’t practice until they did the real thing?”

“It makes education more efficient, and efficiency breeds many advantages,” he adds. “They can be here in the hospital less and incorporate material for a better work-life balance.”

Lee is among those in the surgical community who believe residents graduate with too little experience to enter independent practice — a subject of much contention. In addition to

today’s limits on training hours, surgery residents no longer spend time in the operating room on their own. Changing government reimbursement practices, which require an attending physician to be present, as well as more scrutiny of medical procedures by government and regulatory groups, have limited the autonomy of surgeons-in-training.

As a result, nearly 40 percent of surgery residents said in a recent survey that they lacked confidence in their skills after five years of training, according to a study published in September 2013 in the *Annals of Surgery*. Moreover, 43 percent of fellowship directors interviewed said incoming residents couldn’t do 30 minutes of a procedure on their own, though most said the residents were up to speed by the time they finished the fellowship program.

Gholami bristles at the idea that today’s surgery residents aren’t as well-trained because they don’t have enough exposure to different experiences and procedures. “I think that’s inaccurate,” she says. “Overall you can’t say we’re less trained. Training today is just different than it was in the past.”

Moreover, she says residents now routinely hone their skills and gain added expertise in specialty areas by pursuing one- or two-year fellowships after their four to seven years of residency, depending on the specialty, and their four years in medical school. Indeed, more than 80 percent today choose to go on to fellowship programs after residency, according to the *Annals* study.

To help smooth the transition from residency to general surgery practice, the American College of Surgeons has developed a fellowship. The program supplements the residency curriculum so trainees have the confidence and mastery to lead independent practices.

NOT ONLY HAVE SURGICAL PRACTICES AND TRAINING CHANGED, SO HAVE THE FACES OF SURGEONS — LITERALLY. Where women were once *personae non gratae* in the operating room, they are now entering it in record numbers, accounting for 21.3 percent of the nation’s nearly 136,000 practicing surgeons in 2009. Though women comprise a smaller portion of the surgical workforce than of the medical profession as a whole — where they account for 30.5 percent — a growing number of female trainees are entering the pipeline, according to the American College of Surgeons. Women accounted for 37.5 percent of surgical residents and fellows in accredited programs in 2008.

Surgery traditionally was considered a demanding job, designed for tough guys, so that even getting married was given

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a second thought. Krummel remembers one of his mentors at Johns Hopkins University having to seek permission from his supervisors to marry. And Spain says in his day, for a surgeon to have a wife who was pregnant was considered “marginally acceptable,” as children could prove to be a distraction from work.

As department chair, Krummel has made recruiting women to the department a priority. When he arrived at Stanford in 1998, women accounted for only 9 percent of surgery’s full-time faculty, including those in emergency medicine. Now, 35 percent of the faculty and 45 percent of trainees are female, he says.

“We’ve been lucky here at Stanford to have female mentors who are great role models,” Gholami says. “So the issue of women in surgery is not a problem here, though I’ve heard stories of difficulties elsewhere — that there is a gender imbalance.”

“I think if you don’t have a role model, it’s hard for women to imagine how they could be surgeons,” Krummel says.

Sherry Wren, MD, a professor of surgery, says she had to almost fight her way into the field more than 25 years ago. “People actively tried to discourage me from going into surgery,” she says. “It was the boys’ sport.” But she loved the profession’s artistry and the process of puzzling through patient problems and making decisions. Her role model was a feisty male surgeon in medical school who urged her to get surgical training.

When she arrived at Yale as a resident in 1986, she was one woman among 17 men and had to endure lectures about the style of her curly red hair — which drew more attention than her performance — and the need to wear pearls in the operating room, she says. “It was a really different world then,” says Wren, associate dean for academic affairs at Stanford’s medical school. “It’s an easier road now.”

Wren helped ease the way for younger surgeons, like transplant surgeon Amy Gallo, MD. By the time Gallo began her training at Stanford in 1999, she says gender was less of an issue in the profession.

Today, Gallo, 38, an assistant professor of surgery, balances her practice with her life at home with her husband, an accounting researcher, and two children — an infant and a toddler. She eats dinner most evenings with her family and is fortunate that

her husband likes to cook and is willing to console the children in the middle of the night when she is called away to the operating room to transplant a new kidney or liver.

Maintaining a work-life balance “is definitely a work in progress,” she says, though “I have the family life I expected I would have.”

Gholami says it’s a matter of setting priorities and realizing that at times, “friend and family events will be missed. You just have to have a very good support network.” With the new work hours, she gets a day off a week and occasionally has time for herself. “I do work out. I do see my friends. It’s not a disastrous black hole where I disappear for seven years,” she says.

She has a boyfriend, who recently moved to this area to be closer to her, and says she sees marriage and family at some point in her future. But she knows it will not be an easy road.

“I still think because of the difficulties of having families and children, it’s going to be tough. I’ve seen multiple examples of where it’s worked, but it takes someone special as a partner who understands. ... This is probably my biggest challenge, the constant struggle of balancing a career in academic surgery with my personal life.”

After her residency, Gholami plans to pursue a two-year fellowship in surgical oncology, ideally at an academic cancer center such as Memorial Sloan Kettering in New York, where she spent two years during her residency developing a breast cancer therapy. The treatment, a genetically engineered smallpox virus, has done well in preclinical testing, and she hopes to see it enter clinical trials, she says.

At the moment, her patients fuel her passion for surgery, the ultimate cure for many tumors. She recalls one young man who came in recently with an ailing appendix. He was fearful of surgery and left the hospital against doctors’ orders. He returned that same evening, feeling poorly, and apologized for leaving. He’d gone home to pray, he’d said, and had hoped his condition would improve. But it had become clear to him that surgery was his best road to recovery.

“There are certain things where you know surgery is the only way,” Gholami says. “That for me is the ultimate gratification.” **SM**

— Contact Ruthann Richter at richter1@stanford.edu

WEB EXTRA

Hear an
interview with
photographer
Max Aguilera-Hellweg
at [http://stan.md/
1hPmAaS](http://stan.md/1hPmAaS).



SHERRY WREN THINKS OF HERSELF AS A SURGEON FIRST.



INSIDE JOB:

Surgeons at work

HER LEFT HAND

A SURGEON'S JOURNEY BACK

As the mental fog from the surgery began to lift, surgeon Sherry Wren asked a friend visiting at her bedside for a dab of lip moisturizer. Her lips were dry, as is common after surgery.

• “I took it with my right hand,” Wren says. “I could move my hand, but I could not find my face.” Her right hand with the drop of petroleum jelly headed for her chin, completely missing her lips. Her friend had to help. The two chuckled, assuming that it was the anesthesia, that she was still a bit drugged up. *Everything's fine. Everything's fine*, she thinks. The spinal cord surgery, a roughly 90-minute procedure on the morning of June 29, 2012, went well. *Except, why can't my hand find my lips? And my left hand, why can't I move it yet?*

Tracie White

PHOTOGRAPHY BY MAX AGUILERA-HELLWEG

From the Stanford operating room, Wren, 53, professor of surgery and associate dean for academic affairs at the Stanford School of Medicine, had been moved to the post-anesthesia care unit. The searing pain of the previous three weeks was mercifully gone. The neurosurgeon had entered through the front of Wren's neck to fuse two vertebrae and remove a ruptured disc. Her family and friends blamed the disc injury on a high-seas shipwreck three weeks earlier, but she wasn't so sure. Wren had been one of 26 tourists and crew who abandoned a sinking diving yacht in rough seas 15 miles off the coast of Layang-Layang Island, Malaysia. All of them survived by navigating motorized rafts to shore.

In the post-anesthesia care unit the morning after her surgery, Wren next remembered the nurse coming in to check her motor functions. About then, the fog lifted, and she began to think more clearly. "My left hand was like a claw. I couldn't lift my left knee. Then my surgeon came to see me, and I recognized that 'Oh shit!' look on his face, because I've had that 'Oh shit!' look many times."

Wren, who has operated on hundreds of patients herself over nearly three decades, who has prepared so many others for the possibility of post-surgical complications, who has made it ever so clear that no surgery is risk free. This time, she's the one with odds in her favor but who still loses the roll of the dice.

It was the correct diagnosis. The correct treatment. There was no surgical error. And yet somehow, the veteran surgeon who makes a living with her hands woke up partially paralyzed. The unexpected complications included paralysis of her left hand and her left leg, and a weakened right hand. Already she thinks, *Will I still be able to operate?* Already she thinks, *What am I if I'm not a surgeon?*

"Look, something can always go wrong. I'm the poster child for that," she says, telling the story almost two years later, sitting at her desk in her office at the Veterans Affairs Palo Alto Health Care System. "I see a lot of patients. I tell them what the 'percentage of chance' is for a certain complication, but that's pretty much meaningless. Sometimes stuff just happens that you can't predict. I am the person who really understands that. I'm the one case in a million that went wrong."

SURVIVOR

THREE WEEKS PRIOR TO HER SPINE SURGERY, WREN HAD AWOKEN AT 3 A.M. IN HER BED AFTER THE 24-HOUR JOURNEY HOME TO PALO ALTO FROM MALAYSIA AND STARTED DIAGNOSING HERSELF. *What could cause this crushing chest pain that radiates out my back? Aortic dissection? A heart attack?*

The shipwreck had occurred during one of her many deep-sea diving vacations. The 130-foot yacht, the Oriental Siren, started taking on water while most passengers and crew were asleep in the early hours of June 8, 2012. At 4 a.m., a crew member knocked on cabin doors yelling: "Must-er with your life jackets!"

"I never thought I'd hear that," Wren says. "I knew it was serious." The boat was taking on water in the rear, but the crew didn't know from where. They were setting up an auxiliary pump because the main one was damaged and irreparable.

Two hours later, the power went out on board, and the crew could no longer steer the boat as it rocked and rolled through 15-foot swells. The decision to abandon ship was made at 7 a.m., and all 26 passengers and crew climbed into the two rafts.

"The Thai captain, who couldn't speak English, was curled up in the fetal position in the front of one of the life rafts," Wren says. "He had totally checked out. So it was the dive masters and the passengers who had to make the decisions. Some people did start to lose it." With no response from the Malaysian navy to the crew's mayday radio calls, the survivors decided to make their own way to the bits of land

visible between ocean swells. All 26 made it. All survived.

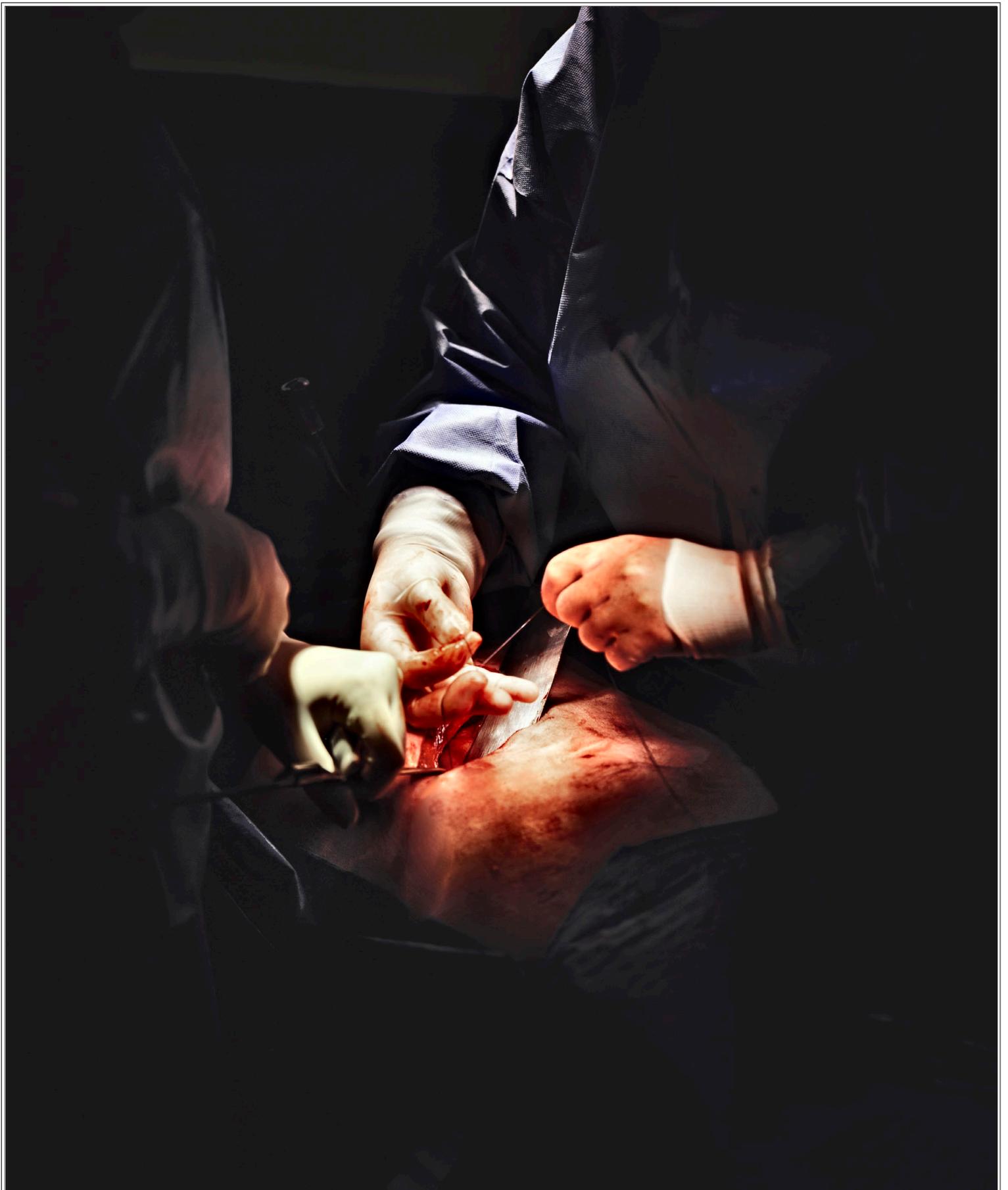
"Shipwreck almost over!!!" Wren posted on Facebook once she made it to shore. "Still can't believe all my gear and stuff is 6,000 ft. below the ocean."

The survivors spent the night in the lone hotel on the island then hopscothed across Asia to get home. Wren's trip involved five connecting flights, with a particularly long lay-over in the Narita airport in Japan.

EXCRUCIATING

SHE'S STILL NOT SURE WHAT CAUSED THE HORRIBLE PAIN. MAYBE IT WAS THE STRENUOUS TWO HOURS SPENT IN THE RESCUE CRAFT. Wren stepped in to help refill the outboard engine's tank, lifting heavy gas cans as the craft crashed through those 15-foot swells. Or maybe it was the

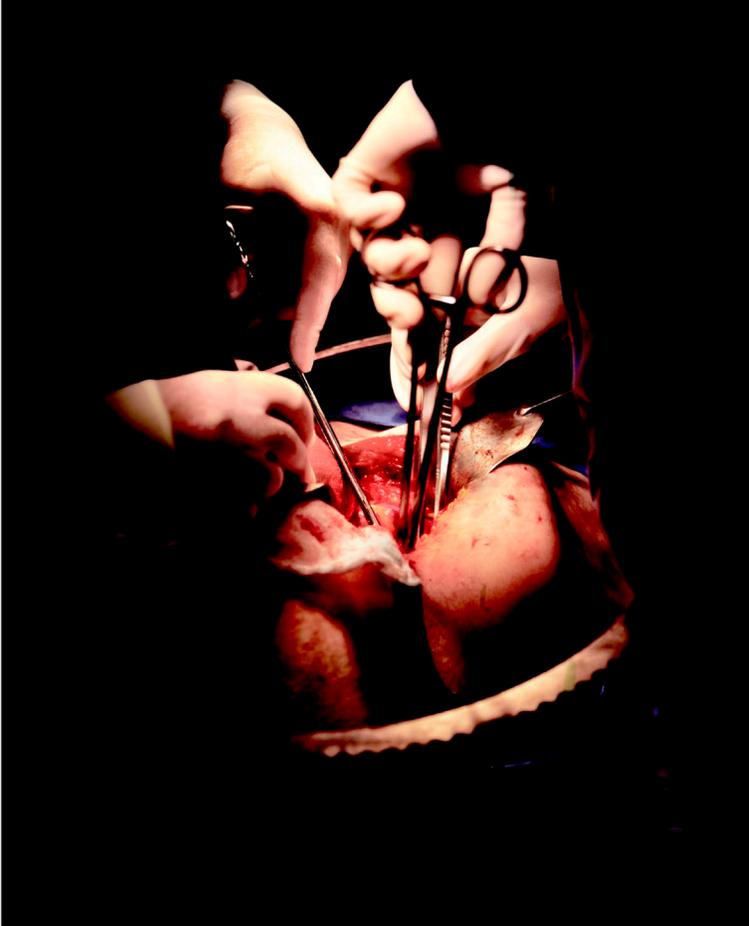
'SOMETIMES
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case in a million
that went
wrong.'



CLOSING TIME

Wren sutures an incision in a patient's abdomen at the end of a surgery to remove and examine his gallbladder.

Wren and general surgery resident Arghavan Salles, MD, PhD, cut, retract, grasp, clamp, cauterize, suction and suture.



six-hour layover in Narita where she slept upright in a chair, her head drooping. Or maybe it was just an accumulation of damage from the many years she has spent standing up on a stool in the operating room so that her 5-foot, 3-inch frame could bend over and she could tilt her head down to see inside her patients' abdomens as she cut and sutured and toiled to save their lives.

Whatever the cause, the pain that ripped through her chest was so excruciating she was forced to wake her husband. He wanted to rush her to the emergency room right away, but she held out until 7 a.m. — advice she would never give anyone else. “No one wants to be seen naked in front of their friends at work,” she says.

At the Stanford ER, the potential diagnoses came and went until finally someone suggested nerve damage and the neurologist arrived to examine her. There were more tests, more speculations, then somewhat randomly, the medical staff started flicking the middle finger on each of her hands.

“I’m thinking ‘What the heck?’” she says. She had tested positive for the Hoffman’s reflex test, apparently rarely seen. When the middle finger is flicked and the last joint of the thumb

flexes at the same time, this indicates problems in the nerve system of the spine. The diagnosis: acute spinal cord compression. A spinal disc herniation was bulging onto the spinal cord, flattening it like a ribbon. The solution: surgical removal of the bulging disc and fusion of vertebrae 5 and 6, and 6 and 7.

For the next three weeks while waiting for surgery, she slept sitting up to control the pain. When the day of surgery finally arrived, the pain was so unbearable that the surgical team had to knock her out with medication before she could be laid flat on the operating table. Perhaps that’s when the complications occurred — the damaged disc bulging just the right way, putting pressure on the nerves just the wrong way.

A SURGEON’S LIFE

IF SURGEONS HAVE A STEREOTYPE, WHICH THEY DO OF COURSE, WREN FITS MUCH OF THE BILL: TOUGH, FEARLESS, STRONG, IMPATIENT, EFFICIENT. Her specialty as a professor of surgery at the Palo Alto VA is high-risk gastrointestinal cancer surgeries — like taking out a 25-pound liver tumor or removing a tumor from the pancreas with the notoriously difficult Whipple procedure. That’s what she lives



to do. Like most surgeons, she has always been commander-in-chief in the operating room. It is her stage. She jokes. She picks the music. She hums along. She gives the orders and then taps her fingers with irritation on the sides of the operating table until they are followed. The OR is her universe, her world. Self-confidence is key in this life-or-death arena, where slipshod work is not an option. Once a body is sliced open, time is precious. Speed is essential. The sooner the patient gets sewn back up, the better. Surgery is always a risk. Minimizing that risk and achieving results is her job.

It's more than her job, of course. It's her calling.

"The first time I saw surgery, I thought, 'Oh my God! That's what I want to do. You get to fix it!'" says Wren.

It wasn't her lifelong dream to become a surgeon. Wren was just a good student who grew up in Chicago, where her father had a TV repair and car radio installation shop, and her mom stayed at home to raise Wren and her three brothers. She was the first and only person in her family to graduate from college, studying biology at Carleton College, in Minnesota, then attending medical school at Loyola University in Chicago. That was where she first saw surgery and

fell in love. Once she became a surgeon, "I've always defined myself first as a surgeon," she says.

Wren is married with no children. Her two bull terrier dogs have personalities to match her own — stubborn, independent, lovable. Almost equal to her passion for surgery is that for deep-sea diving that has taken her to the wilds of New Guinea, where she danced in the rain with the natives, ate foot-long tree worms and survived a cyclone at sea.

"Sherry will try anything," says her friend and diving partner Lynne Maxwell, MD, an anesthesiologist from Philadelphia who saw firsthand the eating of the worm and was with her during the Malaysian shipwreck.

That same fearlessness is present in the OR.

Wren likes the challenge of performing high-risk surgery. She takes on the "peek and shriek" cases: "Another surgeon will open up a patient and say, 'Ohmigod, it's too this or too that,' and close him back up," Wren says. Not Wren.

"She's just a powerhouse," her friend and fellow surgeon Myriam Curet, MD, says. "She takes care of very sick patients with very difficult problems. Everybody trusts her."

The scuba diving gives her a release from this stress-

ful world of high-risk surgery, she says, although others say that she's just an adrenaline junkie — a stereotypical surgeon.

"I do operations where I really can kill somebody," she says. "I'm always worrying about whether the patient will be OK. It's critical to unwind. Diving is the only time I can shut that out." Which she does on a boat out in the middle of nowhere with no cell reception, no Internet service. Just the deep blue sea and swimming with the fish four to six hours a day.

In her spare time, Wren volunteers for Doctors Without Borders, performing medical missions to Chad, the Congo, Ivory Coast. She has saved many lives with the power and skill of her hands — popping dislocated hip joints back into place, relieving brain bleeds with a hand drill, doing C-sections.

"You have no idea how physically hard it is to crank a 6-millimeter pin into someone's femur with a hand drill," Wren says. "And I'm strong.

"I could survive with my legs paralyzed, but not my hands."

She takes enormous pride in her powerful hands. They are blessed hands, no question. So when, suddenly, those hands lost their strength, when the left hand began to shrivel before her eyes and started to look skeletal, it shook her to the core.

These aren't my hands. They're an alien's hands, she thinks. They don't belong to me.

GOING IN

THEY ARE SMALL, FEMININE HANDS. THE FINGERS ARE SLENDER. THE WHITE, UNMANICURED NAILS ARE VISIBLE THROUGH CLEAR, SURGICAL GLOVES. HER VOICE IS LOUD. HER PERSONALITY FILLS THE ENCLOSED, WHITE-WALLED OPERATING ROOM. Her hair is naturally curly and red. She's a bit like a small tank, one that can bulldoze its way through walls. Not much can stop her.

It's 9:30 a.m. The abdomen incision is made. Six scrubs-wearing, plastic-gloved medical professionals surround an operating table at the Palo Alto VA hospital. The workday begins.

Wren's hands slip nicely into the open, bloody abdomen. They work in sync with each other, and gently push around the internal organs, the small and large intestine, folding back the peritoneum — the lining of the abdominal cavity — searching and uncovering the vena cava, the gallbladder and the pancreas. She reads the internal anatomy of her patient

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business.'

like a well-known neighborhood map. Her students, the young doctors and surgeons gathered around the patient's chest, watch her hands closely. They study those hands. The hands teach them their anatomy lessons so that someday they too can save lives. So that they too someday can perform the Whipple, the crown jewel of surgeries.

"That's why I keep telling you you've got to know your anatomy," Wren says, as she constantly quizzes them on the names of organs and veins.

Like a ballplayer, it's said that she has "good hands," that she has amazing hand-eye coordination.

"Don't dig into the liver," she warns the chief resident as she guides his hands through the labyrinth of intestinal organs. The liver, a large, dark mass, rests a bit ominously just above the intestines.

"I can feel his pulse behind his bile duct, which makes me...," her voice trails off. The room tenses. "That makes me want to get down to business."

The minutes tick past as the surgeon and chief resident cut and sew, cut and sew. Back and forth they pass the scissors and the needles and the suctioning instruments.

The wall clock moves past 10:30 a.m., past 11:30 a.m.

Her left hand works as hard as the right. It's the support hand. The stalwart, dependable, indispensable force. The left hand digs down deep into the guts.

"All right, let's get this gallbladder out," she says. The surgery had really only just begun.

REHAB

FOR ABOUT A MONTH AFTER HER SURGERY, WREN HAD TO USE A WALKER. SHE NEEDED HELP TO WASH HER HAIR. SHE COULDN'T DRIVE. SHE WAS FORCED INTO DEPENDENCY, AND SHE HATED IT. She started seeing a psychiatrist to help adjust. Still, the day after she returned home from neck surgery, she was back at work. Friends told her to go back home to finish recovery, but she returned again the next day. She could still perform many of her duties, treating patients at the clinic and continuing her teaching rounds.

But the doors to the OR were closed.

"It's not easy to slow her down," says her friend Kim Rhoads, MD an assistant professor of surgery at Stanford. "It takes a lightning strike from the universe, something like a shipwreck. Seriously, it took that whole ship sinking."

Nerve recovery can continue for up to two years after damage. But it happens slowly, nerves growing about 1 millimeter per day. Without the nerve innervation the muscles will atrophy. Exactly how much the damaged nerve will grow back in Wren's case remains an unknown. Some of her motor functions came back quickly. Soon enough, she could walk, drive a car and wash her own hair. The right hand regained much of its strength as well. But the left hand, the one frozen in the shape of a claw immediately after surgery, remained a problem.

In the first few months after surgery, Wren's No. 1 motivation was not just getting back to operating, but to return to those marathon surgeries. The ones that last eight, 10, 14 hours. Even though she's right-handed, she needs a strong left hand as well to do those surgeries. She wanted the Whipple back.

"My left hand is the control hand that sets everything up," she says. "There are no one-handed surgeons."

But as the months passed, her left hand began to atrophy. At some point during those months of rehabilitation — even though she knew objectively that it made no sense — her hands started to look foreign to her. *My hands are stronger than these. These are someone else's hands.*

"It was so depressing," Wren says. "My entire life I've always had really good hand-eye skills. I was really strong for a woman. I regained my dexterity quickly after surgery, but the nerves were not innervating my muscles. My muscle strength would die in like a second."

For the next six months, she did six to eight hours of occupational and physical therapy each week. Her competitive nature kicked in, and she tended to overdo it. Her home filled with rehab equipment — weights, exercise bands, exercise balls. She pushed hard. Sometimes she met Rhoads for lunch on Fridays and talked about her goals. What would she do if she didn't get enough hand strength back to be able to do the Whipple?

"We'd talk about, 'Do you have to keep doing Whipples?'" Rhoads says. "There's a kind of pecking order of operations, according to their risk. The Whipple is the Cadillac of operations and at-tests to a surgeon's technical skills. It's the tippity-top of the pecking order of operations. It's very high-risk surgery."

"She was trying to figure out who would she be without this part of herself. I think that's when she started teaching others her global health skills, holding classes for other surgeons,

developing a reputation as an expert in another area."

After six months of hand rehab, Wren finally walked through the operating room doors once again dressed in scrubs. She started with the short, 45-minute, easy-to-do surgeries — the hernias, the gallbladders. Her technical skills were still good, she could see that. The surgeries went well. But still, there was something wrong.

"I went back in very slowly. Everyone said, 'You're doing fine.' But I made my partners watch me to make sure I was doing everything right. I would go into the scrub sink and look at my hands and think, 'These are not my hands.'

"For the first time in my life, I felt I'd lost all confidence. I felt horrible. I could see objectively that I was operating fine. But I couldn't get it out of my mind that I was doing something dangerous." The depression descended over her like a blanket, blinding her. She didn't want to get out of bed in the morning.

"Like many people, I saw it as a personal weakness that I could not dig myself out of. I was in such a dark place. I thought, 'My hand is horrible. I'm a horrible person.'"

On a sunny Sunday morning in the winter of 2012, Wren sat in the backyard of her friend Curet, the fellow surgeon and consulting Stanford professor. While they watched Curet's 6-year-old twins jump on a trampoline, Wren opened up about the depression.

"I remember being really surprised how deeply this had affected her," Curet says. "What all of us saw at work was that she was back to doing cases. She had this external confidence. Everything looked fine."

"She seemed too depressed to be able to focus. I told her about my own experience with this. I told her it seemed to me like her depression might do well with medication, maybe antidepressants."

Within a week and a half after taking an antidepressant, Wren says she began to feel better. She took the medication for six months, saw the psychiatrist for a year. Today, her left hand is still weaker than it was, but that's OK. The depression is gone.

"It makes no sense to me why the medication worked, but within a week and a half, I began to feel better," Wren says. "It allowed me to have confidence again. I stopped looking at my hands as if they were an alien's. Myriam telling me about her

'I FELT HORRIBLE. I COULD SEE OBJECTIVELY THAT I WAS OPERATING FINE. But I couldn't get it out of my mind that I was doing something dangerous.'

WEB EXTRA

Hear a conversation with surgeon Sherry Wren at <http://stan.md/lipsp9C>

CONTINUES ON PAGE 49

INSIDE JOB:
Surgeons at work

MEDICAL COVERAGE

A CONVERSATION WITH CNN's SANJAY GUPTA, MD

He's a practicing neurosurgeon and chief medical correspondent for CNN. But right now, Sanjay Gupta, MD, is making news for "doubling down" on his support for medical marijuana and apologizing "for having not dug deeply into the beneficial effects of this plant, and for writing articles dismissing its potential."

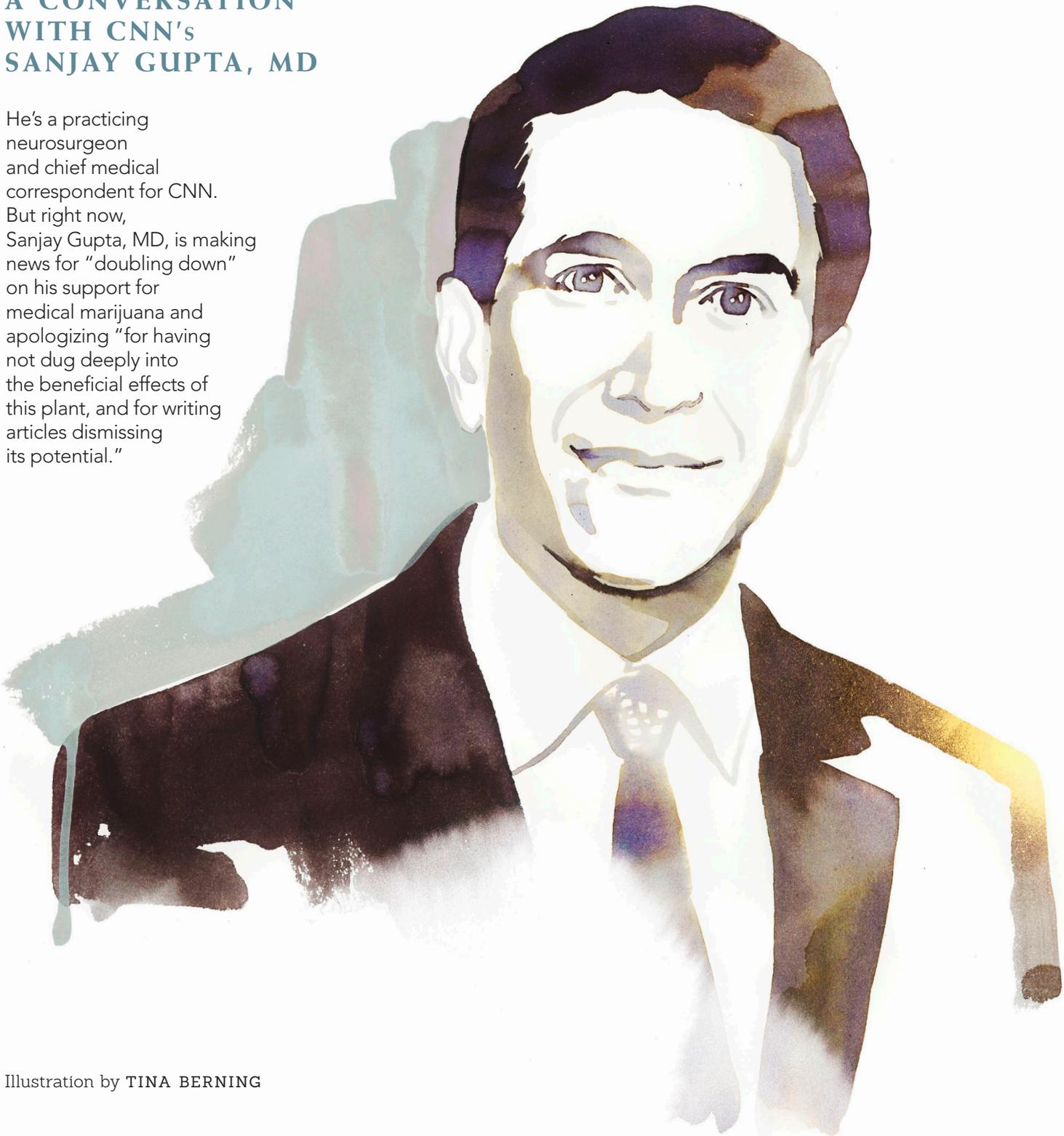


Illustration by TINA BERNING

Gupta joined CNN in the summer of 2001. Since that time he's covered floods and earthquakes, tsunamis and oil spills along with the wars in Iraq and Afghanistan. He's also an assistant professor of neurosurgery at Emory University School of Medicine and associate chief of the neurosurgery service at Grady Memorial Hospital in Atlanta. So where, you wonder, does he find time to write a novel, *Monday Mornings*, about life in the ER? Responding by email from Guinea where he was reporting on the Ebola outbreak, Gupta said that it took him 10 years on and off to write the novel. "I write a lot on weekends, at night and on planes. Many of the characters were amalgamations of people — real and fiction. Once I understood my characters (which took the longest time), the stories came more quickly." Paul Costello, executive editor of *Stanford Medicine*, spoke with Gupta about surgery, medical reporting and his efforts to combat loneliness in America.

PAUL COSTELLO: In 2009, you wrote an article in *Time* opposing efforts to legalize the medical use of marijuana. You've changed your position. Why?

SANJAY GUPTA: Typically as a reporter, I survey the medical literature on various topics, everything from heart disease, diabetes, neurodegenerative disorders, but also things like medical marijuana, potential new treatments for all sorts of things. When I looked at the literature [about marijuana] coming out of the United States, I just wasn't that impressed. But I started to become aware of literature from smaller labs outside of the U.S. I also realized that many of the studies that were being done in the U.S. were designed to *find* harm.

COSTELLO: Do you worry at all about the long-term risks of marijuana on cognitive and psychiatric disorders?

GUPTA: Yes, I do. Yet the literature is pretty compelling with regard to the treatment for specific diseases, such as epilepsy, neuropathic pain and muscle spasms brought on by M.S. This is in addition to the things most physicians think marijuana may have a use for: curbing

spending my time on pediatric rotations. I did a rotation in neurosurgery and it was one of those things where I immediately fell in love. If someone has a problem in their brain or their spinal cord, you're going to address it that day. It feels very concrete. I found the ability to take care of patients more immediately to be very gratifying.

COSTELLO: What makes a great surgeon?

GUPTA: One of the misconceptions is that these people are physical geniuses — extremely talented with their hands. There's a small percentage of people who can't do it, the coordination and dexterity just isn't there. But I think the vast majority of people can be trained.

You have to be somebody who works well under pressure but is also not afraid to ask for help. That's key. What you find among the very best surgeons: Their judgment is impeccable. They know not only where to operate but what operation to do. If they're in a situation that is challenging or they don't feel like they have complete control, they can ask for help.

COSTELLO: Have you thought about how surgical training could be improved?

GUPTA: When patients come to my office, fewer than half of them really need an operation. They're coming to be evaluated. But what they are really coming for is knowledge — sometimes the most important knowledge that they're going to hear for a long time, as it directly affects their lives. So it's really important to make sure we train people to dispense that knowledge in a careful, compassionate way.

COSTELLO: You recently launched a campaign to combat loneliness. How did this come about?

GUPTA: The campaign, Just Say Hello [<http://www.oprah.com/health/Just-Say-Hello-Fight-Loneliness>], emanated from a lot of conversations I had with professionals in the field of psychology and psychiatry after the multiple mass shootings over the past couple of years. As a medical reporter I find myself reporting on a lot of these

'DESPITE ALL THINGS THAT WOULD suggest otherwise — social media and seeming to be more interconnected than ever before — we may have become more lonely as a society.'

the side effects from chemotherapy, stimulating appetite.

Right now it's a schedule-1 drug, ordained to have no medicinal benefit. It's very hard to do double-blinded, randomized, prospective trials on something that is already preordained to have no medicinal benefit. No one is suggesting there aren't any potential downsides to this as a medication. But in order to get answers to some of these questions and obtain the more satisfactory evidence in the United States, you have to make it easier to study.

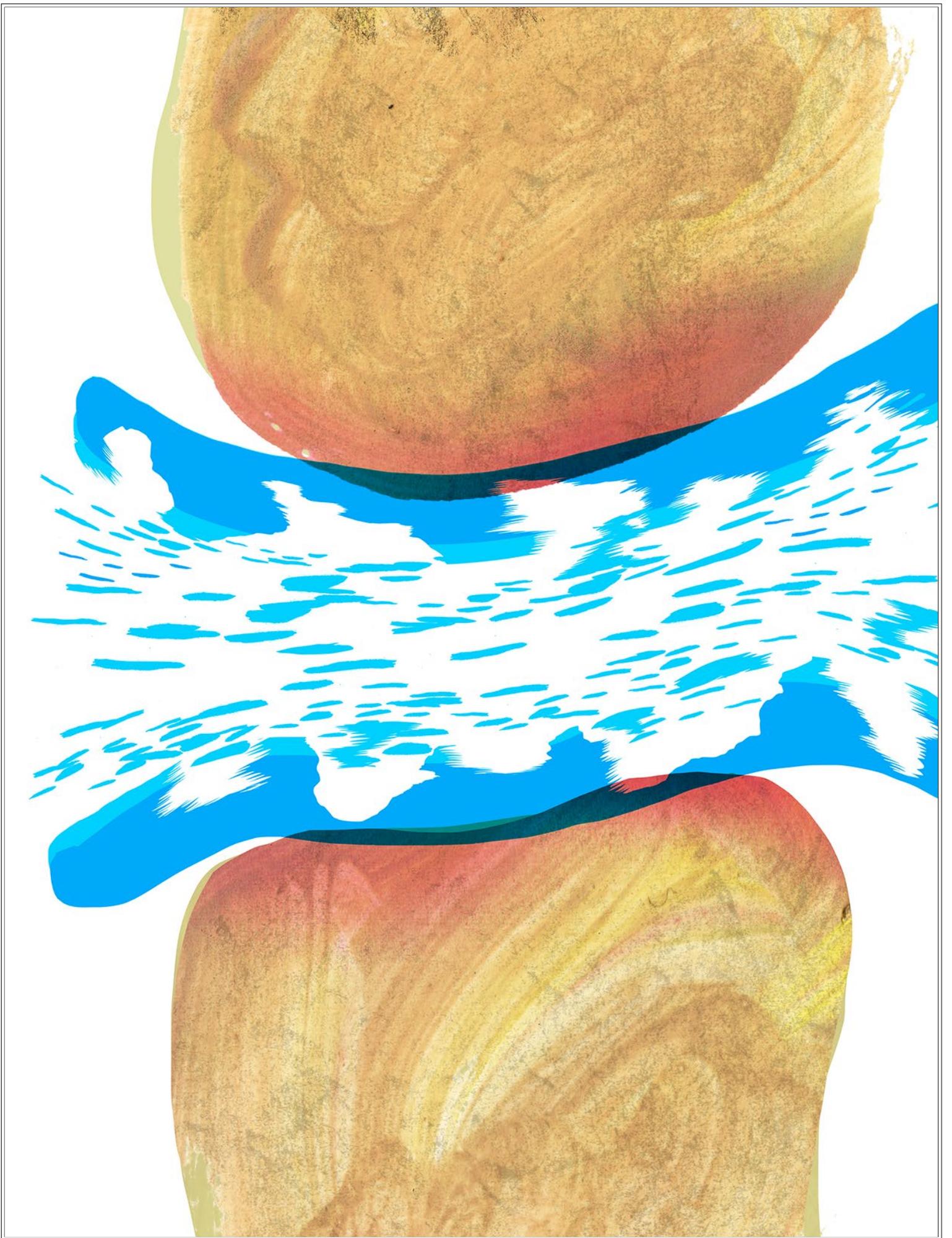
COSTELLO: Why a career as a neurosurgeon?

GUPTA: A lot of my colleagues wanted to be brain surgeons since they were kids. That wasn't the case for me. I thought I was going into pediatrics when I started medical school. I loved kids and loved

things. People always ask the same question, of why this happened. There's never a satisfactory answer.

But I spent a lot of time with specialists just trying to understand what they thought of these shootings. Often someone is described as a loner or as lonely or isolated. That came up many, many times. Despite all things that would suggest otherwise — social media and seeming to be more interconnected than ever before — we may have become more lonely as a society. The consequences of feeling lonely, feeling that you live on the fringe, that's what really fascinated me. When I talked with scientists who study loneliness, they told me a person relegated to the fringe would perceive things that seemed innocuous to most people as a threat.

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



INCREDIBLE CARTILAGE

FOCUSING ON GRISTLE IN THE EFFORT TO IMPROVE JOINT REPLACEMENTS



ONSTANCE CHU WAS A MEDICAL STUDENT OBSERVING A SURGERY PERFORMED BY HER TEACHER WHEN SHE CAUGHT HER FIRST GLIMPSE OF HUMAN ARTICULAR CARTILAGE, THE SMOOTH, GLISTENING COATING THAT COVERS THE ENDS OF BONES AS THEY MEET AT THE ANKLE, KNEE AND HIP. • “YOU ONLY HAVE ONE CHANCE AT THIS,” HER TEACHER, HENRY MANKIN, MD, CHIEF OF ORTHOPAEDIC SURGERY AT MASSACHUSETTS GENERAL HOSPITAL, TOLD HER. “IF YOU DAMAGE THIS CARTILAGE, IT DOESN’T GROW BACK.” • This was the early ’90s, and Mankin was considered one of the 20th century’s leaders in research on cartilage — especially articular cartilage, which is thought to be incapable of recovery from injury because it lacks nerves and blood, the body’s two most important tools for healing. Its basic metabolism was believed to be so slow that the tissue was considered nearly inert. With that set of characteristics, the only hope for damaged joints was to replace them with something artificial. • Although she started her career replacing joints with artificial materials, Chu is now a Stanford professor of orthopaedic surgery, treating the kind of cartilage and ligament injuries that typically lead to joint replacement. She is convinced, however, that articular cartilage can heal itself. She and several Stanford colleagues are researching ways to predict and track the damage to this all-important bone protector, to find new approaches to its repair and to stem the rapidly rising flood of people whose joints are wearing out. • “The next generation of orthopedic devices,” says William Maloney, MD, professor and chair of orthopaedics at Stanford, “is going to be biologic in nature: protein and cells, not metal and plastic.”

By Sara Wykes

ILLUSTRATION BY JON HAN

Cartilage research has only recently gained wider interest. In fact, when she was a young researcher looking for ways to grow cartilage from stem cells and to capture images of articular cartilage behavior, Chu says, “people were acting like I was crazy. Now everybody wants to be able to do it.”

Understanding articular cartilage is at the heart of that next generation of orthopaedic devices, pushed by a rapidly rising need for joint replacement. Many people — 27 million of them in the United States — are familiar with the pain caused by damaged articular cartilage, otherwise known as osteoarthritis. That condition is the primary impetus for the knee and hip replacements already given to more than 7 million Americans. Osteoarthritis is distinctly age-related, so the aging of the 49- to 68-year-old baby boomers — now about 15 percent of the population and estimated to rise to nearly 20 percent by 2030 — will push even higher the numbers for osteoarthritis and the joint replacements that usually follow.

Just last year, another 800,000 knees and hips were replaced. Joint replacement numbers are rising so fast that the American Academy of Orthopedic Surgeons projects that by 2030 the combined demand for hip and knee replacements may outstrip the availability of surgeons to perform the procedures.

The current plastic and metal replacement parts are good but not perfect, and don't function as well as a normal joint. Ultimately many of the implants must themselves be replaced. The metal alloys in implants can corrode; plastics, too, will wear out. And metal particles shed by some implants can destroy healthy tissue or cause poisoning.

Cost is also a driver. In 2005, orthopaedic-implant costs in the United States were \$5 billion, double what they had been in 2002. Now, nearly half of Medicare's annual \$20 billion tally for implanted medical device coverage is spent on orthopaedics. Effective prevention or earlier biologic treatment might reduce the rate of replacements and the subsequent cost of those surgeries.

Orthopaedists are now aiming their work at the key puzzle of how bones and articular cartilage behave. Articular cartilage is perhaps the most challenging component of developing new biologic devices for joints. Most of us might look to our bones as the workhorse of our skeleton, but it is articular cartilage that, ounce for ounce, does the most with the least. Generally no thicker than a dime, it helps our joints remain strong against forces that with each step can add up to three times our body weight.

No small job, that. The average adult takes 1.2 million steps annually. Stair climbing triples the load joints bear. Mankin and two co-authors of a 2005 lecture on articular cartilage called it the biggest contributor to the “extraordi-

nary functional capacities” of the joints it protects, allowing those joints to move with a level of friction less than any artificial substitute, putting to scorn all machinery, including the metal joint replacements then available.



THE FIVE ZONES OF ARTICULAR CARTILAGE'S INTERNAL ARCHITECTURE ARE A MARVEL OF FUNCTIONAL DESIGN — A SERIES OF DISTINCTIVELY DIFFERENT CELLULAR ARRANGEMENTS THAT CONTROL AND DIRECT WATER, THE MAIN COMPONENT of articular cartilage. That water acts as the primary weight-bearing element in the cartilage. The cartilage's layers — some horizontal, some vertical and some in random array — work with the cells' biochemical reactions to manipulate water within cartilage. “Mother Nature did a brilliant job of engineering,” says Jason Drago, MD, associate professor of orthopaedic surgery at Stanford, “to the point that it is difficult to re-create. This is one of the body's most complex tissues.”

If researchers succeed in re-creating articular cartilage, it won't be the first time that a natural substance has been chosen to replace a damaged joint. The first experiments in joint replacement began in the late 19th century with a German physician who used ivory to replace a young woman's knee. He had already tried aluminum, wood, glass and nickel-plated steel. In the 1930s, an American doctor tested a tempered glass called Pyrex before finding a chrome-cobalt alloy to be more stable.

The surgery has evolved since the first total knee replacement in 1968. Surgeons make a long incision from about 2 inches above the knee to about 2 inches below. The surgeon cleans and prepares the ends of the thighbone and the top of the shinbone to accommodate the replacement parts. The thighbone is capped with a metal covering that mimics its old, rounded end. Into the top of the shinbone, surgeons insert a stem that will support a circular, plate-shaped metal covering. On top of that covering rests a similarly shaped layer of plastic whose upper surface is curved inward to accept the rounded end of the thighbone. The back of the kneecap is fitted with a metal or ceramic button. With those components in place, the thighbone is rotated around on the shinbone's tray, with the patella in place to cover the joint.

The great hope is that insight into the biology of cartilage will allow damaged cartilage to revive, making such drastic intervention unnecessary.

Clinical trials are taking place around the world to test implants made of materials designed to stimulate new bone and cartilage formation. Many of these materials, however,

are created from cadaver tissue, which isn't easy to come by. Treatments that rely on the patient's own cells to make replacement cartilage are also plentiful, though not very successful so far, Maloney says. It will take another decade before cell-based cartilage repair will protect joints well enough for any activity that stresses our knees and hips beyond basic movement, he says.

Later this year, Dragoo plans to start testing a knee joint repair treatment that uses stem cells from the fat pad under the kneecap as a repair material. He will harvest those cells using minimally invasive instruments, put them in a centrifuge to concentrate them, add biologic glue made from blood, and insert that mix into the cartilage defect. "We think the fat pad is there for a reason," Dragoo says. "We're taking an immature cell and supplying it with the right environment in the hopes that it stays a cartilage cell."

that can lead to early osteoarthritis and early joint replacement.

Cartilage and the discs between vertebrae in the spine have many similarities. Another professor of orthopaedic surgery, Serena Hu, MD, has focused on the discs of the spine, searching for new ways to preserve disc strength and function. "By the time a patient comes in with a worn-out disc," Hu says, "it's too late to repair or regenerate it. We want to be able to predict if someone with early degenerated, non-painful discs is likely to develop more-degenerated, painful discs. Understanding more about the genetics of disc degeneration will help us determine who will benefit from early intervention." She has also seen in her research that movement of the spine reduces deterioration. "I've always believed that you should stay active," she says.

When Chu started her career, she was one of only a few researchers working on articular cartilage, but now she has plenty

' MOTHER NATURE DID A BRILLIANT JOB OF ENGINEERING. THIS IS ONE OF THE BODY'S MOST COMPLEX TISSUES. '

Even more reliable, Dragoo says, will be the ability to instruct a 3-D printer to re-create articular cartilage. That may be possible in a couple of years on a small scale to test as a repair for the pothole version of cartilage defects. "And when we can treat potholes," Dragoo says, "then we can resurface the whole street."



OTHER STANFORD RESEARCHERS ARE FOCUSED NOT ONLY ON BETTER UNDERSTANDING HOW TO WORK WITH TRANSPLANTED FORMS OF CARTILAGE REPLACEMENTS, but also on how to prevent and predict cartilage damage. Marc Safran, MD, professor of orthopaedic surgery, has years of experience treating athletes' cartilage injuries. He and Garry Gold, MD, a professor of radiology, are studying the knees of marathon runners using imaging to capture what the stress of running does to cartilage, and to investigate ways to prevent such damage. Safran has also been identifying the anatomic differences that make someone more vulnerable to joint damage. "If we can prevent this damage from happening, that will be the real key."

That kind of research is valuable because articular cartilage can be damaged by more than just the aging process. If the contact points of the knee joint are altered, then the cartilage's protective barrier no longer makes contact properly. And the most often damaged element of that arrangement is the anterior cruciate ligament, known more colloquially as the ACL. Young athletes who tear their ACLs set in motion a deterioration of cartilage

of collaborators. In fact, the International Cartilage Repair Society, formed in 1997, now has more than 1,300 members in 64 countries. At Stanford, Chu and Tom Andriacchi, PhD, a professor of mechanical engineering and of orthopaedic surgery, are studying how abnormal movement patterns damage articular cartilage. She is working with radiologist Gold on the next generation of MRI techniques to detect cartilage behavior. And she is collaborating with Bill Robinson, MD, PhD, an associate professor of medicine, to develop a blood test "to give us an idea of what is going on with articular cartilage without having to do imaging," she says.

But her longest-running project, funded since 2006 by the National Institutes of Health, seeks a way to diagnose osteoarthritis noninvasively before joints start hurting. The key is to recognize damage inside cartilage before the tissue is beyond repair. The current method for diagnosis, arthroscopy, is a surgical procedure in which a camera is inserted inside the joint. She has been looking for a noninvasive alternative.

So Chu is thrilled by the results of one of her recent experiments, published this summer. The study examined the ability of a new imaging technique called ultrashort echo time MRI mapping to assess cartilage health. It was a small study of 42 subjects: 31 with ACL tears and 11 uninjured. It showed that the MRI method was able to detect damage, and something far more exciting, something that her mentor told her more than 20 years ago was impossible — that articular cartilage could recover. It took time, but after a new type of ACL reconstruction and a year of rest, most of the subjects' injured cartilage did heal. **SM**

— Contact Sara Wykes at swykes@stanfordmed.org

SCULPTING

BONES

A TECHNIQUE THAT REQUIRES PRECISION, ARTISTRY AND, FROM THE PATIENT, TRUE GRIT

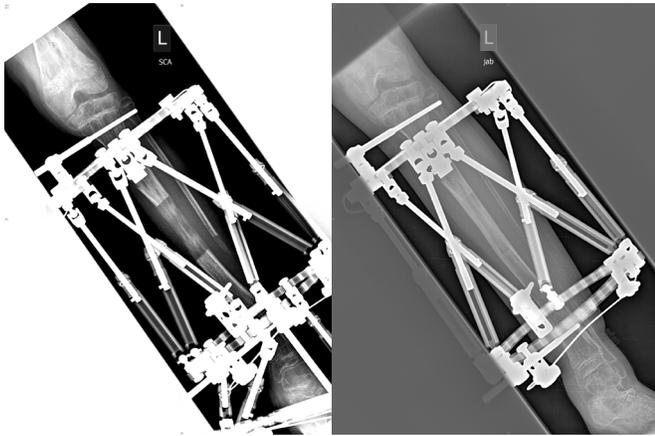
IN A LITTLE RED HELLO KITTY BAG, 7-YEAR-OLD GIANA BROWN KEPT HER SURGICAL ADJUSTMENT TOOLS: TWO SMALL WRENCHES, SIX COLORED PENCILS AND A PRINTED ADJUSTMENT PRESCRIPTION SHEET. TWO OR THREE TIMES EACH DAY FOR MORE THAN SIX MONTHS, SHE SAT DOWN, TOOK OUT HER TOOLS AND CHECKED WHICH SETTINGS SHE NEEDED TO CHANGE ON THE BRACE AFFIXED TO HER LOWER LEFT LEG. The brace, known as an external fixator, formed a cage around her limb, with six color-coded, extendable metal bars, called struts, connecting two flat, metal rings — one encircling her leg just below her knee, the other near her ankle. The rings were fastened to her leg by long, thin pins that went into her tibia — the larger of the two long bones in the lower leg. Giana, with temporary flower tattoos encircling her wrists, used one of her wrenches to turn adjustment knobs on the struts to the prescribed numeric setting, checking each one off with a matching colored pencil. • When Giana turned the knob, it lengthened the fixator, thereby widening a surgically created gap in her bone. In that gap, bone-producing cells called osteoblasts were collecting across a bridge of collagen that the bone itself had created in the first days after surgery. Stretching this gap gradually, exactly 1 millimeter a day, fostered the process of cellular generation, called “distraction osteogenesis,” which ultimately increased the length of her tibia bone by nearly 3 inches. • Though it’s not a stretch to say an external fixator resembles a medieval torture device, orthopaedists and patients

By Julie Greicius

PHOTOGRAPH BY MAX AGUILERA-HELLWEG

GIANA BROWN'S LEFT LEG WAS LENGTHENED BY 3 INCHES
TO MATCH HER RIGHT.





GIANA'S X-RAYS AT TWO MONTHS (LEFT) AND SEVEN MONTHS AFTER LENGTHENING BEGAN. RIGHT: WEARING THE FIXATOR.

alike see it as a modern technological wonder. The apparatus on Giana's leg, called a Taylor Spatial Frame, makes possible highly precise, computer-guided bone lengthening and repair. But it's not for the faint of heart.

"Sometimes it would take us 15 minutes to get to the number we needed," says her dad, Greg Brown. Giana was particularly sensitive to even the slightest pain, but like all patients using the brace it was up to her or her caregivers to make the daily adjustments. "She'd move it a little, feel it and stop for a moment. But she was in control."

SUKI AND GREG BROWN FIRST NOTICED AN INCREASING UNEVENNESS IN THEIR DAUGHTER'S LEGS WHEN SHE WAS ABOUT TWO AND A HALF. "The first sign was when she was running," says Greg. "Her left foot looked like it was pointing out way off to the left, more than 45 degrees, and her left leg wasn't as long as the other."

Her parents began by putting inserts in her shoes, and eventually had lifts — platforms that would equalize her leg length — added to the soles of her shoes. "We realized that her hips weren't lining up," says Greg. "It was getting worse."

Shortly after Giana's fifth birthday, her primary care doctor referred her to Lawrence Rinsky, MD, chief of pediatric orthopaedic surgery at Lucile Packard Children's Hospital Stanford and professor of orthopaedic surgery at Stanford's School of Medicine. The X-rays Rinsky ordered for Giana showed benign tumors inside her bones, mostly at the ends of her long bones — the femur (in the thigh) and tibia (in the shin). He also found some in the middle of her femur. Rinsky diagnosed her with "non-ossifying fibromas," a disorder that would make her bones vulnerable to fracture.

Just a few months later, in October 2011, it became clear that Giana's bone disorder was more rare and complex than anyone had suspected. At her school's after-care program, she slipped on a book and fell, and in the next moment she was curled in a ball on the floor. "She wasn't screaming or crying. She just wouldn't budge," says Greg. "It was frightening because I couldn't help her. So we called an ambulance."

At the hospital, Rinsky was out of town, so orthopaedic surgeon Jeffrey Young, MD, took the case. X-rays revealed a spiral fracture that twisted smoothly down Giana's femur, splitting it clear through. "We couldn't believe it," says Greg, who quickly learned a lot about bones. "That's the strongest bone in the body, and it broke so easily." The fragility of Giana's bone, and skin pigment marks known as "café au lait" spots, led Stanford pathologist Jesse McKenney, MD, to make the rare diagnosis of Jaffe-Campanacci syndrome.

Jaffe-Campanacci can include a range of symptoms, from non-ossifying fibromas and café au lait spots — both of which Giana had — to intellectual impairment, eye and heart malformations, failure of one or both testicles to descend in boys, and, in both sexes, diminished or absent sex hormone production that can result in infertility. "Fortunately," says Greg, "Giana didn't seem to have these other aspects of the syndrome."

Giana needed two repairs: to have her broken left femur set and her left tibia lengthened and straightened. Although this would not make her bones less fragile or prone to breaking, it would make her more stable on her feet in a way that shoe platforms could not. Her surgeon knew that these corrections would each take several months to heal, but would require different approaches: for the femur, an internal fixator that would be bolted directly alongside the bone; for the tibia, the Taylor Spatial Frame, which could lengthen and

straighten at the same time. He explained the process. Then it was up to the family to decide whether to do both repairs at the same time. “I told them I would be there for them every step of the way,” says Young, a clinical assistant professor of orthopaedic surgery at Stanford.

“We could have started the lengthening right then,” says Suki. “But mentally we didn’t have our heads around this yet.”

Giana’s parents decided to let her femur heal first — which would take about a year — and then begin the lengthening and straightening process the following summer.

“Between two and seven people per 10,000 in the United States are affected by longitudinal deficiencies,” says Young, referring to conditions of unequal limb length. But the Taylor Spatial Frame is used for a variety of conditions, he explains, including deformities that happen after a bone break or injury, such as when bone growth stops, when there is bone loss, or when a broken bone heals incorrectly (also called “malunion”). Orthopaedic surgeons also use the frame to heal limb deformities caused by infection, which can cause bones to stop growing or grow at the wrong angle, or cause areas of bone loss. Some surgeons use the frame to extend limbs for people with achondroplasia, also known as dwarfism. In California, Young says, only a handful of surgeons are trained to use the spatial frame, and even fewer use it on children.

“Approximately 1 percent of surgeons nationally are qualified to use the Taylor Spatial Frame, with the community growing slowly given what it enables the surgeon to address,” says Mark Waugh, vice president, extremities and limb restoration for Smith & Nephew, the company that distributes the device. “It’s not a surgery you do and step away from,” he adds. “Surgeons tend to build a relationship with the patient and their family given the interactive nature of the healing process.”

On July 12, 2013, Giana went into surgery. Young had already planned where to affix the frame, and where to cut her tibia to minimize complications from her bone disease. Once Giana was asleep and anesthetized, Young cleaned her leg and placed a 1.8-millimeter stainless steel wire — called the reference wire — through her leg and bone. This wire served as a guide for the most important part of the frame: the reference ring. Acting as the point of origin for all the measurements that would go into the prescription, the reference ring also served as the top of the frame. Young further secured the ring with three metal pins that poked through skin and flesh to reach the bone.

With the top ring affixed, Young set about cutting the tibia, making two 1- to 1.5-centimeter incisions about an inch apart, halfway between the top and bottom of the frame. He then passed a wire, called a Gigli saw, through one incision, into Giana’s leg, circling most of the bone, and back out the other incision. “Using that wire like a cheese slicer,” Young explains, “I cut the bone, sawing back and forth. We avoid using a motorized saw because the heat can burn and kill the bone cells, effectively cauterizing the areas we need to heal.” Around every bone is a thin membrane called the periosteum — meaning, literally, “around the bone” — which Young was careful to keep in place. “It creates a safe boundary and is important for the bone healing as well.”

Young completed half the cut, affixed the rest of the frame, then finished cutting with the bone fully stabilized by the frame. He also placed a second frame on Giana’s foot to support her ankle. The resulting apparatus looked like the steel frame of a giant, open-air boot.

Although Giana didn’t have the full spectrum of symptoms often seen with Jaffe-Campanacci syndrome, she was extremely sensitive to pain. She spent a few nights recovering at the hospital, but at home the pain was unbearable. “She didn’t leave her bed for five days,” says Greg. “We were supposed to be able to move her, but she was in so much pain that we couldn’t.” She’d reached her limit on pain medications, and they didn’t seem to be working. Suki and Greg were deeply concerned, so they called Young, who did what few surgeons are known to do: He went to Giana’s house to assess her, and helped the family decide to bring her back to the hospital.

“I’ll always thank him for that,” says Suki. “He knew what was good for that child.”

That night, Young connected the two braces — the one on Giana’s foot and the one on her tibia bone — which he had originally left separated to allow her ankle to move. Connecting them relieved the pressure on Giana’s ankle. “Once that was fixed, it seemed to help,” says Greg.

Greg, Suki and Giana all learned how to turn the struts to the prescription settings for each day. “After the first two weeks, Giana didn’t let anybody else turn the struts. She had to turn them herself,” says Suki. “She had two little wrenches, like they were made for kids’ hands. Every day at a certain time, she would turn them, then mark the paper with a little colored pencil. She never complained, just got on and did it.”



WEB EXTRA

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lengthens and
straightens bones.
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C O N T I N U E S O N P A G E 5 0

HEALING WOUNDS

THE FIRST TIME DAVID KAUFMAN SAW A HYPERBARIC CHAMBER HE THOUGHT IT WAS THE SCARIEST THING HE'D EVER SEEN. ALTHOUGH THE MACHINE DIDN'T LOOK ESPECIALLY FRIGHTENING — A CLEAR-WALLED CYLINDER WITH ENOUGH ROOM FOR A LONG BED AND A VIEW OF A PERSONAL MOVIE SCREEN — IT WAS THE LAST STOP IN AN EIGHT-MONTH EFFORT TO HEAL A STUBBORN FOOT WOUND. IF THIS TREATMENT DIDN'T WORK, HE MIGHT LOSE ANOTHER TOE. OR MAYBE EVEN HIS WHOLE FOOT. THE CHAMBER REPRESENTED THE ONLY THING BETWEEN HIM AND AMPUTATION. THAT SCARED HIM A LOT. • “It did take some getting used to,” says Kaufman about the treatment chamber. “You’re all alone once they slide you in and lock the door. Then your ears start to ring when the pressure changes and they add the oxygen.” • Although the hyperbaric chamber treatment was designed to save deep-sea divers from a deadly condition called the bends, it can help landlubbers too. By running pure oxygen in the chamber — room air is mostly nitrogen and has only about 21 percent oxygen — red blood cells can pick up more oxygen to deliver to the rest of the body. For wounds that aren’t recovering, that extra oxygen boosts new blood vessel growth to help old wounds heal. • Getting old wounds to heal is a big problem. In the United States, about 6.5 million patients suffer from persistent wounds — from bedsores to burns. Experts anticipate those numbers will only rise as the three major demographic groups that suffer from non-healing wounds are also expected to grow: people who have diabetes, are obese or are over 65. More than \$50 billion — at least 10 times the yearly budget for the World Health Organization — is estimated to be spent annually on managing wounds, according to an analysis of data from the U.S. Wound Registry. Most of the treatments, like the hyperbaric chamber, have been in use for decades. • “The problem with wound healing

CLOSING THE GAP

BY ELIZABETH DEVITT

ILLUSTRATION BY HARRY CAMPBELL



is that it's been a backwater of medicine — a lot of snake oil and poultices — with no evidence-based medicine,” says Geoffrey Gurtner, MD, a professor of surgery at the Stanford School of Medicine. But that appears to be changing. Wound healing as a medical specialty and as a subject of medical research is coming of age. Ironically, the old-fangled hyperbaric chamber is part of the reason that change is coming.

Throughout the United States, wound-care centers are popping up, with about 1,500 of these treatment centers nationwide. Housing technology like hyperbaric chambers and a spectrum of specialists — from surgeons to infectious disease experts — these centers give patients a place to get comprehensive care for wounds. Revenue more than tripled over three years for Healogics Inc., which operates 540 wound-care centers across the country: from \$75.4 million in 2009 to \$271.5 million by 2012. Bellevue, Wash.,-based Accelecare has opened about 25 new wound-care centers every year, going from zero to 120 since launching in 2008, says Thom Herrmann, senior vice president of business development. Still, there's room for more: Only about a third of U.S. hospitals have a physician-led wound-care center, according to Jeff Nelson, president of Healogics.

In September, Stanford plans to open its own wound-care center, including a hyperbaric chamber — in partnership with Healogics. Stanford physicians will provide care while the company provides business management expertise and services such as hyperbaric equipment, staffing and training. But unlike most wound-care centers, Stanford's will be a site not only for care but for research and training.

The front lines of wound care and research focus on diabetes like Kaufman because long-standing diabetic ulcers are the most common, most expensive and most notoriously difficult wounds to heal. “For many diabetic patients the medical clinic is a revolving door,” says Ronald Dalman, MD, chief of Stanford's Division of Vascular Surgery.

The more doctors understand how skin heals — or doesn't — the better they'll be able to help people having trouble recovering from wounds, such as cancer patients getting radiation therapy or burn victims. If the hardest-to-heal wounds can be improved, then those benefits will trickle down to everyone else.

SKIN REPAIR KEEPS US WHOLE

WHEN THE SKIN IS INJURED — WHETHER BY ACCIDENTAL TRAUMA, SURGICAL INTENTION OR ILLNESS — THE BODY USUALLY RAMPS up to start healing immediately. A call to arms signals the start of an orderly process involving all sorts of cells that guide an influx of new blood vessels, tamp down

infection, build the scaffolding for new skin growth and ultimately lay down a new barrier to the outside world.

If our skin is working, it's a multilayered shield that can mend any chink in our armor. But when the skin's healing ability goes awry, it can put the health of our whole body at risk. Unresolved wounds are a breach in the body's defense system: a painful portal for infections that can invade the rest of the body — sometimes with life-threatening consequences.

No one appreciates that fact better than Kaufman, who has dealt with diabetes for 20 years. When glucose stays too high in the bloodstream, it blocks skin cells' ability to repair themselves and weakens the white blood cells that fight off infections. That slow healing coupled with poor circulation and loss of a sensation in the lower legs — two other common problems with diabetes — can lead to the loss of toes, feet or even limbs. Diabetes is the reason behind most leg amputations in the United States, and foot ulcers are a big, red warning flag. These wounds presage more than three-quarters of diabetes-related amputations, according to the American Podiatric Medical Association.

Kaufman, 62, never had a problem with wounds until he suffered a stroke in 2009. Then he lost much of the movement on his right side. With less activity, ulcers started showing up on his left foot, prompting his podiatrist to refer him to a surgeon. “But the first surgeon wanted to take off all my toes right away,” says Kaufman. He'd already lost one toe from a previous infection and the surgery was intended to save the rest of the foot. “I was only having trouble with my pinkie toe then. So that didn't sound like such a good idea.” The next physician he met was Dalman, a man Kaufman credits with keeping him on his feet.

NEW WAYS TO HEAL NEEDED

TO STAVE OFF SURGERY FOR A TOE AMPUTATION, KAUFMAN FIRST UNDERWENT A SUCCESSFUL PROCEDURE TO IMPROVE BLOOD FLOW TO HIS FOOT. Then Dalman recommended a series of hyperbaric treatments — at a non-Stanford site, as Stanford had no such facility at that time. Using multiple approaches is often essential to manage complex wounds, says Dalman. The high-oxygen treatment was the last little push toward healing that Kaufman needed, but it isn't an option for everyone. With chamber pressures that hit more than twice the normal atmospheric pressure, patients with congestive heart failure or lung disease would fare worse than their wounds. Newer treatments have been developed, such as skin substitutes and using suction to improve circulation, but more is needed.

“It's like the early days of infectious disease where simple

hand washing went a long way to prevent disease, but people still needed antibiotics. We're in the same place with wound healing with diabetics; we tell people to watch their feet so we can catch ulcers in the early stages, but they still get chronic wounds that need treatment," says Gurtner.

Spurred by the plight of burn patients with debilitating scars, Gurtner first took a surface approach to the problem of wounds: He wanted to help people heal without thick scars. After studying the problem with biomechanical engineers, Gurtner led a team that developed a "stress shield" to reduce surgical scars. Since tension drives the skin to lay down thicker tissue, they designed a device to keep tension from pulling on the wound's edges. Although the technique works well for some patients, such as those with surgical incisions, it didn't help the burn patients. But it was a step in the right direction.

hydrogel matrices were made to act just like the skin of a developing fetus. They look like a dry wafer, but can be rehydrated with a fluid containing stem cells, and then added to the wound.

Early test results show these hydrogels accelerate wound healing. Now, the researchers are figuring out the best source of cells: fat, bone marrow or other sources. In the next round of clinical trials, in which Gurtner hopes to start enrolling patients before the end of this year, the hydrogel matrices will be tested on diabetic foot ulcers.

But ultimately these stem cell sponges are intended to help heal any chronic wound. It could be the perfect personal bandage if Gurtner's team learns how to seed the hydrogel with whatever type of tissue needs regrowing. Skull wound? Add early bone cells. And some types of cells might be guid-

'WHY WOULD THE SAME DNA HEAL WITHOUT A SCAR WHEN YOU'RE IN THE WOMB AND THEN HEAL WITH A SCAR FOR THE WHOLE REST OF YOUR LIFE?'

To find new ways of preventing scars, Michael Longaker, MD, director of the Stanford Program in Regenerative Medicine, dug deeper under the skin for answers. His work is driven by one of the major mysteries of skin healing: In the womb, we can heal without scars — right up until the third trimester. "Why would the same DNA heal without a scar when you're in the womb and then heal with a scar for the whole rest of your life?" he asks.

That question focused his attention on stem cells — the cells that are blank slates until called to do a more specialized job, such as becoming a cell that makes up bones or heart muscle. Or scars.

"Maybe the rapid restoration of tissue — a scar — was an advantage if it kept you from bleeding to death or being eaten by a saber-toothed tiger," says Longaker. "But scar tissue isn't always good. If we can figure out how to knock down the cells that make scars but still recruit cells that make blood vessels, then we could have scarless healing."

IT TAKES BLOOD TO HEAL

BLOOD VESSELS ARE THE PIPELINES THROUGH WHICH ALL SORTS OF GROWTH FACTORS SHOW UP and start rebuilding after a skin defect. But injuries can destroy blood vessels.

So Longaker, Gurtner and a group of their Stanford colleagues tried another approach to getting those growth factors where they were needed: stem cell sponges. These

ed to become other types. In the right matrix, for instance, fat cells (which have the advantage of being relatively easily accessible) might be persuaded to become new cardiac cells.

It may sound like a far-fetched treatment plan but the underlying science is compelling enough for the Department of Defense to fund some of this research. "It only makes sense," says Gurtner. "More of our soldiers are coming home wounded. In World War II, three were wounded for every one lost in battle. In Afghanistan, 13 soldiers are wounded for every one killed."

Researchers around the country are trying other strategies to rebuild blood vessels. One example is Robert Kirsner, MD, PhD, vice chair of dermatology and cutaneous surgery at the University of Miami Miller School of Medicine, is studying a spray that delivers blood vessel and other growth factors directly on the wound surface — sort of like spreading fertilizer to get a healthier lawn. With this foaming gel, a combination of keratinocytes from the top layer of skin and fibroblasts from the layer below it, early studies showed that patients with venous leg ulcers healed an average of three weeks faster than those treated by standard care.

"The stakes are high," says Kirsner. "For some of the chronic wounds we treat, if we fail to heal these ulcers then patients have close to 50 percent mortality in five years — that's worse than the rates for someone with breast cancer."

C O N T I N U E S O N P A G E 5 1

GOING UNDER

**RESEARCH INTO HUMAN
CONSCIOUSNESS HAS CROSSED FROM PHILOSOPHY
TO NEUROSCIENCE AND MEDICINE**



ONE DAY THIS SPRING, STANFORD ANESTHESIOLOGIST DIVYA CHANDER, MD, PHD, DONNED HER SCRUBS, WASHED HER HANDS, AND WALKED INTO THE OPERATING ROOM FOR A ROUTINE SURGERY. A RESIDENT ANESTHESIOLOGIST-IN-TRAINING HAD ALREADY STUCK FLAT, ROUND ELECTRODES ON THE PATIENT'S FOREHEAD, AND WIRES SNAKED FROM THE ELECTRODES TO AN ELECTROENCEPHALOGRAPHY MACHINE BESIDE THE OPERATING TABLE. Chander glanced at the machine's readout, a mountainous terrain of lines pulsing up and down, representing the complexity of information zipping between cells in the brain. These EEG patterns didn't look like those of an awake person, she thought to herself. • "Oh, have you pushed the anesthetics already?" she asked the resident. He shook his head. Chander frowned, then reached down and shook the patient's shoulder. Suddenly, the man's eyes snapped open and the EEG returned to a more expected pattern. He'd been napping. • A decade ago, it's unlikely that any clinician could glance at the raw squiggly lines of an EEG readout and determine whether a patient was awake or asleep, anesthetized or not. If they had an EEG machine in the operating room at all — a trend that began in the mid-1990s — it likely displayed only some numbers. But now, many neuroscientists and anesthesiologists are tackling an area previously claimed only by philosophers: consciousness. Their research over the past dozen years has begun to illuminate how the brain's patterns of activity shift as a person's awareness of their environment changes. By bettering their ability to track consciousness, anesthesiologists hope they can learn how to detect when a patient loses

By Sarah C. P. Williams

ILLUSTRATION BY JON HAN

and regains consciousness, fine-tune drug levels to optimize individual patients' sedation, and develop more effective and safer anesthesia drugs.

Chander is among those who have immersed themselves in the few measures of consciousness available, like EEG, to get a grasp on what changes during sedation. Being under general anesthesia, researchers like Chander have found, closely resembles being in a deep sleep, hence her mistaken assumption in the operating room. In both cases, neurons have slowed their telltale rhythms and fallen into a more stereotyped pattern that prevents one region of the brain from communicating well with other regions.

Consciousness is often defined as being awake, having a sense of self, or an awareness of your surroundings. For doctors, classic measures of consciousness include testing patients' level of awareness and attention, and asking them whether they know the date and where they are. But historically, the concept of consciousness has also had a more spiritual definition — some believe consciousness is unique to humans; some link it to the idea of a soul.

For many centuries, scientists and philosophers alike saw consciousness as something to ponder and discuss, but not something that could be explicitly measured. For them, consciousness was more than a physical process. They believed that even if one could re-create an entire brain from scratch, a conscious being — with self-awareness and introspection — wouldn't result because it would be missing a soul. But as neuroscientists have developed new ways to study what happens within brain cells when people engage with their environment, they've noticed patterns — like those Chander can see on an EEG readout — linking physical processes in the brain to consciousness.

"It is not that there was a single, dazzling neurobiological experiment showing that consciousness is a biological phenomenon," says Patricia Churchland, a neurophilosopher at the University of California-San Diego, who regularly works with neuroscientists and anesthesiologists to probe conscious-

ness. "Instead, there has been an accumulation of important results that collectively render that conclusion fairly obvious."

Such realizations don't just have implications in the realm of anesthesia, but could lead to new ways to gauge brain injuries, reverse comas, define sleep problems and treat cognitive disorders.

TRACKING CONSCIOUSNESS

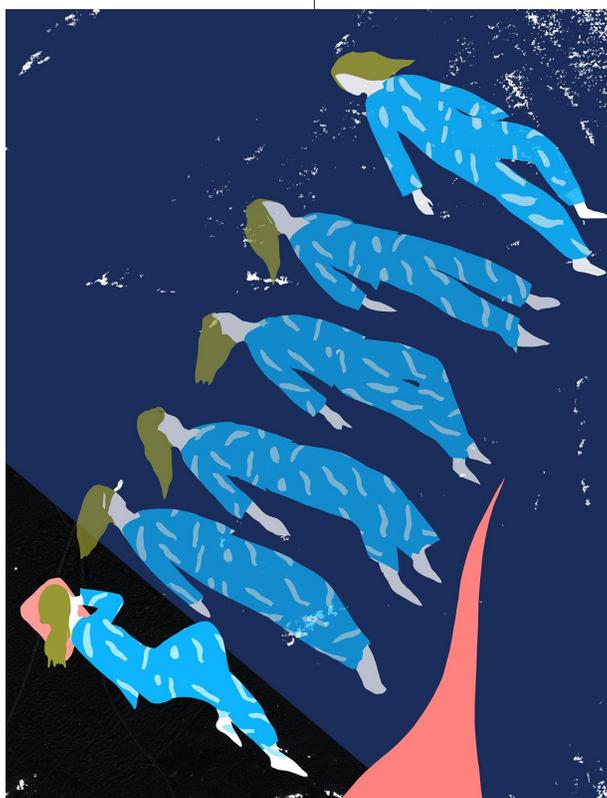
By any definition of consciousness, there are countless ways to lose it. Epileptic seizures, some recreational drugs and many brain injuries knock people unconscious. But most of those situations that cause diminished consciousness — head trauma, for instance — are both unpredictable and dangerous and can't be studied in a controlled way in a lab or hospital.

Anesthesia, though, provides a perfect testing ground for concepts of consciousness.

"There are very few situations where you can probe human consciousness except when it is depressed," says Chander. "Anesthesia is one of the best model systems we have because we can both remove and restore consciousness with drugs and we can study the loss of consciousness in the absence of brain damage."

Typically, anesthesiologists track sedated patients' levels of consciousness through crude, indirect measures of bodily function — during surgery, they keep an eye on a patient's blood pressure and heart rate. Although the EEG has been

around for the latter half of the 20th century, medical device companies have only recently begun promoting the use of EEG in the operating room. In the early 1990s, companies first developed machines designed specifically to monitor anesthetized patients — they each developed their own proprietary formula that analyzes raw EEG readouts and spits out a number indicating a patient's depth of unconsciousness. But anesthesiologists like Chander think the single number is a poor measure of what's happening clinically. The number, between 0 and 100 on most systems, involves a complex calculation that can take minutes to generate, making it difficult to use for real-time decision making. It also doesn't



take into consideration the variety of drugs that can be used — and that have varied effects on physiology, Chander says.

“That number doesn’t mean much during critical periods,” she says. “If you relied on the number to make clinical decisions, you’d be in real trouble.” So most anesthesiologists, she says, don’t rely on EEG at all.

Chander — who already had a PhD in neuroscience before choosing anesthesia as her clinical specialty — thinks the time is ripe, though, to start turning to raw EEG data to get a more nuanced view of how consciousness changes during anesthesia. A few years ago, on the suggestion of a mentor and colleague, she started displaying the raw waves of data rather than the processed index number on the EEG machines of every patient she puts under, a change that takes the simple click of a button but is rare outside of research labs.

Over time, she began noticing particular patterns of brain activity as a patient drifted in and out of consciousness and as she administered different drugs. Now, she’s organizing those observations into more concrete data on consciousness. Chander is interested in understanding what changes take place in neural networks during changes in level of consciousness. If she can see them in real time on the EEG in the operating room, that information may ultimately be used by clinicians to monitor anesthetic depth. She and her colleagues are also finding that the way in which people emerge from anesthesia may influence how they feel after surgery. “Some people have a very gentle, easy wake-up from anesthesia and feel great,” she says. “Other people are very agitated, disoriented or in pain.”

But even if Chander nails down exactly what happens in the brain as an anesthetic causes a patient to lose consciousness, or as the patient emerges back to consciousness again, there’s no guarantee that the same changes occur when a person is made unconscious through other means.

“It’s clear that there’s no one switch that flips to go from conscious to unconscious,” says Stanford anesthesiologist Bruce MacIver, PhD. “All the ways you can lose consciousness — falling asleep or getting anesthesia or a head injury — all have different underlying mechanisms.”

To aid in understanding the neural basis for some of these consciousness state-switches, Chander has worked with Stanford professor of psychiatry and of bioengineering Karl Deisseroth, MD, PhD, a developer of a technique called optogenetics, and Stanford associate professor of psychiatry Luis de Lecea, PhD, who uses optogenetics to study sleep. Using genetically engineered mice with special light-sensitive proteins in their brain cells, researchers can control when different neurons fire by shining light on them. Chander is using

optogenetics to control areas of the brain that she suspects might play a role in consciousness. She can test whether firing certain neurons makes a mouse go from an unconscious to conscious state — or vice versa.

“Optogenetics is the way I control the system, and EEG is the readout device,” says Chander. The patterns she observes in patients during anesthesia help inform which areas she studies in mice. She hasn’t published results yet, but thinks that combining clinical data with the latest molecular approaches — like optogenetics — will be key to discovering which neural networks support the consciousness state of the brain.

BUILDING BETTER ANESTHETICS

As far back in history as ancient Egypt, healers searched for drugs — from alcohol to opium to other herbs — that would ease patients’ suffering during surgical procedures. By the early 19th century, doctors had discovered mixtures of natural compounds that would not only ease pain, but induce temporary states of paralysis and unconsciousness. The use of chloroform and barbitol to sedate patients soon followed. Through chance and happenstance, trial and error, the field has settled on a handful of drugs that put patients into a deep, but reversible, state of unconsciousness — somewhere between a normal night’s sleep and a coma.

Many of today’s drugs are derivatives of the compounds that have been used for centuries, and none is as effective nor as safe as doctors would like. One in 1,000 patients remembers parts of their surgery afterward, indicating that they had some level of consciousness during it. And for some patients, anesthetics cause plummeting blood pressure and the risk of death. “Not a single one of these drugs has been designed rationally to achieve any known mechanism or desired effect in the brain,” MacIver says.

He thinks that by uncovering what defines consciousness and unconsciousness he can design better anesthetics and improve the tracking of a patient’s state while they’re under. Anesthesiologists, he says, want to ensure that every patient remains unconscious for the duration of a procedure, but using the least amount of anesthetic possible. “There’s increasing evidence that the lighter we keep patients, the better their speed of recovery,” he says.

To characterize different anesthetics and how to detect the right dosage, MacIver’s lab administers the drugs to rats, and uses EEG to observe what happens. They’ve pinpointed a few key changes to the EEG that tend to happen at the exact moment that rats go from being able to respond to a stimulus to being unresponsive.

But applying these data to the operating room is tricky.

Interpreting the pulsating lines of raw EEG data on the spot is a skill that few clinicians have. “An EEG is this weird, random, squiggly line that changes quite a bit from moment to moment,” MacIver says. And like Chander, MacIver doesn’t put much weight in the processed index numbers that EEG machines display in most operating rooms. But while Chander thinks one solution is to teach more anesthesiologists to read the raw form of the EEG data, MacIver and Chander are also teaming up on another solution: an entirely new way to display EEG data. “We’re using the exact same data that’s been recorded for decades,” MacIver explains. “But we’re finding new ways to visualize it.”

His EEG visualizations look like balls of yarn — the more spherical they are, the more chaotic the brain’s signals are. And chaos, in this case, means consciousness. “When a rat is awake,” he says, “it’s a perfect sphere.” When a rat is unconscious, rather than a tight sphere, lines project far outward from an oblong ball.

But neither Chander nor MacIver has achieved a perfect method to track consciousness. Based on his data from rats, “we can get about 80 or 90 percent accuracy in humans for loss of consciousness,” MacIver says. “But we’d like that to be 100 percent. Already by tracking vital signs we can get better than 90 percent accuracy.”

One step toward getting better, they say, is having the chance to put patients under anesthesia at a much slower rate than is usual during surgery. MacIver and Chander are currently recruiting participants for a study that will observe subtle EEG changes in their brains as they’re very slowly anesthetized.

DIGGING DEEPER IN THE BRAIN

A few years ago, Brett Foster, PhD, was a graduate student in Australia trying to understand how different anesthetics and sedatives influence brain activity in different ways and can make the EEG index numbers hard to interpret. Time and time again, his results and his literature searches pointed toward the importance of the midline parietal lobe — a region of the brain sandwiched in the center, between the two halves, called hemispheres. But EEG can’t accurately record the activity in the midline of the brain.

“Where the two hemispheres of the brain push up against each other, the brain curves down between them,” Foster explains. “When you’re using electrodes on the scalp to record activity, this valley is too deep. Any signal gets smeared and smoothed out before it reaches the electrodes.”

But Foster learned that Stanford neurologist Josef Parvizi, MD, PhD, was more accurately recording the activity in this area of the brain in patients with epilepsy. In select patients

with especially severe seizures, doctors implant electrodes in their brains to determine where seizures are originating and whether surgery can treat their epilepsy. But Parvizi, an associate professor of neurology, was also taking advantage of the deep placement of these electrodes to study — with the patients’ permission — broader questions about brain activity. With the electrodes, he could either stimulate select neurons or record their activity. Foster saw Parvizi’s work as a perfect inroad to the parietal lobe’s potential role in consciousness and memory and joined his lab at Stanford as a postdoctoral researcher.

Parvizi and Foster can’t knock their epilepsy patients unconscious, but they can study the activity in the brain’s midline as these patients perform simple tasks, recall events, tell stories or go about their daily activities in the hospital. One aspect of consciousness that they’re trying to study has to do with attention — part of being conscious has to do with paying attention to your surroundings. Someone who is zoning out in class can be said to have a different level of consciousness than someone listening to the professor’s every word — though both are quite conscious. Parvizi and Foster are observing how activity deep in the brain is different when someone notices a stimulus compared with when they don’t. Another aspect relates to memory — why does the midline light up when someone is recalling the past, and how does that relate to the fact that patients have no memory of their time spent under anesthesia?

“For us, this is an opportunity to get measurements from this hard-to-access part of the brain,” Foster says. “But what we need to do is build up from very basic questions.”

Parvizi says the implanted electrodes offer far more detail than previous methods, but technology still limits scientists’ understanding of the brain. “We know that consciousness is likely mediated by many regions of the brain and controlled by how those regions are interacting,” he says. “Right now, we can’t simultaneously record from all over the brain at once. We have to pick and choose what to look at.” But a new grant they’ve received will let them focus on how the midline parietal lobe communicates with other areas.

HUMANS: CONSCIOUS MACHINES?

If consciousness is viewed as a spectrum, then the study of consciousness doesn’t just mean finding a single line that people cross from conscious to unconscious. People in a coma are less conscious than those asleep for the night; people who are hyper-alert to their surroundings are more

C O N T I N U E S O N P A G E 5 2

IN THE GROOVE

BEHIND THE SCENES IN THE OR

D

AWN WAS BREAKING OUTSIDE STANFORD HOSPITAL, BUT IN THE OR THE TEAM IN SUITE NO. 4 WAS WRAPPING UP A 12-HOUR ANEURYSM CLIPPING. EVERYONE WAS SPENT BUT STILL FOCUSED. THEY BEGAN TO FALL INTO A RHYTHM, WHICH VISIBLY RECHARGED THE ENTIRE TEAM. Within 30 seconds, they were all operating from the same groove: Heads began to bob, toes tapped, the scrub tech strummed his air guitar with a pair of forceps, and off to the side the circulating nurse did a little Michael Jackson spin-a-roo as she notched up the music. • The OR can be a gnarly place. Same for the emergency room and the catheterization lab. But in the OR, gnarly can go on for hours and hours and hours. Knowing how and when to tame the tension is invaluable, and surgeons consider it an art form. • “It’s a fine balance,” says Gary Steinberg, MD, PhD, professor and chair of neurosurgery at Stanford. “You relax people enough so that they can perform their best, but not so much that they start missing details.” He says that Stanford’s OR is consciously working toward a more relaxed attitude, and that music plays a big role. He shakes his head: “We never used to play music in the operating room when I was training.” • It was during the ’80s that Steinberg went through his training at Stanford. In those days, the hierarchical mode of teaching was as much a rite of passage as it was an education. Ridicule, hazing and tirades were par for the course. These days, the training leans more toward team dynamics, building an esprit de corps. This is partially because the newer generation of surgeons seeks a

By **M.A. MALONE**

ILLUSTRATION BY GÉRARD DUBOIS

more realistic work-life balance. “In the old days, you killed yourself to be a doctor or a surgeon,” says assistant professor of vascular surgery Venita Chandra, MD. “Everything else was put on hold. Today, that’s no longer acceptable.”

Let’s backtrack 12 hours to the start of the procedure in suite No. 4. Neurosurgery chief resident Anand Veeravagu, MD, mulls over the music menu that will accompany this long-haul procedure. To get the team teed up, he puts on Pink’s *Let’s Get This Party Started* and it sparks the desired effect. The anesthesiologist’s focus is on the patient, but you can see he’s feeling the beat. Neurodiagnostic technologist Jackie Varga two-steps around him, attaching electrodes to the patient’s legs. A nurse rhythmically swabs the patient’s head with antiseptic, and the circulating nurse glides in and around them all. This group works together so frequently that the bustle around the table looks choreographed. And even though they’re all grooving to the tunes, the care and safety of the patient is deeply ingrained and permanently paramount. Abruptly, Veeravagu turns off the music and the sudden silence grabs everyone’s attention. He calls for the timeout and review of the surgical checklist, procedures that happen before every surgery at Stanford.

Step by step, they verify that everything necessary for the patient and the surgery is at hand. Everyone, regardless of seniority or position, is encouraged to ask questions or voice concerns. Then, a quick round of introductions — including the surgical team and observers alike — concludes the timeout. The timeout and checklist were instituted about seven years ago with the goal of improving patient safety. But one can see how they also knit the group together, bolstering team dynamics.

With his scalpel, Veeravagu makes the first incision, then fires up the bovie, an instrument that cauterizes as it cuts. It makes a staticky hum, and a thread of smoke spirals up from the patient, producing the vaguely off-putting smell of burning flesh. The visitors around the periphery watch with arms folded, trying to ignore the

chilly air, but the team around the table is oblivious to the temperature. They’re focused on the procedure as they stand under bright lights, swaddled in blue surgical gowns and gloves atop the standard-issue blue scrubs worn by everyone (other than the patient) who enters Stanford’s OR.

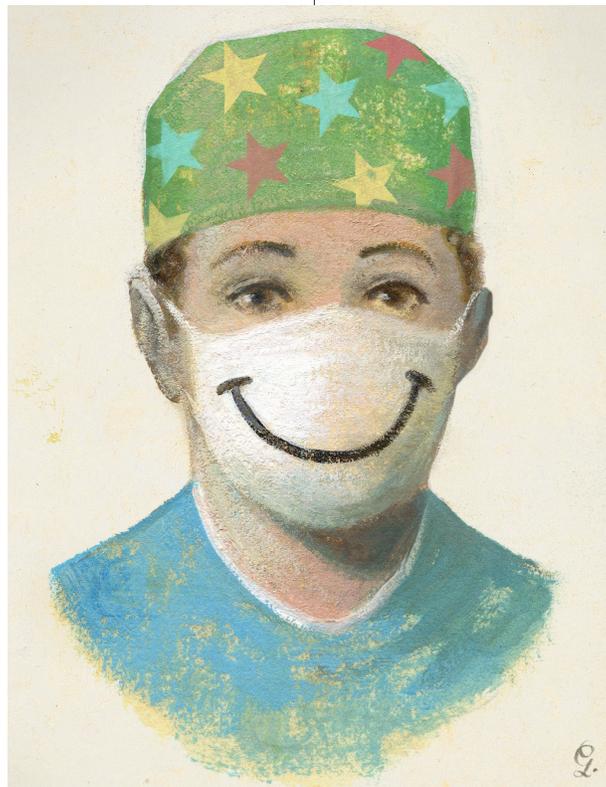
Not all OR attire is blue, though. Clogs have been the OR’s go-to shoe for decades, and Chandra is sporting a new hot-pink pair. She says she got them “just to have a little fun.” Not too good for rock climbing, but their generous arch support makes them great for long bouts of standing and toe-tapping to the tunes.

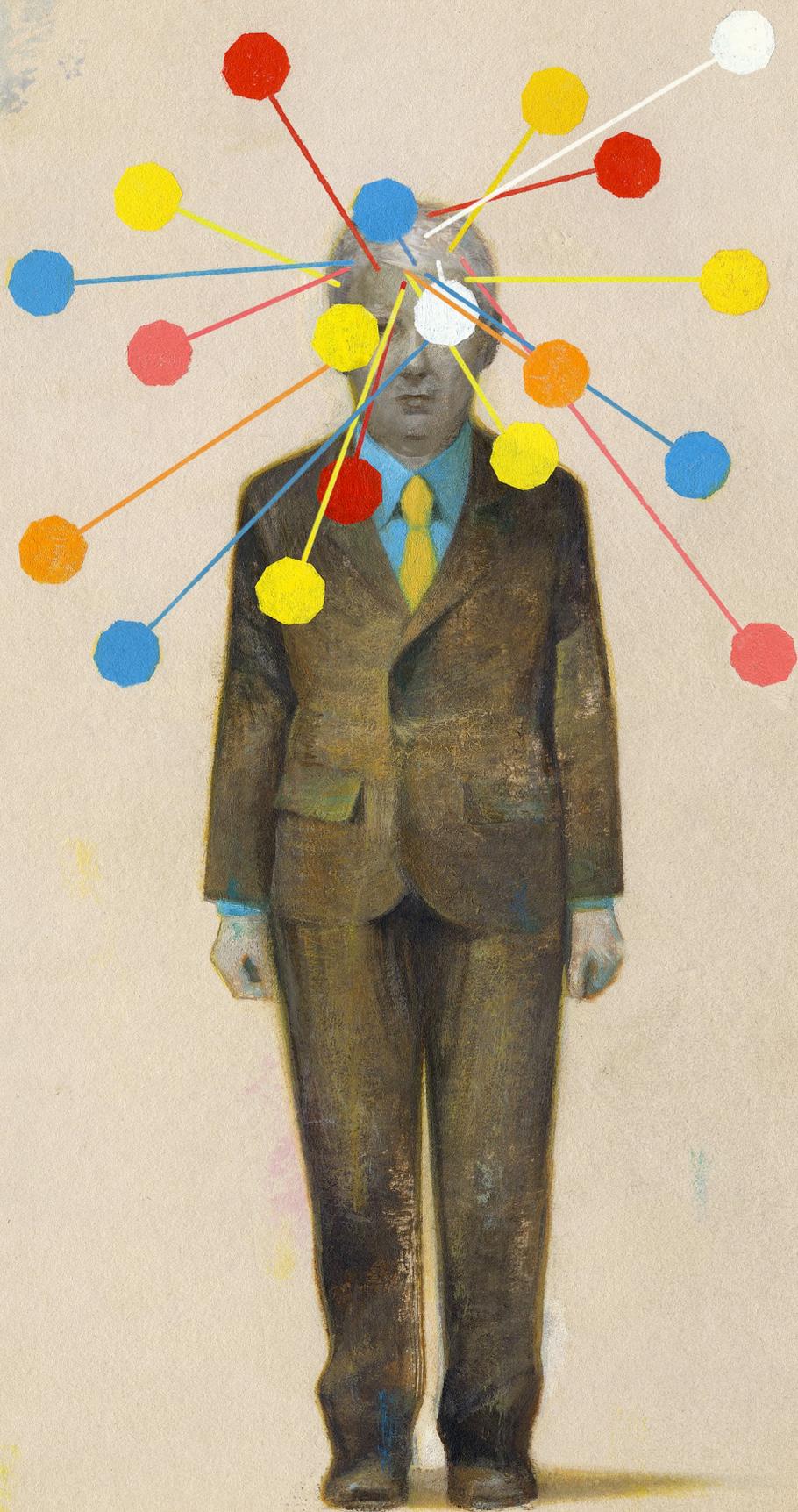
As for the hats everyone in the OR must wear to cover their hair, colorful toppers can be a tip-off to the personality of the soul below. Varga, the neurodiagnostic tech and a kind soul, is a serial hatter. The ubiquitous shower-cap style is good for covering long hair, but bad for flattering the face. Varga decided to make her own hats and soon co-workers began to request them. Now she makes them as gifts. “I go crazy with all the fabric choices. When I see a fabric, and it reminds me of a person, I think: Well, they just have to have a hat.” She guesses she’s made at least 200 over the years.

In suite No. 4, it’s the seventh hour, and the action has ebbed. Now, the surgeons can finally step out to give their kidneys a break. The music picks up, as does the conversation. There’s playful banter, and wisecracks zing between Veeravagu and scrub tech Chip Hamilton. Hamilton has worked closely with the surgeons for nine years, anticipating their next moves, being at the ready with the proper instrument, device or dressing. He says the OR is much less intense than it once was. “There’s no longer room for aggression or embarrassment.” He smiles and adds, “it’s more like family now.”

He calls to a nurse who’s fiddling with the music, “Cue up Sister Sledge!” and he goes back to ribbing Veeravagu. In the background: *We are family. Get up everybody and sing... SM*

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5.

R E T H I N K I N G

A L Z H E I M E R ' S



Six or so years ago, Frank Longo, MD, PhD, Stanford's chair of neurology and neurological sciences, was optimistic that a treatment for Alzheimer's disease was on its way. More than a decade earlier, pharmaceutical companies had begun testing drugs to eradicate one of its hallmark signs — clumps of protein sprinkled randomly throughout the brain. The drugs were antibodies that bind the protein, called beta amyloid, or A-beta for short. • "They poured a lot of money into clinical trials of these antibodies in Alzheimer's patients," says Longo. "And by around five years ago, with the conclusion of early-stage trials, it looked like they might succeed. So, many in the field — including me — had some guarded optimism that when the pivotal phase-3 trials were completed, this approach would have at least some beneficial effect." • On the order of 30 million people worldwide, including more than 5 million Americans, have Alzheimer's, the most common form of dementia, which raids the brain and steals a person's ability to remember, reason and imagine. Barring substantial progress in curing or preventing it, Alzheimer's will affect 16 million U.S. residents by 2050, according to the Alzheimer's Association. The group also reports that the disease is now the nation's most expensive, costing over \$200 billion a year. Recent analyses suggest it may be as great a killer as cancer or heart disease. • It's not really clear what causes the disease, and even rendering a diagnosis involves some guesswork. Genetic factors have been shown to contribute to the likelihood of getting it, but none among them comes close to fully predicting or explaining its onset and progression. What's known is that the diseased brain is characterized by the protein clumps outside of nerve cells and tangles of fibrous filaments within them, accompanied by an accelerating die-off of those nerve cells. And that there is no cure.

By Bruce Goldman

ILLUSTRATION BY GÉRARD DUBOIS

So it was unfortunate that three separate phase-3 trials testing the antibody strategy all failed to have any therapeutic effect on cognition. “I’d like to have something better to offer my patients,” says Longo, who directs the Stanford Center for Memory Disorders. “It’s profoundly disappointing when that doesn’t happen.”

In the wake of this disappointment, research to understand Alzheimer’s has shifted focus. Instead of trying to address signs and symptoms seen in the end stage of disease, researchers are looking at what goes wrong much earlier in Alzheimer’s. Their insights have yielded promising new imaging techniques and new targets for therapeutic drugs, with at least a couple being tested by startup companies Stanford researchers have spun off.

WHEN THE BRAIN’S BRAKES LOCK UP

“By the time visible symptoms of dementia appear and a patient first sees a doctor about it, this process has been under way for years,” says Carla Shatz, PhD, a professor of neurobiology and of biology and the director of Bio-X, Stanford’s interdisciplinary bioscience consortium. • A few promising early signals of impending Alzheimer’s do exist — for example, changes in amounts and ratios of certain chemicals in spinal fluid, or the changes observed by investigators via functional brain imaging. But wide-scale spinal taps or brain scans are hardly efficient ways to screen large numbers of people in the hopes of initiating therapeutic interventions earlier — if indeed there were something to intervene with. What would be great would be to find a molecular mechanism that not only provides a way to detect the approach of Alzheimer’s but also offers a window into the disease process.

Shatz’s recent work has turned up an unexpected player — a molecule once thought to be important only in the immune system but discovered by Shatz over a decade ago to moonlight in the brain. The molecule, called PirB, is a protein that acts like a brake dialing down the ferocity of the immune response — important if, for example, autoimmunity is to be avoided. Shatz found that in the brain PirB appears to serve as a brake on a different vehicle altogether: the synapse. Synapses are discrete, tiny but critical contact points at which each nerve cell conveys signals to others. Your memories are stored at brain circuits’ synapses. A single nerve cell can sport 10,000 or more synapses, each connecting with a different partner nerve cell. In response to our experience and development, synapses are in a throbbing state of flux: being born, enlarging and strengthening, diminishing and weakening, or disappearing altogether. This relentless fidgeting is the

physiological basis of learning, ruminating and daydreaming; of remembering, forgetting and regretting.

But too-much, too-fast alterations in synaptic size and strength could be deleterious. They could, for example, trigger epilepsy. It’s good to have that brake pedal.

Shatz recently found that PirB-deficient mice, even when they’re carrying two mutations that strongly predispose people to Alzheimer’s, develop no symptoms of Alzheimer’s. They get through mazes just fine. Their memories seem intact.

When she and her labmates discovered that small, still-soluble clusters of the infamous A-beta peptide bind very strongly to PirB and that, moreover, PirB concentrated at synapses, she got downright excited. Further experimentation showed that this binding led synapses to break down. Shatz’s lab recently identified the human counterpart to PirB, called LILRB2. If soluble A-beta is triggering synaptic loss long before amyloid plaques become visible, maybe *inhibiting* the A-beta/LILRB2 binding or the chain reaction it sets off could be therapeutic early on, possibly protecting against cognitive deficits.

THE IMMUNE CONNECTION

The brain doesn’t exist in a bottle or a vacuum. It dwells within the body, where it is in constant conversation with the body’s other great communicators — notably the immune and endocrine systems. In August 2013, Ben Barres, PhD, professor and chair of neurobiology, published a study in the *Journal of Neuroscience* revealing that another protein more typically associated with immune function may be a major early player in neurodegenerative processes.

Examining brains from young and old mice and humans, Barres and his team observed a 300-fold uptick in the prevalence of a particular protein called C1q. “No other protein has ever been shown to increase nearly so profoundly with normal brain aging,” he says. And guess what? This accumulation is concentrated at synapses. The buildup begins precisely in portions of the brain (such as the hippocampus) that are the most vulnerable to early neurodegeneration in Alzheimer’s disease. As the brain ages, these C1q deposits spread to synapses throughout the brain.

C1q is no garden-variety protein. As every immunologist knows, C1q bats first on a 20-member team of immune-response-triggering proteins, collectively called the complement system. Abundant in circulating blood, C1q can cling to bacteria or bits of our own dead or dying cells, initiating a molecular chain reaction called the complement cascade. One by one, each of the system’s other proteins gloms on, coating the offending cell or dollop of debris and drawing the atten-

SEX AND THE SINGLE GENE

WHAT IF YOU CARRY THE STRONGEST GENETIC RISK FACTOR FOR ALZHEIMER'S?

AT AGE 65, a woman's chances of incurring Alzheimer's disease are one in six: nearly twice that of a man's estimated one in 11 likelihood. New studies of the strongest known genetic risk factor for Alzheimer's — a gene called ApoE4 — provide insight into why women are more at risk and hints for a solution.

In general, people carrying a copy of ApoE4 are at a heightened risk — about two- to four-fold — of developing Alzheimer's. Those with two gene copies encoding ApoE4 (one inherited from dad, one from mom) are at 10-fold risk and are likely to start showing symptoms earlier in life than most others.

But there's obviously more to Alzheimer's than just having that gene version. "An ApoE4 carrier can live to be 90 and still not get Alzheimer's," says assistant professor of neurology Mike Greicius, MD, medical director of the Stanford Center for Memory Disorders, and al-

most half of those diagnosed with Alzheimer's don't carry any copies of ApoE4 at all.

In a study published in *Annals of Neurology* in April, Greicius and his colleagues examined clinical and biochemical data on some 8,000 older people, many of whom showed no initial signs of dementia, and concluded that the increased Alzheimer's risk conferred upon ApoE4 carriers is much greater in women.

That finding may have clinical ramifications. Another new brain-imaging study led by Natalie Rasgon, MD, PhD, professor of psychiatry and behavioral sciences and director of the Stanford Center for Neuroscience in Women's Health, followed women who were at heightened Alzheimer's risk because, for example, they had at least one copy of ApoE4 or a family history of the disease. Rasgon's study found that those who adopt estrogen-replacement therapy consisting solely of estradiol (the dominant female hormone) shortly after the

onset of menopause, when intrinsic estradiol production dives abruptly, suffer substantially less deterioration in key brain areas that, other studies have shown, faithfully predict clinically significant dementia by years and decades.

So is estrogen replacement the way to protect women from Alzheimer's? It is for some, says Rasgon, but not all.

Estradiol's effects on the body aren't entirely benign. For example, she notes, exposure to the hormone raises the risk of breast and uterine cancer. "Perimenopausal women with risk factors for dementia should talk to their doctors about whether estradiol-based hormone therapy makes sense," she says.

If these results wind up being replicated in a large sample of postmenopausal women not at risk for dementia, estradiol-based hormone therapy could become more broadly a treatment of choice to preserve optimal brain aging, she says.

tion of omnivorous immune cells that gobble up the target.

The brain has its own set of immune cells, called microglia, which can secrete C1q. Other cells called astrocytes secrete the rest of C1q's complement-system "teammates." The two cell types work analogously to the two tubes of an epoxy kit, in which one tube contains the resin, the other a catalyst.

Every cell type in the body except one — nerve cells — produces numerous substances that inhibit different stages of the complement cascade (which would explain why the complement cascade isn't typically activated by events transpiring within those cells).

Barres believes that in the normal aging brain, C1q, but not the other protein components of the complement system, gradually becomes highly prevalent at synapses. By itself, this C1q buildup doesn't trigger wholesale synapse destruction, or even much affect synaptic health. But it does leave the aging brain's synapses perched on the brink of catastrophe. An event such as brain trauma, a bad case of pneumonia or perhaps a series of tiny strokes could incite astrocytes — the

second tube in the epoxy kit — to start squirting out the other complement-system proteins required for synapse loss. Barres says the brains of Alzheimer's patients show a 70-fold increase in levels of complement-cascade activity.

In our early development, our brains sprout a surplus of synaptic connections. This redundancy allows for myriad potential brain circuits, but as the organism begins logging life experiences, the plethora of synapses becomes an embarrassment of riches. Within any single circuit, an excess of extraneous synaptic connections means noise in the system. Like a sculptor chiseling a statue of cognitive efficiency from raw marble, the brain has tools, including the complement system, for pruning unused or misused synapses during fetal and childhood development. Barres thinks the complement cascade ordinarily becomes quiescent in the adult brain after actively assisting in the "pruning" of redundant or counterproductive synapses during early development, but can get induced by a variety of inflammatory events to turn on again.

C O N T I N U E S O N P A G E 5 2

THE DEMISE OF THE SURGEON GENERAL

AMERICA'S DOCTOR FADING AWAY

N

EARLY A YEAR HAS PASSED, AND THE U.S. SURGEON GENERAL POST IS STILL VACANT. DOES IT MATTER? ASSOCIATED PRESS MEDICAL REPORTER MIKE STOBBE'S NEW BOOK, *SURGEON GENERAL'S WARNING* [UNIVERSITY OF CALIFORNIA PRESS, JUNE 2014], EXPLAINS WHY THAT QUESTION IS SO HARD TO ANSWER. HIS LOOK AT THE HISTORY OF THE POSITION AND THE PERSONALITIES WHO FILLED IT SHOWS THE GOOD THAT'S COME TO AMERICA from having a powerful surgeon general. It also examines how politics are draining that power. • But don't take our word for it. In these three excerpts from the first chapter, read what Stobbe has to say about the position's decline and its sequelae.

REGINA BENJAMIN took her place in front of dark-velvet curtains, set her smile and waited. • The scene was a bit like “pictures with Santa” at a busy shopping mall on the Saturday before Christmas. More than 150 people patiently stood in line to have their photo taken with Benjamin, some with emotions akin to the awe of a child about to meet St. Nicholas. They craned their necks to see her up ahead; some were even a little giggly. Benjamin's helpers, wearing uniforms like hers, managed the crowd. • But the similarities stopped there. This was weeks after the holiday (Jan. 11, 2010, to be exact). These were adults standing in line. The venue was the foyer of a federal building in downtown Washington, D.C. And this wasn't Kris Kringle they were waiting to see; it was the new U.S. surgeon general. • Minutes earlier, in a packed, 625-seat auditorium, Benjamin had been formally sworn in as the nation's 18th surgeon general. It had been an unusually florid affair, even by Washington's standards. Rows of federal health officials were dressed in the formal, militaristic uniforms of the commissioned Corps of the U.S. Public Health Service. Some formed a saluting gauntlet that Benjamin passed through at the end. A passerby might have mistaken the event for some kind of war-hero homage. • Benjamin had many supporters there that day, and they were thrilled. • “It's wonderful to know that someone whose values you respect is in such a posi-

ILLUSTRATION BY TINA BERNING

tion of leadership,” said Brenda Smith, an American University law professor standing in line with a group of friends.

“This is a great day for our state. For the world,” said Betty Ruth Speir, an elderly gynecologist who, like Benjamin, was from Alabama.

Was it, though?

The surgeon general is indeed a public health celebrity, a post rooted in a rich history and automatically held in high esteem. Surgeon general reports remain hallmark documents in our society, cited in everything from student term papers to legislative policy debates. Surgeon general warnings are fixtures on magazine liquor ads and cigarette packaging. Polls assessing the surgeon general’s credibility award the position higher marks than most other government health officials. Indeed, the surgeon general is commonly perceived (or, rather, misperceived) to be the government official responsible for the health and well-being of the general public. The surgeon general stars in public service announcement commercials and speaks frequently at university commencements and national conferences. The uniform and title still conjure importance and wisdom, and — for some Americans — a belief that there is still such a thing as a government health official who will level with the public when other bureaucrats won’t.

Some of that aura comes from dewy memories of the surgeon general’s power, independence and integrity as it was many decades ago (when the federal health bureaucracy was smaller). “He did not have to kowtow to the administration,” said Daniel Whiteside, a dentist who served for years in the Public Health Service. “He could say, ‘I don’t care what the administration’s policy is on any health issue. I’m going to tell you what is in the best interest of the American public, so far as a health issue is concerned. I don’t care who likes it. I don’t care who doesn’t like it. I’m here for four years and you can’t touch me.’ And we had surgeon generals who did that; I mean, who went up against the administration and said, ‘Kiss off.’”

Whiteside was speaking mainly about the men who held the position in the early 20th century — the long-ago kings

of U.S. public health who served multiple terms while presidents came and went. But the perception that surgeons general are science-above-politics monarchs, acting as the uncensored health consciences of the nation, occasionally has resurfaced. Jesse Steinfeld, who held the job in the early 1970s, angered Nixon administration officials by attacking the cigarette and television industries. C. Everett Koop, in place through most of the 1980s, led a benevolent education campaign on the emerging AIDS epidemic when some Reagan White House officials disdainfully considered it a gay disease. Joycelyn Elders, surgeon general in the early 1990s, dismayed the Clinton administration with her frank remarks about whether to legalize marijuana or teach kids to masturbate.

But in truth, tolerance for outspoken surgeons general has always been limited.

Elders was fired. Steinfeld was forced to resign early. Even the powerful surgeons general of old were careful not to cross certain political overlords. An example: Hugh Cumming, who held the job from 1920 to 1936, was considered one of the most powerful surgeons general of all time. In 1925, after a rash of industrial worker poisonings tied to leaded gasoline, Cumming was publicly pressured to look into it. But he declined to

take any action until he first discussed it with Secretary of the Treasury Andrew Mellon — whose family had financial interests in the oil industry. (Mellon, to his credit, recused himself and told Cumming to use his own judgment.)

Surgeon General’s Warning is a brief history of the office that includes the proud moments and the despicable ones, the perception and realities, the heroes and the scoundrels. The book explains how the surgeon general became the most powerful and influential public health officer in the country and how those powers were later stripped away. It discusses the unique bully-pulpit role the post retained, and the prowess of some surgeons general in using that pulpit and the meekness of others. It examines how the Office of the Surgeon General reached its current nadir. And it concludes that it no longer makes sense to have a surgeon general.



SO WHAT DOES THE SURGEON GENERAL DO?

At one time, he oversaw nearly all of the federal government's civilian health agencies. It was a surgeon general in the 1870s who resurrected the first federal hospital system. His successors instituted quarantines to fight deadly yellow fever and cholera epidemics and calmed the nation during the deadly Spanish flu epidemic of 1918-19. They handled the medical care of hundreds of thousands of veterans at the end of World War I, and spearheaded the desegregation of U.S. hospitals in the 1960s. They also issued warnings to the public about health dangers ranging from unpasteurized milk to laundry detergent. Perhaps most famously, Surgeon General Luther Terry in 1964 released the report that finally settled the question of whether smoking causes lung cancer. Arguably, no government official has had a greater personal influence on the public's health than the U.S. surgeon general.

SURGEONS GENERAL HAVE ALWAYS HAD TO TAKE ORDERS FROM THEIR POLITICAL BOSSES. What's changed is that other federal health officials — like the HHS secretary and the CDC director — have developed an enduring taste for the bully pulpit, and have come to see surgeons general as unworthy competitors for it. They have a point: Some surgeons general have been quota-filling, just-happy-to-be-here appointees with little expertise in influenza or some of the myriad other topics they were expected to speak about to a worried public. That was as much a failing of the surgeon general selection process as of the people who held the office.

In the past decade, in both Republican and Democratic administrations, surgeons general have become essentially invisible. Benjamin's predecessor, Richard Carmona, was repeatedly muzzled by the George W. Bush administration, and important reports he worked on were never allowed to see the light of day. Benjamin had an even lower profile, partly because of how she was controlled by her bosses and partly because of her own diffidence. ...

There's no longer a realistic expectation that lawmakers or executive branch officials will restore the Office of the Surgeon General to its past status. In an era of perennial government budget shortfalls, when local public health departments have eliminated tens of thousands of jobs — including care-providing nurses and outbreak-controlling epidemiologists — an invisible surgeon general is an indefensible waste of money.

But it is also the purpose of this book to mourn what has happened. The weakening of the office has led to a vacuum in health policy leadership. The federal bureaucrats who have

taken the surgeon general's place in the spotlight have tended to walk a politically correct line and to steer clear of controversies that might trigger “nanny state” complaints that the government is meddling in the lives of individuals. They almost refuse to openly acknowledge a central tenet of public health — that the state's responsibility is to look after the health of everyone, which sometimes means guiding or restricting people's choices. Their aversion to risk and confrontation has allowed a parade of misinformed talkers to fill the airwaves and Internet with wrongheaded theories that, left unchallenged, lead to the detriment of public health. Rantings about vaccines as a cause of autism have contributed to a resurgence of measles and other infectious diseases in areas where vaccination rates have been low. Manufacturers of sugary and fatty foods and beverages have persisted in marketing campaigns that propel the nation's obesity problem. And gun makers and their enthusiastic customers have so far cowed every substantial attempt to limit the purchase of firearms and ammunition, as U.S. gun-related deaths continue to surpass 30,000 each year.

A Koop or Elders would have said something about such shenanigans, and their strong words would undoubtedly have emboldened some lawmakers and policymakers to take action. But the last couple of surgeons general were wimps. In recent years the bold, speak-truth-to-power public health figures in government have resided at the local level. Take former New York City Mayor Michael Bloomberg and his city health commissioners, for example, who pushed for complete smoking bans, limitations on serving sizes of sugary sodas, and a variety of other measures irritating to libertarians and certain corporate interests.

It was William Stewart, the ill-fated surgeon general of the late 1960s, who perhaps best described the historical standard for true public health leaders. “From the 1880s onward,” he once said, “the public health movement always included rebels: men and women ready to strike out with new approaches at the roots of evil; crusaders who never lost faith that the movement possessed the breadth of vision, as well as the spirit and competence to meet the health needs of a growing and changing society.” Surgeons general have played that crusader role better and more often than any other national public health figure. Absent such a crusader, the public's health is prey to the misinformation and self-interest of tobacco companies, snake-oil salesmen and other malefactors. There are other heroes at work, to be sure, some with substantial resources and policymaking powers. But the true, traditional leader is missing, and the fight has suffered as a result. **SM**

WEB EXTRA

Hear a conversation with author

Mike Stobbe at <http://stan.md/1xLtFOG>

FEATURE

Her left hand

CONTINUED FROM PAGE 21
own experience made me feel it was OK to get help. It's a good thing to have friends."

STILL AT IT

The goal of the pancreatoduodenectomy, the Whipple procedure, is to remove the head of the pancreas, where most tumors occur. Because the pancreas is so integrated with other organs, the surgeon must also remove the first part of the small intestine (duodenum), the gallbladder, the end of the common bile duct and sometimes a portion of the stomach. The Whipple procedure is a difficult and demanding operation for both the person undergoing surgery and the surgeon. — MAYOCLINIC.ORG ONLINE DEFINITION

At 11:30 a.m., two hours into surgery, Wren's hands are in constant motion inside her patient's abdomen, cutting, suturing, mopping up blood with pads of gauze.

"We're going to start seeing the vena cava soon," she tells her excited students.

She's singing along softly with the Grateful Dead song playing from her iPhone.

"Truckin', got my chips cashed in. Keep truckin', like the do-dab man. Together, more or less in line, just keep truckin' on...."

Her hands continue their tour inside the patient's body, until they find what they are searching for: the pancreas, hidden deep inside the abdomen.

"Damn it, I love it when anatomy works," she says. She holds the still-attached pancreas gently in both gloved hands, passing it around for the outstretched fingers to feel the life-threatening tumor embedded there.

"It's a gigantic rockasaurus," she says.

"Oh my gosh!" says one of the residents.

"Now will be the decision-making time," Wren says. "Now we are going to decide whether we do this bad

boy." The tumor has grown around a vein, making it both difficult and dangerous to remove. The four hours of surgery up to this point have all been prep work to determine if the tumor is operable. Now it's time to decide whether they will be able to save the patient's life. Wren, of course, makes the decision.

It's a go.

The hands on the clock move from 1 p.m. to 2 p.m. to 3 p.m. The surgeons cut and sew. Cut and sew. One of the tiny cut veins suddenly spurts blood across the surgeons' faces.

"Jesus!" Wren says, looking around at her students. "You can't flinch. You've got to learn how to sew while your face gets splashed."

As the hours pass, Wren's left hand continues to work. It holds back the intestines with a pair of large, metal forceps while the chief resident cuts and sews. And holds. And holds. Five minutes stretch into 10, stretch into 15. Finally, the chief resident ties off the suture and Wren's left hand can relax.

She grimaces and shakes out the cramping hand.

"Is it still bothering you?" someone says.

"Still not enough nerve innervation," she says. Then shrugging, she gets back to work.

"Now let's get this tumor out."

During this eight-hour-long Whipple surgery in March 2014, Wren's left hand cramps only once. The tumor is successfully removed. Now she's left to worry about her patient's recovery.

A NEW LIFE

The Whipple is back to being a routine procedure for Wren. Six months after waking up partially paralyzed in June 2012, she was back at it. The following month, she bought all new dive equipment to replace what she had lost at the bottom of the South China Sea. She wasn't yet strong enough to put it on herself, but seven months after that — August 2013 — she was back deep-sea diving with Maxwell

and swimming with the whale sharks of Indonesia.

"Everyone thought I was crazy," Wren says. Her first question when she boarded the diving boat was, "Does the captain speak English?"

Life is different for her today, two years after her paralysis. She's lost some extension and flexion in her neck. Her left hand isn't as strong as it once was. But she can tip her head back in the shower to wash her own hair. For that, and so much more, she is grateful.

"I learned some important lessons," she says. "One is that confidence is not something you can pick up off of a store shelf." In the past, she had told many of her students that they just needed more confidence to be good surgeons. At the time, she had no idea how difficult it could be to get that confidence. She had never experienced what it was like not to have it.

"As a teacher of surgery, I will never tell another student that you just need more confidence."

The journey to return to surgery has made her both a better physician and a better teacher, she says. She understands better what her patients want. She knows better what her students need.

She thought long and hard before deciding to tell her story to others but ultimately decided that maybe someone else could learn from her experience, says Wren, always the teacher.

"This was a real life test for me," she says. "I truly understand now, there always can be unexpected complications." **SM**

— Contact Tracie White at traciew@stanford.edu

Q & A

A conversation with CNN's Sanjay Gupta

CONTINUED FROM PAGE 23
Just Say Hello, obviously, is not an answer to the problem by any means. But it could be a beginning to an answer. It's saying, "Look, I want to help. I know somebody at my workplace or

my apartment building who is that guy or gal who is lonely.” Reaching out in some way could help set their lives on a different trajectory.

COSTELLO: As you travel around the globe are there universal questions you’re asked about medicine, health care or the human condition?

GUPTA: I think the thing that ties us together is our quest for good health. Most everyone wants to do good by their bodies, understand health, understand how they could improve the health of their family. I think the desire for good health and the desire for improved function is pretty universal.

COSTELLO: In addition to a career as a physician, why did you want to be a journalist and storyteller?

GUPTA: I always liked to tell stories. That’s what my parents and friends say. I wasn’t the best student when I was younger. One of the tricks I learned as a student that carried me through medical school was to really understand the stories behind things. Even when I was in medical school studying biological chemistry, understanding the stories behind the people who had made interesting discoveries and why they made those discoveries made it stick in my brain. I just like stories. I was a voracious reader. I remain somebody who likes to read all sorts of different topics. When I started writing, I felt it was a strength and just ran to it.

COSTELLO: It’s well-known you had talks with President Obama about being surgeon general and turned it down. As you look down the road, do you see yourself in public service?

GUPTA: I worked in the White House — in the Clinton administration. My interest at the time was in public service. I could absolutely see myself doing it again. The timing for the surgeon general job wasn’t right for me. I would have had to give up my job as a neurosurgeon, which I found quite ironic.

COSTELLO: When you parachute into disasters around the globe what do you look for to tell a compelling story?

GUPTA: Whether it’s Haiti, Japan after the tsunami or an earthquake in Pakistan, I think a lot of times it’s just getting out of the way of the camera. Pointing things out for people to see and draw their attention to, but not over-reporting.

There is a desire for me to reinforce the point that what is happening here is not so different from what could happen where you are. I think health more than anything else serves as a common denominator for that. People want good health. They also understand when people have been injured and they don’t have access to health. They may not be able to identify Damascus on a map but if I explain to them that when the bombs came raining down, the same family that had been driving their kids to school the day before, grocery shopping after that, stopping at a bank to withdraw some money from an ATM, that they are now fleeing with whatever few possessions they could gather and running for the border, that’s a family like a lot of families in your neighborhood. If they feel more compassionate, more compelled in some way, that’s what’s really important to me as a reporter.

This interview was condensed and edited by Paul Costello.

WEB EXTRA

Hear the conversation at <http://stan.md/1u9MCFO>

FEATURE

Sculpting bones

CONTINUED FROM PAGE 31

The greater challenge was cleaning the pin sites, which needed to be done at least every other day. “It was extremely painful,” says Suki, “far worse than adjusting the struts.” The frame’s size was also somewhat cumbersome, causing some bumps and bruises on her healthy leg, sometimes on *other* people’s legs, and often bringing unwelcome stares from other children.

“It was draconian-looking,” says Greg, “and horrible to imagine what it was doing to her leg. But it was also magnificent, extending her leg and bringing her foot forward in one operation.”

For Young, the frame stands alone as

an ideal tool for healing his pediatric patients. “I really like how the technology allows me to basically sculpt the bone,” he says. “It’s the perfect blend of engineering and art.”

THE TECHNIQUE WAS DISCOVERED BY CHANCE more than 60 years ago, by a doctor working alone in a remote province of Siberia, Russia.

In *Limb Lengthening and Reconstruction Surgery* — a textbook for orthopaedic surgeons practicing this approach — Svetlana Ilizarov, MD, tells the story of her father’s discovery. Gavriil Ilizarov, MD, PhD, started out as a general practitioner, but learned orthopaedic surgery by necessity as the only doctor in an area “the size of a small European country.” For his patients, many of whom were Russian soldiers returning from World War II with a variety of bone injuries, he developed a new type of external fixator device. Unlike previous models, his completely encircled the limb, with parallel bars screwed to rings above and below the break. By tightening the bars on the fixator, bones with missing fragments or gaps could be healed using grafted bone and compression to encourage the pieces of bone to fuse back together. Just as Giana would decades later, and as the majority of patients using an external fixator still do, Ilizarov’s patients were also responsible for adjusting the screws on the fixator — only their job was to tighten, not lengthen, the screws to increase compression until the bone healed.

On one occasion in the early 1950s, a patient turned the screws in the wrong direction, separating the bone pieces instead of closing them, writes Svetlana Ilizarov. Her father was shocked to find that new bone had grown in the gap. This accidental discovery led to his method of distraction osteogenesis, through which non-healing fractures could be corrected, deformed limbs straightened and uneven limbs lengthened. Only muscles and tendons — which can stretch only so far — set the limits.

“The Ilizarov method ... revolutionized the process of deformity correction,” writes Svetlana.

Ilizarov’s method did not reach the United States until the late 1980s. When it did, two early adopters, Charles Taylor, MD, an orthopaedic surgeon in Memphis, Tenn., and his brother, Harold Taylor, an engineer, redesigned it. In the early 1990s, they replaced the long, parallel bars that

ADJUSTING TO A TAYLOR SPATIAL FRAME

TIPS FROM GIANA

1. When first getting the frame: “It’s kind of hard at first, but you’ll get used to it. It’s a little scary, but you’ll be fine if you’re brave.”
2. “Take your clothes and get snaps put in them.”
3. When sleeping: “Put a pillow under your foot so it doesn’t just hang there.”
4. When taking your first step: “Start with the foot without the brace and take your brace foot and try a little weight at first.”
5. “Turning the struts was painful and scary. Turning them myself made it easier because I could stop when it hurt and start again after I took a break.”
6. Dealing with pain: “If you’re having a hard time dealing with your pain, just take a few deep breaths and it will feel better.”

screwed into the frame with hinged struts that could change length like a telescope, one end fitting inside the other. They set the struts at angles to each other, making three triangular formations that encircled the limb in a zigzag. Each strut could be adjusted individually, allowing complete flexibility of the rings in relation to each other, with no equipment changes required during healing.

The new design also greatly increased

the complexity of the device’s settings. So, with the new Taylor Spatial Frame came a computer program that used the exact settings planned before surgery to generate a prescription for correction in the weeks or months following surgery. “The computer program is mathematically accurate to within a millionth of an inch and a ten-thousandth of a degree,” writes Charles Taylor in *Limb Lengthening and Reconstruction*.

Stanford’s Young, who was first introduced to the device during his residency at Northwestern Memorial Hospital, has also used the frame to treat patients during orthopaedic medical missions in Nicaragua and Haiti. “The computerized prescription sits on the spatial frame website, so it provides the ability to share cases and adjust prescriptions remotely,” he says.

In October 2013, Young removed the frame on Giana’s foot. Physical therapy helped her get her ankle back in motion again. Then, on Valentine’s Day 2014, with her left leg lengthened by close to 3 inches and rotated so that her foot was aligned, Giana’s spatial frame was removed and a cast was put on for one month. From the cast, she graduated to a boot, which she could remove at night — a welcome relief.

Giana will need to be assessed again when she’s in her early teens, and her left leg may need further lengthening if it continues to grow at a slower pace than her right. Because the fragility caused by her rare bone disease will continue, she’ll need to steer clear of the highest impact activities like gymnastics or soccer, but still has a lot to look forward to.

“I want to do cannonballs into the water,” Giana says. “I want to climb up onto the play structure and swing from the monkey bars and run and play tag. I want to go to the beach — that’s what I want to do most of all.” And now that her leg is healed enough that there’s no risk of sand getting into the wounds left by the pins, that’s exactly what she’s ready to do. **SM**

— Contact Julie Greicius at jgreicius@stanfordchildrens.org

FEATURE

Healing wounds

CONTINUED FROM PAGE 35

OUTSIDE HELP

It isn’t just physicians who are taking up the challenge of helping wounds heal. Interdisciplinary teams of engineers, chemists and other specialists are also creating new technologies to help skin that can’t readily heal itself.

At Vanderbilt University in Tennessee, Craig Duvall, PhD, an assistant professor of biomedical engineering, is taking an approach that could be called “the enemy of my enemy is a friend” technique. He collaborated with chemical engineers and a pathologist to develop a spongy scaffold filled with small molecules that order wound-area cells to shut down production of an enzyme that blocks blood vessel growth in chronic wounds.

In normal wound healing, a molecule called HIF1-alpha helps trigger the growth of blood vessels when there isn’t enough oxygen getting to cells. But HIF1-alpha is thwarted in the oxygen-depleted tissue of chronic wounds by an enzyme called PHD2. With fewer blood vessels, the skin defect is left without a way to get the repair factors and cells that it needs to heal.

When Duvall injects the foamy scaffold onto wounds, a steady trickle of small interfering RNA molecules work their way into wound cells and stop PHD2 production, giving HIF1-alpha a chance to go back to work and help blood vessels sprout again. “We stop the negative feedback loop that impedes wound healing,” says Duvall.

Someday, scientists might just print a new patch of tissue to heal those wounds. A Harvard University team led by materials engineer Jennifer Lewis, PhD, took the first step by printing a three-dimensional tissue scaffold — complete with blood vessels.

Lewis and her colleagues used a 3-D bioprinter, a hulking custom-built machine that resembles a 2-ton version of

an old-fashioned laser printer. The printer uses four “inks” that progressively layer a silicone-based outer border, an inner matrix with two kinds of skin cells called fibroblasts, and an interwoven vascular network that can be lined with living cells, to create three-dimensional tissues.

“We’re nowhere near the goal of making fully functional living tissue,” says Lewis. “But these vascularized tissue constructs represent a foundational step.” As a materials scientist, Lewis says it was a grand challenge to apply her background to create living things. Although she’s creating a new kind of toolbox, she’s quick to point out that scientific advances like this take expertise “on both sides of the aisle.”

PREVENTION IS THE BEST MEDICINE

Improved methods for healing wounds would be wonderful, but preventing them would be even better. Along with other Stanford scientists, Gurtner is working to stop diabetic ulcers from developing in the first place. His group is repurposing a drug called deferroxamine, or DFO, already approved by the Food and Drug Administration for treating diseases that cause a toxic overload of iron in the blood. When a DFO-treated bandage is applied to the at-risk skin on a diabetic’s foot, it improves the skin condition — making it thicker and maintaining blood vessel growth.

But more research trials are needed before these new treatments are prescribed for patients. “Ultimately, the answers will be found in the clinics,” says Gurtner. It will be easier to get those answers at Stanford’s new wound center.

“Patients are realizing that wound care is very specialized,” says Subhro Sen, MD, clinical assistant professor of plastic and reconstructive surgery and co-director of the new center. When people cut a finger, they head for an emergency room or their primary care doctors. But if treatment is needed for chronic wounds, patients end up seeing a number of different specialists. “Now we’ll be able to

give focused, multidisciplinary care. Instead of making multiple appointments at separate locations to see surgeons, get tests and consult with other specialists, patients can get that care all under one roof.”

That’s something Kaufman says he would have appreciated when he was making three-hour round trips from his home in Dublin, Calif., to see Dalman and the other doctors on his team at Stanford, plus twice-weekly journeys for hyperbaric oxygen therapy even farther afield. And while he’s happy that Stanford’s getting a wound treatment center, he’s hoping not to visit anytime soon. Wound-free for almost two years, Kaufman would rather spend his time taking long trips with his wife — like the round-the-world journey he was recently able to make, taking in the sights on his own two feet. **SM**

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FEATURE

Going under

CONTINUED FROM PAGE 39

conscious than people sleep-walking. Determining how to comparatively measure such different states of awakesness and awareness in the brain would give scientists an unprecedented look into what it means for a person to be a living human being.

Some philosophers, Churchland says, remain skeptical that consciousness can be gauged in such a concrete, physical way. But she prefers to think about the limits of science to study consciousness as a known unknown. “We cannot be sure whether we’re up against a solvable or an unsolvable problem,” she says. “But when philosophers claim we’ll never understand the brain basis of consciousness, they are making a rash prediction about the future of science. Against that prediction is the significant progress that has already been made. The fact is, the naysayers cannot really know what science will discover.”

Much of the drive to understand con-

sciousness comes from basic human curiosity: What makes us tick? What makes you have a different view on the world than me? Can we download someone’s memories from their brain? But there are also more practical questions that the science can lend a hand in answering: How can we measure consciousness in patients who appear to be in comas? How can we develop better anesthetics?

“What I’m always hoping is that hearing about this kind of work makes people ask more questions about what it means when they themselves enter different states,” says Chander. She challenges people to pay attention to what’s happening in their brain when their state of attention, or awareness about the world around them, changes.

“Some people still think consciousness can’t be accessed by scientific methods,” says Parvizi. “But that’s a very unfortunate view.” Scientists are already there, he says, getting at the heart of consciousness every day. **SM**

— *Contact Sarah C.P. Williams at
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FEATURE

Rethinking Alzheimer’s

CONTINUED FROM PAGE 45

Long-slumbering synapse-scouring pathways can be awakened by those inflammatory signals, causing massive synapse loss akin to “a fire burning through the brain,” he says.

Annexion, a startup biotechnology company co-founded by Barres, is already making drugs that selectively and powerfully target elements of the complement cascade. Barres has high hopes. “I believe that drugs that block the complement cascade may not only stop neurodegeneration in Alzheimer’s — and, perhaps, other neurodegenerative disorders — but may buy time to allow the brain to repair lost synapses, quite possibly restoring lost neurological function.” Time will tell. Annexion is actively raising money to finance early-stage, proof-of-principle clinical trials of the new drugs, beginning with

patients who have other, easier-to-track neurodegenerative diseases.

MORE SCRUTINY OF THE BRAIN'S IMMUNE CELLS

In their day-to-day life, microglia are beat cops. Among their many roles beyond secreting C1q, one is devouring odd bits of circulating glop or suspended intercellular debris. • Tony Wyss-Coray, PhD, a professor of neurology and neurological sciences, has shown that defects in microglial glop-gobbling capabilities can impair their ability to gobble up early-stage A-beta accumulations, resulting in a buildup of A-beta in aging brains. One rare mutation causing such a defect is known to triple or quadruple Alzheimer's disease risk. When Wyss-Coray's team compared autopsied brains from five Alzheimer's patients and five people who had died of other causes, they found that microglia in the Alzheimer's patients' brains were riddled with precisely those A-beta-ingesting defects his group had identified.

Even healthy microglia have anger-management issues. When chronically hyperactivated, as for example occurs in the chronic presence of excessive A-beta, they get stuck in overdrive, squirting out inflammatory substances that can have deleterious effects on brain cells. They also lose their ability to clear the offending A-beta or other toxic substances, generating a destructive inflammatory vicious circle. Katrin Andreasson, MD, professor of neurology and neurological sciences, recently identified a new way of selectively soothing microglial cells, thus halting the cycle of violence and potentially quenching that synapse-destroying "fire burning through the brain" that inflammatory mechanisms appear to induce. She's continuing this research and hopes the work leads to better anti-inflammatory drugs.

GOOD NEWS FOR OLD BRAINS?

In the end, Alzheimer's is above all a disease of old age. Some time ago, Wyss-Coray's group discovered that something — they weren't sure what — in the blood of old mice messed up new nerve-cell production and cognitive performance

in young mice, and they suspected that young mice's blood might have a beneficial effect on old brains. In a recently published study in *Nature Medicine*, Wyss-Coray and his colleagues showed just that. Not only did old mice whose bloodstreams were experimentally interknit with those of young mice exhibit numerous positive neurophysiological changes, but regular old mice given blood plasma from young mice got better at tests of spatial learning, memory and other cognitive functions.

"Exposure to young blood late in life," Wyss-Coray says, "is capable of rejuvenating an old brain's nerve-cell function and behavioral performance." He's bent on learning what it is in young blood that is recharging the brain. Isolating that factor, or those factors, could lead to pharmacological methods of preventing or delaying the onset of Alzheimer's in aging people (and that's all of us). But meanwhile, he's not waiting around. He's started a biotechnology company, called Alkahest, to speed the initiation of clinical trials in which Alzheimer's patients will receive infusions of young donors' blood and be monitored via brain imaging, standard neuropsychological tests and interviews with patients and caregivers to see if the treatment provides any benefit.

Longo's group has pioneered the development of small-molecule drugs that target the same receptors used by much bulkier growth-factor proteins involved in restoring nerve cells frayed by conditions such as Alzheimer's. In animal models, these molecules counteract a number of key Alzheimer degenerative mechanisms, including inflammatory processes, and can restore the loss of synaptic connections in mouse models of late-stage Alzheimer's disease. One of these compounds has made the rare leap from mouse to human studies and is in early-phase clinical trials sponsored by Pharmatrophix, a company Longo founded before coming to Stanford.

He says he will be happy to see the success of any or all of these diagnostic and therapeutic approaches, most

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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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of them geared toward discovering and treating the disease before symptoms get too advanced. And he is particularly happy that his team's compounds can reverse synapse loss in mice. "We need drugs like this," he says. "Even if we could stop new Alzheimer's cases in their tracks, there will always be patients walking in who already have severe symptoms. And I don't think they should be forgotten." **SM**

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GLOBAL EYE

GATHERING MEDICAL NEWS FROM AROUND THE WORLD

On a Thursday this spring I was sitting at my desk at NBC News in New York City. By Friday, I was walking through the squalor and mud of a Syrian refugee camp in Lebanon with the chief medical editor for NBC News, Nancy Snyderman, MD.

- I am a fourth-year medical student — but as the Stanford-NBC News Fellow in Global Health and Media I'm getting exposure to global health and medical journalism.
- Already since last summer, I've worked in Haiti at a hospital, in New Delhi as an intern for the World Health Organization and in Thailand to help with an international summit on leprosy. I spent the fall at Stanford's graduate program in journalism. I have interviewed a mind-boggling array of people: a man with leprosy in India, the president of the American Academy of Dermatology, illegal immigrants living in a Northern California garage, a California state senator, countless medical researchers at the cutting edge of their fields.

- And for a week in March I found myself at the refugee camp in Lebanon, following the stories of Syrian children living there in tents with their entire families on the bank of a trash-filled river. I interviewed the kids — about their toys, their squabbles, their memories of Syria and their hopes for the future. One girl, 7, with piercing blue eyes, became my shadow and my companion. At one point she leaned over to whisper something in my ear. When I asked her to tell the translator, she shook her head. "She's telling me that what she wants to say is between you and her only," he informed me. I could only smile back at her.

That chilly, rainy week I saw birth, death, laughter and tears. I am used to seeing those things through a medical caregiver's lens, but not through a journalist's. My job was not to

intervene, but to observe, document and report.

One unforgettable story was that of 19-month-old Nevine, who arrived with her right side paralyzed. Doctors were worried — justifiably — about polio. Syria's vaccination rates have plummeted: from 99 percent before the war to 52 percent in 2012. When Nevine's mother looked at me with pain in her eyes and asked whether her child would ever walk again, I wanted nothing more than to offer her assurances — but I couldn't. In journalism and in medicine, it's important not to jump to conclusions.

One lesson I learned is that, consciously or not, physicians always function as health-care reporters. We are cast in this role when we interpret data for our patients, recommend certain interventions or review information patients have printed from WebMD. Doctors know firsthand what an honor it is to be with people at their most vulnerable and listen to their stories.

Sometimes those stories have happy endings. We later found out that Nevine's test results were not consistent with polio. An MRI showed a small area of bleeding deep in the part of her brain that controls movement on the right side of her body. By the time I left, she was already improving. — HAYLEY GOLDBACH



Children play on the outskirts of a Syrian refugee camp in Lebanon's Bekaa Valley.

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Sea lion seizures

ILLNESS PROVIDES INSIGHT INTO EPILEPSY

In the first four months of this year, 40 sea lions turned up on Northern California shores suffering from seizures caused by a neurotoxin found in algae. That's 13 more of the animals than last year during the same period and more than double in previous years. The sea lions had been feeding on small fish contaminated with domoic acid, a toxin that has increased along with the growth in algae blooms on the coast.

A recent study led by Stanford scientists characterized the brain damage caused by this toxin. What they found could lead to better therapies not only for the pinnipeds but also for humans.

Paul Buckmaster, PhD, DVM, a professor of comparative medicine, and his colleagues examined the brains of the affected sea mammals and found a pattern of damage in the hippocampus — the brain's memory center — similar to that in humans with temporal lobe epilepsy, one of the most common forms of the disease. The animals had lost 50 percent of the neurons in the hippocampus, with the damage occurring on just one side of the brain.

"That was really surprising," says Buckmaster, a veterinarian specializing in epilepsy. "That is what you find in people — 80 percent of the time the damage is just on one side." In rodents, the animals typically used in epilepsy studies, damage appears on



both sides of the brain. The ailing sea lions also showed a pattern of nerve cell reorganization in the brain matching that of humans with epilepsy.

Since 1998, the Marine Mammal Center in Sausalito, Calif., has rescued a few hundred sea lions with epilepsy every year. And while anticonvulsive drugs can help control symptoms in both species, the disease has no cure.

Buckmaster has been collaborating on the project with the marine center for the last four years and continues to study the brains of those animals that are beyond rescue.

"What we need is an interventional treatment — both in humans and sea lions," Buckmaster says. "You'd give the treatment right after the brain injury, and that would prevent them from developing epilepsy. That's the dream, but we are not there yet." — RUTHANN RICHTER

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