STANFORD MEDICINE

Spring 2013

special report

BLOOD
What do we know about it?

Roll up your sleeve
There's no substitute for blood

A lone voice
An early call for AIDS screening

Seeing red
Blood phobia's odd pathophysiology

Living with hemophilia
One doctor's saga

Against the flow
Why transfusions are declining

plus

Nobel prize
Brian Kobilka's extraordinary adventure

STANFORD MEDICINE

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DO I KNOW YOU?

EXPERIMENT PINPOINTS BRAIN AREA LINKED TO FACE BLINDNESS

What's up with those rude characters you see coming down the hall every single day who never acknowledge your presence? Just as you get near enough for the standard, semiconscious exchange of glances that (for you, anyway) invariably leads to saying hello — they avert their eyes and walk past you as if you're a perfect stranger.

It's doubtful that they're all suffering from out-and-out prosopagnosia, or face blindness, although as many as one in 40 people may have inherited some degree of it. (Famed author/scientist Oliver Sacks, MD, suffers from a congenital case.) But there's no question that we differ in our ability to recognize faces. And that may have a lot to do with how things are going in a small, hand-rolled-cigarette-shaped brain structure called the fusiform gyrus that dwells at the bottom of each of our two temporal lobes, according to a recent *Journal of Neuroscience* study by Stanford neurologist Josef Parvizi, MD, PhD.

Stanford neuropsychologist Kalanit Grill-Spector, PhD, has been studying the fusiform gyrus' role in face recognition as well as in prosopagnosia. People with prosopagnosia simply cannot distinguish one face from another, although all other aspects of their vision and visual-information processing are normal. Some people, like Sacks, are born with the condition while others acquire it as a result of an injury to the fusiform gyrus, Grill-Spector says.

"We can learn a lot about the function of different brain regions by studying these disorders and relating them to the anatomical sites where brain damage has occurred," she says. "But the injuries vary a great deal from one affected person to the next, and they are typically not confined to the fusiform gyrus. This limits our ability to localize a particular deficit to a particular brain site."

But Parvizi, collaborating with Grill-Spector, has nailed it in a striking experiment made possible because of a courageous epilepsy patient named Ron Blackwell.

Blackwell, who'd had part of his skull temporarily removed so that electrodes could be placed at the surface of his brain to monitor his seizures, decided that while he was lying there more or less immobilized for a week, he might as well pass the time doing something for science. So, working with Blackwell, Parvizi used electrical brain stimulation (it's completely painless) to prove that the fusiform gyrus plays a key role in processing information about faces.

To his own surprise as well as Blackwell's, Parvizi showed that mild electrical stimulation of two tiny sites in the 2- to 3-inch-long fusiform gyrus on the right side of Blackwell's brain could cause his perception of faces to instantly become distorted while leaving his perception of other body parts and inanimate objects unchanged.

The push of a button enabling current to flow between those two spots caused Blackwell to immediately exclaim to Parvizi: "You just turned into somebody else. Your face metamorphosed!" As soon as the electrical stimulation stopped, so did the distortion. (Blackwell's reaction can be viewed in this publicly available video made while Parvizi was pressing the brain-bending buttons: http://stan.md/Z6OAsD.) — BRUCE GOLDMAN

JEAN-FRANCOIS MARTIN

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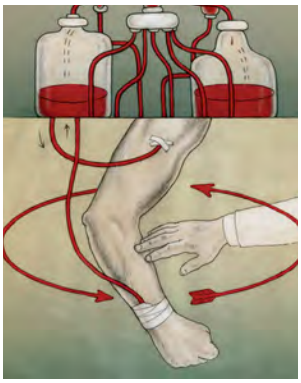

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COVER: RENPHOTO

letter from the dean

As a surgeon, I have become accustomed to the sight of blood. Mostly, it just gets in the way, obscuring the view of what really matters.

You try to look past it, hoping for a textbook view. But it's constantly there, bright red, flowing effortlessly, a messy reminder of the vitality of human life and its remarkable capacity for regeneration. This issue of *Stanford Medicine* magazine is all about this liquid of life.

On Dec. 1, I became dean of the Stanford University School of Medicine. As the new blood, I'm enjoying getting to know better this amazing institution. At Stanford, our students love debating and discussing ideas. Through this magazine, thought leaders beyond our campus can join in this lively exchange of ideas on leading issues in biomedicine.

On campus we are now engaged in a lively discourse of our own about the future of Stanford Medicine. The challenges facing us in academic medicine are daunting. Society is demanding more from us — more value in health care, more scientific breakthroughs, more physicians ready for a rapidly changing health-care delivery and discovery environment. And yet we must face these growing challenges with fewer and fewer resources.

While many in academic medicine are hunkering down, our faculty and students are passionately pressing forward. Here at Stanford Medicine we see every day as opening up new possibilities, new ideas and new hope. As I consider our future, I am guided by three priorities: advancing innovation, empowering future leaders and transforming patient care.

Innovation is about the good ideas that change the world. At Stanford, our scientists are exceptionally creative. Last fall when the National Institutes of Health announced funding for its High Risk-High Reward program, researchers at Stanford received more awards than any other institution. But in a tough funding climate, we will have to work harder to attract and retain the most innovative faculty and students and give them the time and freedom they need to pursue the visionary science that can improve our lives.

If advancing innovation is in our blood, empowering future leaders is the legacy we leave to future generations. At Stanford we want our educational experience to be the best it can be, with integrated training opportunities for medical students, graduate students, postdoctoral scholars, residents and clinical fellows. As leaders in online education, we will share our interactive tools broadly with our peers so that we can enhance medical education and continuing medical education not just at Stanford but at schools across the country.

Last, but not least, we at Stanford will become a leader in the transformation of patient care by bringing the very best science to the treatment and prevention of disease, by focusing on the health and well-being of each patient who receives care through our system and by communicating our knowledge and advances to others.

I am delighted to be dean of such an outstanding institution, and I hope you will engage with us as we debate ideas and push forward, guided by our commitment to the priorities and principles that are our lifeblood: advancing innovation, empowering future leaders and transforming patient care. In closing, I thank the Stanford Blood Center for its partnership in producing this issue of *Stanford Medicine* magazine.

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

GLENN MATSUMURA

upfront

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

Dr. DMV?

PAINFUL AS IT IS TO LEARN FROM YOUR DOCTOR YOU'RE UNFIT TO DRIVE, it prevents serious accidents, according to a new study.

The researchers gathered data on 100,075 adult patients in Ontario, Canada, who received formal medical warnings between 2006 and 2010. Ontario, like six U.S. states including California, requires physicians to notify the department of motor vehicles of any patient with a condition making it dangerous to drive. Such reports sometimes lead to licenses being revoked.

The study, which appeared in the Sept. 27, 2012, *New England Journal of Medicine*, found a 45 percent reduction in the risk of serious road crashes in the year following the warnings; the patients had a total of 1,430 crashes over the study period, averaging about 466 per year. In the year post-warnings, the rate dropped to about 273 road crashes.

While medical warnings may protect people from road crashes, the researchers also found that patients who received these warnings were more depressed and less likely to pay a return visit to their doctor, note the study's leaders, Robert Tibshirani, PhD, professor of health research and policy and of statistics at Stanford, and Donald Redelmeier, MD, professor of medicine at the University of Toronto.

"This doesn't mean that doctors should stay silent about the situation," Redelmeier cautions. Instead, he says, "Physicians need to be sensitive, compassionate and prepared to address adverse consequences in the aftermath of a warning." — MARGARITA GALLARDO

JEAN-FRANCOIS MARTIN

The School of Medicine now has 4 living Nobel Prize winners among its nearly 900 faculty members.

Wait training

LOSING WEIGHT IS HARD; keeping it off can be even harder.

But School of Medicine researchers have found that women who spent eight weeks mastering weight-maintenance skills before losing any weight kept off more pounds than women who immediately started a weight-loss program.

Both groups on average lost about 17 pounds after 28 weeks. But a year later, the maintenance-first women had regained only 3 pounds on average, compared with the 7-pound average gain for the control group.

"Those eight weeks were like a practice run," says Michaela Kiernan, PhD, who led the study published Oct. 29, 2012, in the *Journal of Consulting and Clinical Psychology*. "Women could try out different stability skills without the pressure of worrying about how much weight they had lost." — SUSAN IPAKTCHIAN

upfront

TOO GOOD TO BE TRUE

If a study concludes that a new medical intervention — be it a drug, a device or a social program — has a major effect on a condition or symptom, the study is probably wrong and in reality the effect is probably lower. That's the conclusion of a new analysis led by John Ioannidis, MD, DSc, chief of the Stanford Prevention Research Center.

Ioannidis and his colleagues parsed data from more than 85,000 previous meta-analyses (analyses that can include any number of medical trials on a particular intervention and outcome of interest) and determined that most medical interventions have only small or modest incremental effects, but that those effects are frequently overestimated by small studies.

They published the results of the analysis Oct. 24, 2012, in the *Journal of the American Medical Association*.

The team discovered that in about 10 percent of the medical topics examined, a very large treatment effect was found in a first study, and another 6 percent found a very large treatment effect only in a later trial. But in more than 90 percent of all those cases, the very large effect disappeared when additional studies or meta-analyses were performed.

When Ioannidis looked into what kinds of trials most often concluded very large treatment effects, one thing stood out.

"Almost always, these very large effects are seen in very small trials — usually with fewer than 20 people in the study having the outcome claimed to be the very large effect," he says.

This emphasizes the need for larger studies, Ioannidis says, and the fact that small studies concluding a large treatment effect need to be looked at skeptically. "Yes, a large study can cost more than a small study," he says.

"But performing a well-done, larger, long-term, randomized study is better than wasting money left and right on very small, mediocre studies."

— SARAH C.P. WILLIAMS

Lung bugs

HEALTHY LUNGS TEEM with microbes — and they're a different community of critters from those living in the lungs of cystic fibrosis patients, according to a study published Sept. 26, 2012, in *Science Translational Medicine*.

"This research confirmed a long-held suspicion that a forest of microbes exists in both healthy and diseased lungs," says study author David Cornfield, MD, a pulmonologist at Lucile Packard Children's Hospital and a professor of pediatrics in pulmonary medicine. More surprising, he says, the work suggests that the microbes help preserve lung health.

The researchers extracted and selectively copied bacterial DNA from the sputum and lung tissue of a small group of healthy people and CF patients. Healthy individuals had more diversity among their lung bacteria. Different bacterial phyla also predominated in the two groups.

"I think the tendency toward decreased diversity in CF can be metaphorically viewed as the same phenomenon that might happen in a rainforest," Cornfield says. "When the ecosystem of a rainforest is disturbed and one organism predominates, it undermines a carefully constructed balance and causes disturbances in the overall ecosystem. I think it's reasonable to assume something similar could happen in the lung microbiome."

Future research might test whether CF or pneumonia patients could benefit from doses of probiotic bacteria to their lungs, he adds. — ERIN DIGITALE

JEAN-FRANCOIS MARTIN

Parasite insight

IS THE WORM finally turning? Schistosomiasis, a disease caused by a tiny parasitic worm, ranks as a world-class tropical scourge.

Some 150,000 people die annually from kidney failure when the worm targets the bladder, says Stanford urologist Mike Hsieh, MD, PhD.

Perhaps that will change.

In a study published Nov. 29, 2012, in *PloS-Neglected Tropical Diseases*, Hsieh and his colleagues focused on a variety of the worm known as *S. haematobium*. If you simply infect mice with *S. haematobium*, the parasites head for the liver and intestine instead of the bladder.

But Hsieh's team developed a new mouse model that involves directly injecting the parasite's eggs into the bladder wall.

Examining excised bladder tissue at several distinct time points after infection, the team got the first look at the changes the infections had triggered in the activity of virtually every gene in the tissue.

These observations could lead to new drug approaches. — BRUCE GOLDMAN

STROKE CENTER AWARD

Stanford Hospital & Clinics is the first hospital to earn the nation's newest level of certification for advanced stroke care, awarded by The Joint Commission, a leading healthcare organization accrediting body.

A team of Joint Commission expert surveyors evaluated the hospital and its stroke center in October for its compliance with the new comprehensive stroke center requirements, including advanced imaging capabilities, 24/7 availability of specialized treatments, participation in research, and staff with the education and competencies to care for complex stroke patients.

The surveyors found the hospital met or exceeded all required standards.

Stanford created its stroke center in 1992. "What we recognized from the start was that the best care would come from going beyond issues about turf," says Michael Marks, MD, the center's director of interventional neuroradiology. Marks founded the center with co-director Gary Steinberg, MD, PhD, and director Greg Albers, MD.

— SARA WYKES

Feeling very, very... not sleepy?

SOME PEOPLE CAN'T BE HYPNOTIZED, which isn't necessarily a good thing because hypnosis could help them manage pain, control stress and anxiety, and combat phobias. Now Stanford researchers have discovered differences between hypnosis-resistant brains and hypnotizable ones. Their study used data from magnetic resonance imaging scans to show that highly hypnotizable participants have greater activation of two areas of the brain — including the region that plays a role in focusing attention.

"There's never been a brain signature of being hypnotized, and we're on the verge of identifying one," says psychiatrist David Spiegel, MD, who led the *Archives of General Psychiatry* study published in October 2012. He believes such an advance would enable physicians to better understand the mechanisms underlying hypnosis and to use the therapy more widely and effectively.

— MICHELLE L. BRANDT

25%

That's the estimated portion of Spiegel's patients who cannot be hypnotized.

New dean

Stanford's medical school has a new leader: Lloyd Minor, MD. An expert in balance and inner-ear disorders and a surgical innovator, the new dean of the medical school served on the faculty of Johns Hopkins University for nearly 20 years, the last three as the school's provost — its top academic officer. He came to Stanford in the fall and began his post as dean Dec. 1, 2012.

Minor's focus since his arrival has been on absorbing and synthesizing his new colleagues' insights about the school's challenges and opportunities. "We're engaged in a lot of dialogue about where we are right now and where we want to be in the future."

He's deeply appreciative of the Stanford community's willingness to discuss and debate ideas, he says. "Stanford Medicine has a level of collective dialogue that I think is matched at few institutions. It's part of the DNA."

Out of his conversations have come three organizing themes for leading the school forward: advancing innovation, empowering future leaders and transforming patient care. His work now, says Minor, is to develop a plan that will enable Stanford Medicine to make an even greater impact.

Before Minor became immersed in leadership, his passion was for translating his discoveries in basic science to improvements in patient care. "I'm confident that in my career I've learned more from the patients with whom I've had the pleasure of interacting than they've learned from me," says Minor.

As a result of listening to one patient describe unusual symptoms, Minor changed the field of otolaryngology — by identifying a new disease. The encounter pointed him to the cause of a debilitating type of sound- or pressure-induced dizziness, which he named superior canal dehiscence syndrome. After discovering the cause — an opening in a bone overlying an inner-ear balance canal — he developed a surgical procedure to correct it.

In October, the Institute of Medicine elected Minor as a member, one of the top honors in health and medicine. — ROSANNE SPECTOR

BLOOD AT WORK

VITAE

WHAT WE

A L L U I D

KNOW ABOUT BLOOD

"BLOOD IS A VERY SPECIAL JUICE." Goethe didn't know the half of it when he penned this line for Mephisto more than 200 years ago.

In those days people believed blood held mystical qualities and was a potent life force. No wonder Mephisto wants the contract for Faust's soul signed in this "special juice."

But what exactly does blood do?

Blood transports oxygen to all of our body's cells, which use it as fuel. Blood sweeps away wastes. Blood conveys messages, in the form of hormones, from one organ to another. Blood hosts the immune system — carrying it where it's needed.

There's also blood's dark side. It can turn against us, afflicting us with cancers of the blood cells, sickle cell anemia, hemophilia and many other diseases, and it can carry infection.

Because of blood's many roles, a few drops can serve as a window on the state of our health, making it the go-to material for diagnostic tests.

Our view of blood has greatly altered in the last century, when transfusion was perfected. Earlier, bloodletting — draining and discarding a portion of blood — was a standard treatment. Today blood is a valuable treatment itself, with nearly 5 million people in the United States each year needing a blood transfusion.

Medical science continues to expand our understanding of what goes on in blood and how best to marshal its power. For the latest thinking, read on.

BLOOD AT WORK

ROLL UP YOUR

SLEEVE

THERE'S STILL NO SUBSTITUTE FOR BLOOD

By Jessica Shugart

PHOTOGRAPHY BY ERIN KUNKEL

SURVIVOR: BRENNAH PAYNE

Brennah Payne's desperate need for blood arose the instant a semi-truck crashed into her parents' car. She was 7 at the time. Now 14, she has vague memories of being helicoptered to Lucile Packard Children's Hospital, where she went through nine major surgeries and 22 other medical procedures over the next six months to correct the damage done.

The impact broke her spine in half, fractured her face in 14 places, ruptured her bowels, bruised a kidney and triggered massive internal bleeding. She received countless units of blood throughout the struggle to survive.

"I remember tubes coming into me, but I don't really remember what was in them," she explains. "Now I know that the things that were in them kept me alive."

Today, Brennah is a healthy teenager and a top runner on her school's cross-country team. Although she has recovered from the accident that occurred half a lifetime ago, she has never forgotten how the generosity of blood donors saved her life.

"There were so many people helping me, and I didn't really know why," she says. "I just knew that I felt love from them, and it made me happy because without them I wouldn't be here today."

Her mother, Heather Payne, a nurse, recalls her newfound appreciation of blood donors after her daughter's accident. Before, she says, "I wasn't so tuned in with the importance of blood donation. It was always so easy to just go and get a unit of blood from the lab and give it to a patient. Afterward, it

Opposite, L to R: Plasma, red blood cell and whole blood units hang in a machine used for apheresis — automated blood collection. Top: Galen Poulton donates platelets at Stanford Blood Center's Hillview Avenue site. Bottom: Blood drawn during a donation to test for viral infection.

was really eye-opening to me to consider that concept of people not knowing who they're giving it to."

Brennah is a champion for blood donation these days, speaking at donor appreciation events and blood drives. "It's almost like you can be a superhero," she says, "if you just donate an hour of your time to give blood."

Most donors give blood only a few times a year, if that. But for Linda Johnson, it's a routine part of life. On this fall day in 2012, Johnson reclines in a comfy chair at the Stanford Blood Center, wrapped in a soft, powder-blue blanket, while two pints of blood drain from a vein in her arm. Right next to her, a machine snatches the tiny cell fragments called platelets from her blood and returns the rest of the fluid back into her vein. She's a very familiar face here: This is her 561st donation.

Though Johnson has been donating at the Stanford Blood Center for 25 years, her history of giving blood starts even earlier. She donated in college and — like many who give of themselves to help others — found the experience rewarding. Wanting to make a bigger impact, she got tested to see if she'd be eligible to donate platelets, a blood component

"IT'S ALMOST LIKE YOU CAN BE A SUPERHERO IF YOU JUST DONATE AN HOUR OF YOUR TIME TO GIVE BLOOD."

crucial for clotting. Because only platelets are removed from their blood, these donors can give more than the usual pint at a time, and can do so more often. Johnson donates twice a month, whereas whole-blood donors are limited to once every eight weeks.

"I donate because I can. My fortune is good health," says Johnson. "I know many people who are not healthy, and there is no substitute for blood."

Johnson, the only woman to surpass 500 donations at the Stanford center, admits she's also in the game for a little friendly competition with her fellow donors: At her current pace, she'll hit 600 donations in June 2014.

"I get the satisfaction of knowing I helped save somebody's life, and I've done that more than 500 times," Johnson says. "It's extremely heartwarming. Plus I get cookies — at least two."

Each of us has about 10 pints of nature's life-giving concoction flowing through our arteries and veins — delivering oxygen to vital organs, fighting infection and healing wounds. In spite of striking advances in our understanding of how blood works, no one has come up with a substitute that re-creates all its virtues. To date, the only replacement for lost or damaged blood comes in the form of a gift from a willing donor, which is why donors are vital.

TRANSFUSION'S EARLY DAYS

On the surface, the concept of blood transfusion seems simple (and perhaps a touch unnerving): One person's bodily fluid is harvested to save the life of another. Yet the relatively safe procedure we use today came only after centuries of experimentation — a story rife with both life-saving triumphs and fatal disasters.

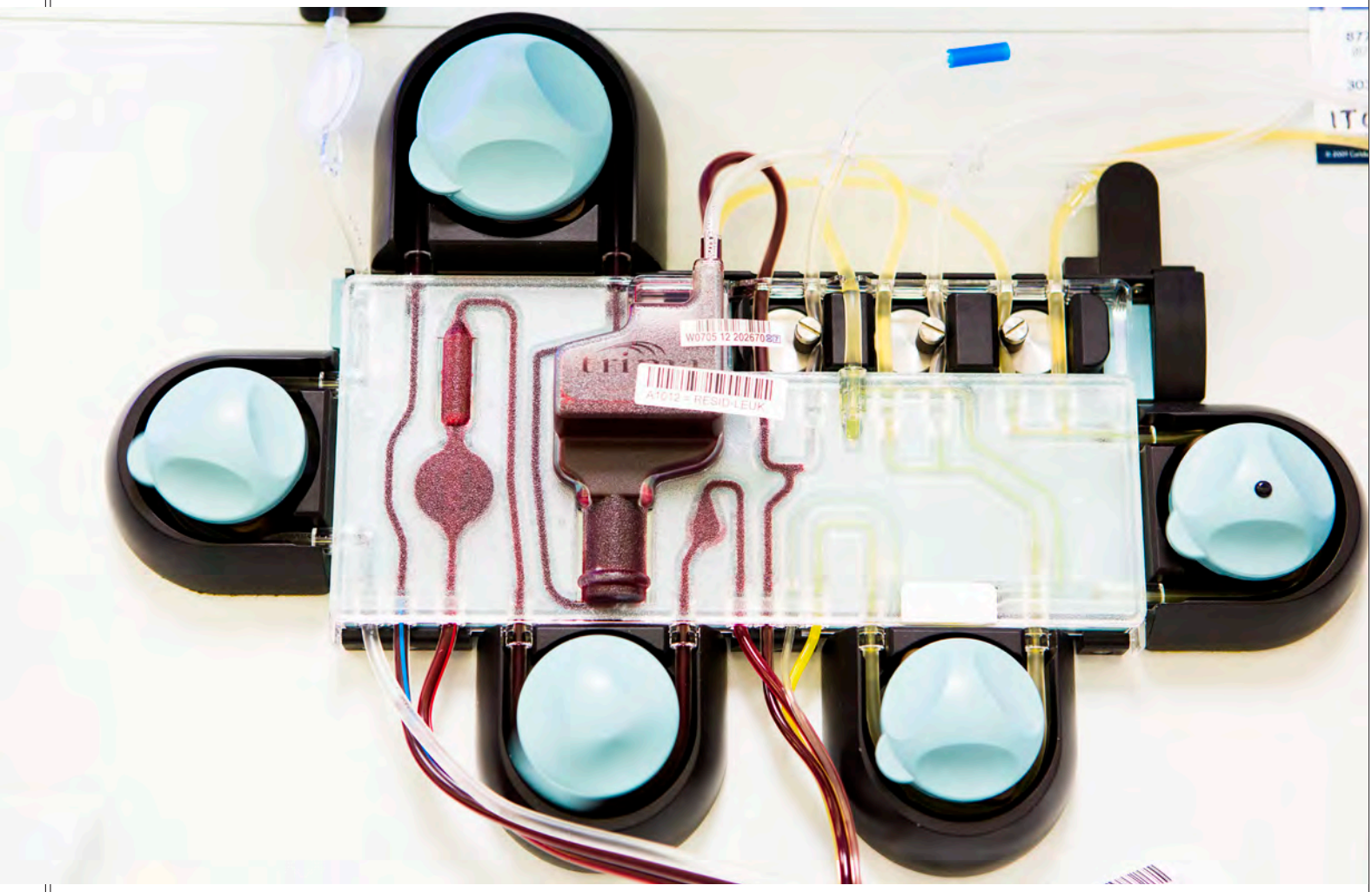
Two dogs served as the conduit for the first of a flurry of transfusion experiments that took place in the 17th century. Using a goose quill for a needle, English physician Richard Lower transferred blood from a mastiff to a medium-sized dog in 1665. Since he had drained the blood of the medium-sized dog beforehand, the transfusion effectively saved its life.

Just two years later, French physician Jean Baptiste Denis made the jump to humans. He transfused 9 ounces of sheep's blood into a teenage boy by attaching the animal's carotid artery to the boy's arm. The boy survived the ordeal, prompting Denis to perform the procedure on several other patients until, eventually, one died. The death triggered a backlash against blood transfusion, leading several countries to ban it. By 1668, the experiment of transfusion had been put to rest as quickly as it had arisen.

It was another 150 years before the first recorded blood transfusion between two humans took place. In 1818, British physiologist James Blundell combined blood from several donors and injected the mixture into a patient suffering from internal bleeding. Though the patient initially improved, he died three days later. The cause of the delayed fatal reaction wouldn't be understood until the next century.

Blood transfusion remained hit-or-miss for the rest of the 19th century — saving lives in some cases and leading to death in others. Then, in 1901 Austrian physician Karl Landsteiner discovered the existence of different "blood groups." Landsteiner found three groups — A, B and O — that contained one (A or B) or neither (O) of two antigens on the surface of red blood cells. Importantly, he found that people receiving mismatched transfusions made destructive antibodies against the blood-borne antigens that weren't theirs. For example, people with type-A blood produced antibodies against type-B blood, and vice versa. The antibodies latched onto the donor blood and caused the red cells to clump, leading to the fatal reaction that explained the variable success of blood transfusions up to that point. A simple cross-matching test was soon developed to check the compatibility of blood samples prior to transfusion. In 1902, the fourth blood type, which carries both antigens, was discovered and named AB.

The final hurdle blocking efficient transfusion would be blood storage. Scientists broke this barrier in 1916 with a sodium citrate solution that prevented donated blood from clotting, allowing for storage over several weeks. Drawing from these discoveries, U.S. Army physician Oswald Robertson opened the first blood bank in 1917 in a military hospital in war-torn France. He stocked the shelves with type-O blood — considered the "universal donor" because of its lack of both A and B antigens.



Opposite left: The donor center. Opposite right: Conard Sill donates platelets. Above: An apheresis kit separates red blood cells from platelets and plasma. The red cells are returned to the donor; the platelets and plasma are used for treatments.

War continued to drive the advancement of blood distribution and storage in the following decades. By the late 1940s blood banks were springing up throughout the United States. After the urgency of World War II subsided, blood-banking challenges shifted to the development of tests for infectious diseases transmitted through blood transfusion. (By that

time, researchers had also discovered another aspect of blood type: the presence or absence of the Rh protein, which got its name from rhesus, the animal in which it was discovered.)

Today, a sample from every batch of donated blood undergoes a barrage of tests to ensure its safety. In a process tightly regulated by the U.S. Food and Drug Administration, each unit of donated blood is screened for HIV, hepatitis B, hepatitis C, human T-lymphotropic virus, syphilis and West Nile virus. All donors also get a one-time screening for Chagas disease. And at Stanford's center, unlike most other blood banks, every unit is screened for cytomegalovirus, a member of the herpes virus family that's harmless for most healthy people but dangerous for transplant recipients and other immunosuppressed patients — who make up a large portion of transfusion recipients at Stanford.

Historically, Stanford Blood Center has been ahead of the game in screening for infectious disease. In 1983, for instance, when it became clear that AIDS was spreading to transfusion recipients through donated blood, Stanford was the first center in the world to screen for the mysterious infection, using an indirect test the blood center's director developed. The center was also the first to routinely screen for cytomegalovirus, which is carried by half the nation's population.

"I GUESS I'M A WEIRD DUCK, BECAUSE I REALLY LIKE THE REGULATION PART, THAT PART OF KEEPING YOUR SHIP TIGHT."

For Jan Webster, supervisor of the blood center's testing lab, adhering to the many rules and regulations of blood banking is actually rather enjoyable. "I guess I'm a weird duck, because I really like the regulation part, that part of keeping your ship tight," says Webster, a medical technologist and educator who came out of retirement to perform donor testing.

NOTHING LIKE THE REAL THING

From the discovery of blood types to the continuing development of tests for new infectious diseases, the past century of blood transfusion research has focused on rooting out the dangers lurking within an otherwise lifesaving product. But all of these dangers could be eliminated if researchers came up with a workable blood substitute. Imagine it: no blood types to worry about, no infectious diseases to transmit.

Several biotech companies have taken a stab at manufacturing an artificial alternative to blood — with frustrating results. In 2006, for instance, Northfield Labs concluded a controlled clinical trial in which trauma patients were infused with either natural blood or a substitute called PolyHeme, designed to replicate the oxygen-carrying capacity of red blood cells. Unfortunately, trauma patients receiving the PolyHeme infusions turned out to be slightly more likely to die of their injuries compared with patients infused with real blood (13.2 percent versus 10 percent). Northfield, which had spent 20 years trying to make a successful blood substitute, closed its doors in 2009.

If blood substitutes are ever to stand in for donor blood, they'll need to fulfill a host of other requirements before they'll measure up to the real thing. In addition to transporting oxygen throughout the body, blood contains platelets and clotting factors that stop internal bleeding, white blood cells that fight infection, electrolytes needed for organ and muscle function, and myriad vital proteins — some poorly understood and others yet to be discovered.

When it comes to blood, so far nature knows best.

EVERY FRACTION SAVES A LIFE

Because of its many complex functions, whole blood is commonly separated into three "blood products" after collection: red blood cells, platelets and plasma. That means one donor's gift of blood has the potential to save up to three lives.

Red blood cells are oxygen-delivery specialists; without them, breathing would be pointless. They pick up oxygen in the lungs and drop it off at organs around the body, constantly returning to the lung for refills.

Red blood cells are the most common type of transfusion. While gravity alone is enough to separate them from the rest of the blood, a gentle centrifuge is used at blood centers to hurry things along. The concentrated red cells — commonly known as "packed" red blood cells — lend their oxygen-car-

rying capacity to trauma victims, anemic patients and cancer patients. The cells, which have a shelf life of 35 to 42 days depending on how they're preserved, save lives by keeping vital organs functioning.

Platelets perform the crucial task of patching potential blood leaks through clotting. Not exactly cells in their own right, platelets bud off of other blood cells called megakaryocytes. The fragile cell fragments live only five to nine days — plugging leaks by forming blood clots. They decline even more rapidly in response to harsh cancer treatments like chemotherapy or radiation, so cancer patients often need platelet transfusions to prevent them from bleeding profusely from even minor wounds.

While platelets can be separated from whole blood, it takes about five whole-blood donations to glean one effective dose of the platelets. That's why donors like Johnson donate platelets specifically instead, through a process called apheresis. A machine next to the donor's chair harvests only the platelets (along with some plasma) and returns the rest of the blood to the donor through the same needle. Because the majority of red cells are returned to the donor, platelet donors can also donate more frequently than whole-blood donors — often, once every two weeks rather than once every eight.

Plasma, the clear, yellowish liquid component of blood, makes up 55 percent of blood volume. Free of all cells and platelets, plasma is 93 percent water and 7 percent vital proteins. Plasma proteins help clot blood, fight infection and prevent shock. As such, plasma may be transfused into people with clotting disorders, patients fighting infectious diseases such as hepatitis, or trauma victims experiencing massive fluid loss.

Opposite: Units ready to go. Type-O blood that's free of Rh proteins (O-) is in great demand because it's compatible with all other types. Above: A unit just out of the centrifuge, separated into red blood cells and plasma. Right: Dianne Geary, components and distribution supervisor, in the blood center's distribution area.

Donors in the United States gave 17 million units of blood in 2008, 70 percent of which came from repeat donors rather than first-timers. While an estimated 37 percent of Americans are eligible to give blood, only 10 percent actually have. Worldwide, transfusions are needed to replace blood lost in traumatic injuries or from hemorrhaging during childbirth. However, in developed countries like the United States, the majority of donor blood is now used during planned surgeries or to replace the treatment-ravaged blood of cancer patients.

In addition to collecting blood from people who come in to donate, Stanford Blood Center hosts mobile blood drives at local high schools, workplaces, churches and

community centers. The blood is collected onsite and then wheeled back to the center for processing and testing. In this way, the center reaches people who might never have thought to donate.

The center, created in 1978 within the School of Medicine, supplies blood products not only for transfusion but also for research. As the primary supplier of blood to Stanford Hospital & Clinics, Lucile Packard Children's Hospital and other local medical facilities, it produces about 100,000 individual portions of blood products for transfusion each year. The center also plays a special role in the research community: With donors' permission, leftover fractions, which at other blood centers are routinely discarded, go to labs studying human health and disease. In 2011, the center produced more than 54,000 samples of blood products for research.

SURVIVOR: ROBERT HENSLIN

Robert Henslin is intimately aware of the lifesaving qualities of every blood product. At the age of 26, just six months after getting married, he was diagnosed with acute lymphoblastic leukemia. The following year and a half of intense chemotherapy and radiation ravaged his blood.

"There were blood transfusions needed all along," says Henslin. "I was getting platelets, whole blood, red cells, basically the whole shooting match just so I could benefit from the cancer treatment and stay alive."

Henslin enjoyed a 20-year remission, highlighted by the birth of two daughters, before the cancer returned. This time, his doctors told him his only real shot at survival was a bone marrow transplant.

Henslin went through months of chemotherapy before the bone marrow transplant he ultimately received. Once again, the treatment decimated not only the cancer cells but also the red blood cells, platelets and white blood cells that he needed to stay alive.

He recalls one instance when his platelets were so low that his blood failed to clot. Blood was leaking out of the I.V. site in his arm just as fast as blood products were being transfused in. "They were changing the bandage every 20 minutes," Henslin says.

Multiple transfusions of platelets — which Henslin describes as looking like apricot nectar — allowed his blood to clot again.

Eventually four good genetic matches were found for Henslin, the best of which was on the other side of the world: a young man in Germany, who had initially signed up with the bone marrow registry in the hope of saving a teacher who had fallen ill. The young man's bone marrow was shipped to the United States and transfused into Henslin's irradiated body at Stanford Hospital's E1

Left: Platelets and red blood cells boxed for shipping. Right: Blood samples for viral marker testing. Six tubes (four purple, and two red) are drawn from each donor. Opposite: Manny Dy, apheresis nurse, with platelets that can be used to treat cancer patients, bone marrow transplant patients, trauma victims and people with blood disorders.

Transplant Unit.

Throughout his recovery from what doctors called a "difficult" transplant, Henslin required countless additional transfusions.

"Every time I received a bag, I thought, 'Somebody gave this up for me,'" says Henslin. "I never took it for granted."

That was four years ago, and though Henslin still suffers from after-effects of the transplant, according to his doctor, he will probably never have to worry about leukemia again. He feels extremely grateful not only to the bone marrow donor, but also to the blood donors who kept him alive throughout his treatment.

"Anything you can do to step out of yourself, out of your comfort zone, do it. The benefits are phenomenal," says Henslin. "You get to help a fellow human being, and you'll feel like you spent part of your day doing something really, really important."

SUPERHEROES OR SUPER HUMANS?

Just what motivates these blood donors that Brennah calls "superheroes"? Some of Linda Johnson's reasons are surprisingly down-to-earth.

She and other Stanford blood donors have online access to individual accounts that track the number of donations they give each year. Fueled by the knowledge of her own stats and by conversations with fellow donors, Johnson's competitive drive causes her to donate platelets the maximum amount of times — 24 — per year. "It's a little game we play. And I'm very good at it," she says.

But even more than the friendly competition, Johnson and others donate because of the lives they know they're saving.

"Every once in a while when the needle is uncomfortable, I think about the folks who are getting blood transfusions, especially little kids, and how much discomfort they are in," says Johnson. "That usually puts things in perspective for me."

Every year the blood center hosts a "Precious Mettle" breakfast honoring donors who have given blood more than 100 times. Several transfusion recipients are invited to speak. Johnson chokes up when she recalls the mother of a 3-year-old girl who thanked the donors for saving her daughter's life.

Some consider blood donation a selfless act. Yet it seems that the experience of saving a life, of being part of a donor community, of *giving* in general, also fulfills a very human need on the part of the donor. Just like an apheresis machine that returns fluid to the donor as they give, the benefits of blood donation are not a one-way street. **SM**

Contact Jessica Shugart at medmag@stanford.edu

A RARE TYPE

STANFORD'S EXTRAORDINARY BLOOD BANK

For 35 years, thousands of hospital patients in the Palo Alto area have directly benefited from the blood provided through the Stanford Blood Center. But because of its research activities, the center also affects the lives of people throughout the world.

Unlike most blood banks, the Stanford Blood Center has a dual mission: to supply blood and blood products to patients, and to engage in research focused on understanding and developing treatments for blood diseases and blood-borne disorders.

Currently, the blood center provides about 100,000 pints of blood and blood components each year to patients at seven hospitals, including Stanford Hospital & Clinics and Lucile Packard Children's Hospital. In fact, the need for a reliable source of highly purified blood for patients at Stanford's two hospitals — many of whom have fragile immune systems — was a motivating factor in establishing the blood center in 1978.

But while blood banking may be the most visible aspect of its work, the Stanford Blood Center is also integrated into the research activities of the School of Medicine. With donors' permission, portions of blood left over from donations are set aside for different types of research. This includes extra tubes of blood not needed for testing, or white blood cells, which are removed to minimize reactions in transfusion recipients. While other blood banks routinely discard the white blood cells, the Stanford Blood Center makes them available to researchers who study their functions.

In some cases, researchers at the School of Medicine who are studying patients with a specific disease may use blood samples from healthy donors as a control sample for an experiment. Or scientists at the blood center may use the samples to test new blood-screening processes.

Some of the current research involving the blood center includes efforts to improve the success of organ transplants. Scientists hope to develop new diagnostic tests that would better identify the degree of genetic match between the donor and the recipient in order to prevent the recipient's body from rejecting the organ. Additionally, they are working to develop better ways of detecting an imminent attack by the recipient's immune system against the transplanted organ.

Other researchers are examining the potential of manipulating dendritic cells (a type of immune cell) to treat cancer and other types of diseases. This approach, conceived of more than 20 years ago by Ed Engleman, MD, director of the blood center and professor of pathology, laid the groundwork for a vaccine approved for use in treating advanced prostate cancer.

And Susan Galel, MD, operations director for the blood center and an associate professor of pathology at the medical school, conducts research to make the blood-banking process more effective and efficient.

"There aren't many blood banks that are involved in research, but it's a critical part of our mission," Galel says.

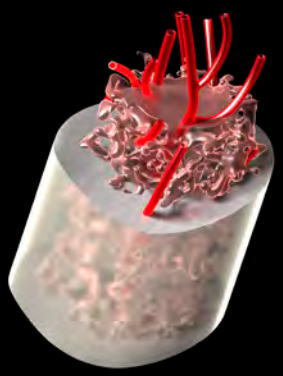
— SUSAN IPAKTCHIAN

LIFE OF BLOOD

A GUIDE TO THE

As you read this sentence, more than 20 trillion blood cells are carrying out widely varying missions to keep you alive. Most of the cells in this horde are red blood cells, stoking your body with oxygen. Other cells stanch blood loss and fight incursions of infectious agents and cancer cells. An average adult's body holds just over a gallon of blood; 45 percent of that blood consists of cells. All told, those blood cells make up more than a quarter of the cells in your body. Each cell plays many roles — in fact, scientists have yet to figure them all out. But if you want to understand how a body works, blood cells are a very good place to start.

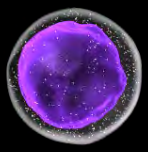
Blood-cell basics: Red blood cells cruise through blood vessels (in red) delivering oxygen to the body's tissues and returning to the lungs for a new load. The other blood cells are platelets, which enable clotting, and many types of white blood cells, which are all important players in the immune system, defending the body against infection and toxins.



Born in bone: Blood cells are formed in the soft insides of bones, called the marrow. Once the cells are mature, they leave through tubes called venous sinuses, which empty into blood vessels. Cells that will become T lymphocytes complete their development in the thymus (orange), a gland resting atop the heart.

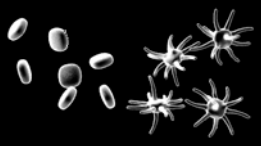
ILLUSTRATION BY BRYAN CHRISTIE DESIGN; SOURCE: WAN-JEN HONG, MD; WRITING AND EDITING: ROSANNE SPECTOR

CELLS COURSING THROUGH YOUR VEINS

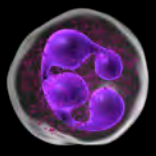


Hematopoietic stem cells are the blood cells' basic model. These simple cells can turn into all of the other types of blood cells.

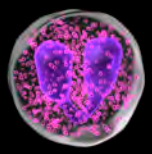
Red blood cells carry the oxygen you inhale to all of the tissues in your body, where other cells depend on oxygen as fuel. They're by far the most common blood cell. When they bind with oxygen, they turn bright red.



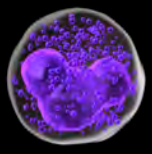
Platelets are fragments of cells that gather at the site of an injury and stick to the wounded blood vessel's lining, creating the foundation for a clot. They also attract other immune cells to sites of injury or infection..



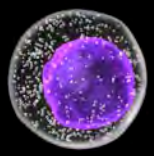
Neutrophils are first on the scene to clean up after bacterial infection or injury. They're the most common type of white blood cell, making up 50 to 70 percent of the total. These cells are a major component of pus, accounting for its yellowish color.



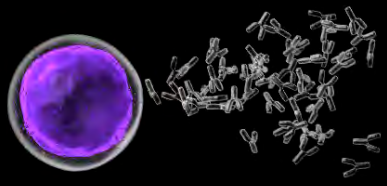
Eosinophils combat multicellular parasites, such as hookworms. They also set off allergic reactions like asthma and hay fever.



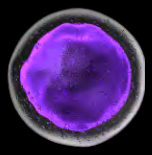
Basophils release chemicals that cause allergic symptoms. Among these are histamine, which spurs blood flow. Like eosinophils, they help fight parasitic infections. They're the rarest of the white blood cells.



Natural killer cells act in a similar way to cytotoxic T cells, killing virally infected cells and tumor cells, but they spring into action faster. Instead of the three days to a week it takes for T cells to act, they go to work within minutes or hours.

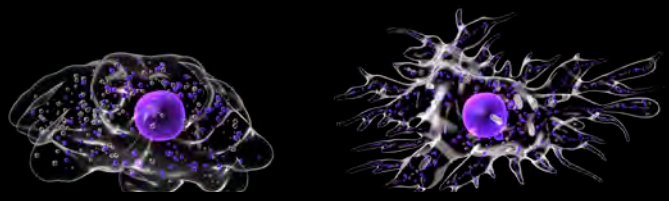


B lymphocytes churn out antibodies, large proteins that can identify and destroy bacteria, viruses and the toxins they make.

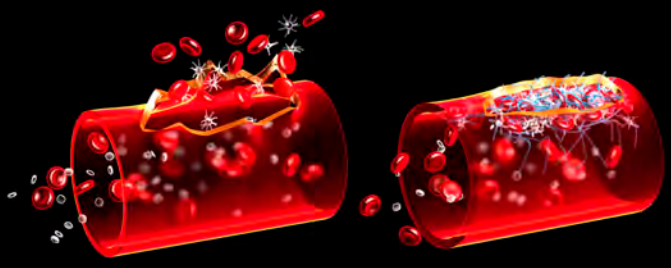


T lymphocytes develop into many different types. Here's a sampling:

- T-HELPER CELLS, also known as CD-4 cells, signal other immune cells to act.
- REGULATORY T CELLS, also known as CD-8 cells and suppressor T-cells, keep the immune system in balance, preventing it from attacking the body's own parts.
- CYTOTOXIC T CELLS release chemicals that kill virally infected cells and tumors.
- MEMORY T CELLS retain an impression of infectious agents they've encountered. If they meet that agent again, they quickly multiply and gear up to respond.



Macrophages (left) and **dendritic cells** surround and destroy bacteria and viruses, essentially eating them up. They also attach bits of the destroyed invaders on their surfaces, which alert the immune system to be on the lookout.



How clotting happens: Platelets gathering at the site of an injury sprout elongated growths on their surface, line the injured blood vessel and clump together to form a platform for clotting. Meanwhile a chain of protein interactions creates fibrin proteins (blue), which mesh with the platelets to stabilize the clot.

BLOOD QUEST

THE BATTLE TO PROTECT TRANSFUSIONS FROM HIV

Ed Engleman, MD, Stanford Blood Center's director, strode briskly into the large lecture hall at UC-San Francisco, eager to describe the screening test he and his colleagues had just developed — a test they thought could help save the nation's blood supply from a looming threat. • It was October 1983, Engleman was 29, and a bizarre, deadly agent was percolating in the population. It had first surfaced among gay men, leading to uncommon cancers, pneumonias and other infections, some of which had rarely been seen before in humans. But the mysterious microbe would soon invade the broader population and present a massive public health threat, becoming an epidemic for all time. The source later came to be known as the human immunodeficiency virus, or HIV — the cause of AIDS. • Faced with the unknown, blood bank officials nationwide resisted Engleman's plea to test blood donors, with the result that at least 20,000 transfusion recipients — surgery patients, hemophiliacs, new mothers and their babies — would become infected with HIV. Few, if any, would be patients who received blood at Stanford, where the screening test likely saved at least 33 people from an AIDS death. • The experience would make him a pariah in the blood banking community and reset the course of his career, which would shift to AIDS. It would also lead to a transformation of the blood banking industry. The blood supply, then

By Ruthann Richter

ILLUSTRATION BY TOMER HANUKA

vulnerable to potentially dangerous agents, would ultimately become much safer, though much more costly to maintain, as a result of the crisis, Engleman says.

The first signs of the new threat emerged in June 1981 in the form of an obscure report from the federal Centers for Disease Control and Prevention. Five gay men in Los Angeles had developed a rare form of pneumonia then known as *Pneumocystis carinii*.

Jeff Lifson, MD, then a medical student at Northwestern University, thought the report was fascinating, but "way too strange" — that it described a rare disease he would never have to deal with in his lifetime. He read it only because it seemed obscure enough that he figured he'd be quizzed on it by his attending the following week.

But this strange disease did not go away, and the number of reports grew, along with public alarm and much acrimonious debate about how to respond. In the spring of 1983, Engleman and Lifson — by then a pathology resident at Stanford and postdoctoral scholar in Engleman's lab — heard from colleagues that two patients had come to Stanford Hospital suffering from early signs of the illness, characterized by unusual infections that generally afflict people with severely reduced immunity.

Neither patient fell into one of the known risk groups of the time, which included gay men with multiple sex partners, Haitian immigrants and intravenous drug users. But when doctors queried the patients about their histories, they discovered they shared one common trait: Both had received blood transfusions.

"We were very anxious to know if our blood bank had been the source," recalls Engleman, who, still at Stanford, continues directing the combined blood bank/blood research center he founded in 1978. "It turned out both had received transfusions from blood that originated in San Francisco."

It was among the early hints that the still-unidentified agent could be transmitted through blood. The previous year the CDC had published a report of a 20-month-old infant in San Francisco with symptoms similar to those seen in ailing adults. The parents had become frantic when the baby boy became sick with a series of strange infections that wouldn't go away; doctors were baffled by the case. The baby had received multiple transfusions shortly after birth, including platelets from a man who seemed healthy when he donated blood but who showed symptoms of the disease eight months later.

"We felt then it was the tip of the iceberg. It was like Armageddon. It was scary," recalls Engleman, a professor of pathology, who was convinced this was a new infectious agent transmissible through blood. The problem kept him up at night; he felt an urgent need to respond to protect patients. But how do you screen for something in the blood when you don't even know what it is?

"We said, 'What can we do? We don't have an agent. We don't have a specific test,'" recalls Lifson, now director of the AIDS and Cancer Virus Program at the National Institutes of Health's Frederick National Laboratory. "The one thing we came up with was that affected individuals had a characteristic anomaly in their T cells," critical immune system cells that fight disease.

> "WE SAID, 'WHAT CAN WE DO?' THE ONE THING WE CAME UP WITH WAS THAT AFFECTED INDIVIDUALS HAD A CHARACTERISTIC ANOMALY IN THEIR T CELLS."

A NEW RESEARCH PROJECT

Engleman, an immunologist, had started the blood center specifically because he wanted to study human immune cells — which include white blood cells such as lymphocytes that course through blood, fighting infection. Blood banks routinely toss out these cells because they can harm transfusion recipients, but for Engleman they were material for his research.

Preoccupied with the disturbing, new, apparently bloodborne disease, Engleman, who tracked the immunology literature, noted that people with signs of the disease had a peculiar immune profile. Normally people have twice the number of a type of lymphocyte called T-helper cells (also known as CD-4 cells) as they do of T-suppressor cells (also known as CD-8 cells). But in people with this new ailment, the ratio was significantly reduced.

What if they just tested donors to see if they had this anomaly? This idea of using a surrogate marker to ferret out an unwanted microbe rather than doing a direct test was a

relatively new concept in blood banking then. Engleman and Lifson did a pilot study in which they screened 100 people — all symptomatic gay men and their partners — to see whether the test would be cost-effective and practical on a larger scale. One of the advantages to being a blood bank embedded in a medical school (an unusual arrangement) is that the reagents and equipment, including a new cell-sorting machine, to do the screening were readily available.

The results of the 10-minute test on the participants were all abnormal. "That suggested they were either carriers or were sick with the disease," Engleman says. He says they concluded it would be cost-effective to do the test, at least in a relatively small center like Stanford's.

Engleman and Lifson decided to present the results to the larger scientific community and prepared for that auspicious gathering, a laboratory medicine grand rounds at UCSF, just over 30 miles to the north. Engleman walked into the large lecture hall expecting to be embraced for his foresight by the several hundred scientists and blood bank officials gathered there.

"I gave this talk thinking that it would be cheered," he recalls. "They would be enthusiastic because it provided the blood bank community with a way to improve the blood supply. But the opposite happened. They were horrified and felt this was the worst thing ever. It was the beginning of a long, painful haul."

Lifson says he doesn't remember the specifics of the meeting, other than the feeling that he'd walked into a lion's den.

"I played quarterback in high school, and I would rather face blitzing linebackers than that audience," he recalls.

Engleman says he was confronted with a series of hostile questions. He was stunned.

"They were extremely critical, publicly so," he says. "They felt that in doing this test we were saying that the blood supply was contaminated…. Ninety-eight percent of people involved in the blood-banking world circled the wagons and argued that there was no proof the disease was spread by transfusions and that screening would create a blood shortage. It had to do with money — the cost of testing. And they didn't like the idea of blood banks being associated with this

ED ENGLEMAN, MD

He thought his blood test for AIDS would be welcomed with open arms.

horrible, scary, deadly illness."

The T-cell test also was impractical for most blood centers because the cell-sorting machines, now a staple in research labs around the world, were at that time expensive and rare.

CLASH OF THE BLOOD BANKS

The talk followed another highly contentious gathering in January 1983 of the blood bank working group at the CDC in Atlanta — a microcosm of the debate that was raging throughout the nation. Dozens of scientists and leaders from the National Institutes of Health, the CDC, New York and San Francisco health departments, the blood banks and the gay community arrayed themselves around a large square table to wrangle over whether the new agent could be transmitted through blood. By this time, there had been isolated reports of patients thought to be infected through transfusion, including seven hemophiliacs and the baby in San Francisco.

Few realized then they were dealing with a different kind of biological threat — one in which a person could be an infectious carrier but show no symptoms, resisting active disease for years. By the time of the working group's meeting, the CDC had received reports of nearly 900 documented cases of AIDS, though there were many thousands more people who were infected and didn't know it.

The scientists and blood bankers argued over the value of surrogate tests and whether they were needed. And though gay men were among those at high risk, blood banks had never asked donors about their sexual preferences and didn't want to tread into that delicate territory. Moreover, they believed that asking donors if they were gay would be useless and possibly even counterproductive.

Donald Francis, MD, PhD, a leading CDC virologist and expert on epidemics, had been convinced early on that the mystery disease was caused by a new virus. He banged on the table, saying, "How many people have to die before you blood bankers have to do something?" recalls Herbert Perkins, then medical director of the Irwin Memorial Blood Bank in San Francisco, now part of the Blood Centers of the Pacific.

Perkins says the atmosphere at the CDC meeting was chaotic. "There was no agreement about anything," he says. "It was a mess in all directions. Everybody was worried about what to do, but we knew so little and didn't have the right tools."

Because the disease then was prevalent among gay men, Perkins, now 94 and a senior research scientist at the blood center, says he initially dealt with the problem by meeting with leaders of the gay community, asking them to get out the message that gay men should refrain from donating. The San Francisco center also devised a new donor questionnaire listing gay men with multiple partners and injection drug users as risk groups; potential donors could check a box and discreetly exclude themselves.

The American Association of Blood Banks, or AABB, a 2,400-member group of nonprofit blood centers, likewise recommended that blood banks hand out information identifying the risk groups and discouraging at-risk people from donating. It did not recommend use of any kind of laboratory screening tests, with the result that most blood banks did not screen blood supplies at all during that critical period of time. Still unconvinced of the threat and concerned about the economic and public relations impact, the AABB, the American Red Cross and the Council of Community Blood Centers also issued a joint statement, based on the U.S. Public Health Service estimates, which assured the public that the odds of getting infected from a transfusion was "one in a million" — a statement that would later prove tragically wrong.

GOOD ENOUGH

Meanwhile, Engleman, impatient and angry at the blood banks' head-in-the-sand approach, bucked the trend and began using the surrogate T-cell test to screen all blood supplies, beginning in July 1983. Stanford thus became the first U.S. blood bank to screen for HIV. The blood center then had some 20,000 donors a year; those samples that did not pass muster were frozen for future testing.

Engleman also submitted an abstract on the T-cell test for presentation at the AABB meeting later that year. Though abstracts are routinely accepted for the meeting, this one was not; Engleman received a form letter of rejection, which he kept for

ENGLEMAN BUCKED THE TREND AND BEGAN USING THE SURROGATE

T-CELL TEST TO SCREEN ALL BLOOD SUPPLIES, BEGINNING IN JULY 1983.
STANFORD THUS BECAME THE FIRST U.S. BLOOD BANK TO SCREEN FOR HIV.

"I FELT THE BLOOD BANKS WENT AGAINST SCIENCE AND RATIONAL BEHAVIOR BECAUSE THEY REFUSED TO USE OUR TEST OR OTHER TESTS, LIKE THE HEPATITIS B TEST."

posterity. In his mind it was yet another indicator of the industry's unwillingness to come to grips with the problem.

At that time, Stanford Hospital & Clinics received much of its blood from Peninsula Memorial Blood Bank in Burlingame, not the Stanford Blood Center, says Susan Galel, MD, then a postdoctoral scholar in pediatric hematology/oncology in Engleman's lab. Because of the hospital's safety concerns, she says the Stanford center ramped up its production to become the hospital's primary supplier. At the same time, the hospital notified Peninsula Memorial that its supplies would no longer be accepted unless the center screened blood with the T-cell or other surrogate test, says Galel, now the Stanford Blood Center's director of operations. Peninsula Memorial complied by adopting a test that detects antibodies to hepatitis B, which at the time was seen as another way to screen indirectly for AIDS.

The hepatitis B test then was also the focus of hot national debate. The test indicates exposure to hepatitis B, though not necessarily infection. Early CDC studies had shown that more than 80 percent of patients with AIDS also had hepatitis B antibodies. In early 1983, the U.S. Public Health Service recommended blood banks evaluate the test as a way to screen out donors with AIDS.

San Francisco's Irwin Memorial began evaluating the hepatitis test for this purpose in 1983, but its initial study indicated it wouldn't be useful in San Francisco, in part because of its large Asian population. Hepatitis B exposure is common among Asians.

Irwin officials also were worried about the test's high rate of false positives, which could create donor hysteria, as well as the likelihood that screening would attract people who wanted the test to find out whether they had AIDS — which as a result could pump more infected blood into the supply, says Michael Busch, MD, PhD, now director of the Blood Systems Research Institute at the Blood Centers of the Pacific.

Perkins at Irwin initially had this same concern but by the spring of 1984 most gays in San Francisco had stopped donating, and the blood bank felt it was safe to introduce the hepatitis B test, he says.

Some Bay Area blood banks followed suit in implementing the hepatitis B test, but others around the country did not. One of the few blood banks to use a screening test was Tulane University, which adopted the Stanford T-cell technique.

Meanwhile, Stanford was starting to get some validation for its approach. Eight months after it began using the T-cell test, Lifson says he got a call from a doctor in Southern California who was treating a man dying from Kaposi's sarcoma, a rare skin cancer often seen in particularly aggressive form in AIDS patients. The patient said he had donated blood at Stanford and elsewhere. Lifson was able to trace back the Stanford donation to a unit donated within the first few weeks of the screening program and found to have a dramatically abnormal T-cell profile; the unit had been withheld from transfusion because of the abnormal result.

"My response was, 'Boy, I'm glad we pulled that unit,'" Lifson recalls. "We were using a test that we knew was not completely specific, and many of the units we were withholding were not going to be from people with AIDS, but by losing 1.5 percent of our donated units, we felt we had a good chance of reducing the risk. We thought that was worthwhile, and having that case was validation for that."

Ultimately, the blood bank ended up discarding 586 donations that did not pass muster, Galel says. When a federally approved screening test became available in 1985, Stanford was able to confirm that 11 of those donations — or 1.9 percent — were positive for HIV. Because each unit of donated blood is typically divided into three components — red cells, plasma and platelets — for transfusion into different patients, the removal of those 11 HIV-infected units potentially saved 33 people from an AIDS death, Galel says. It's quite likely additional lives were spared as most donors give blood repeatedly, and some with abnormal tests were deferred from future donation, Engleman says.

Although the T-cell test was not that specific, as some critics would note, and some "good" blood was wasted, he says he believes it eliminated the majority of the contaminated donations.

CONTINUES ON PAGE 51

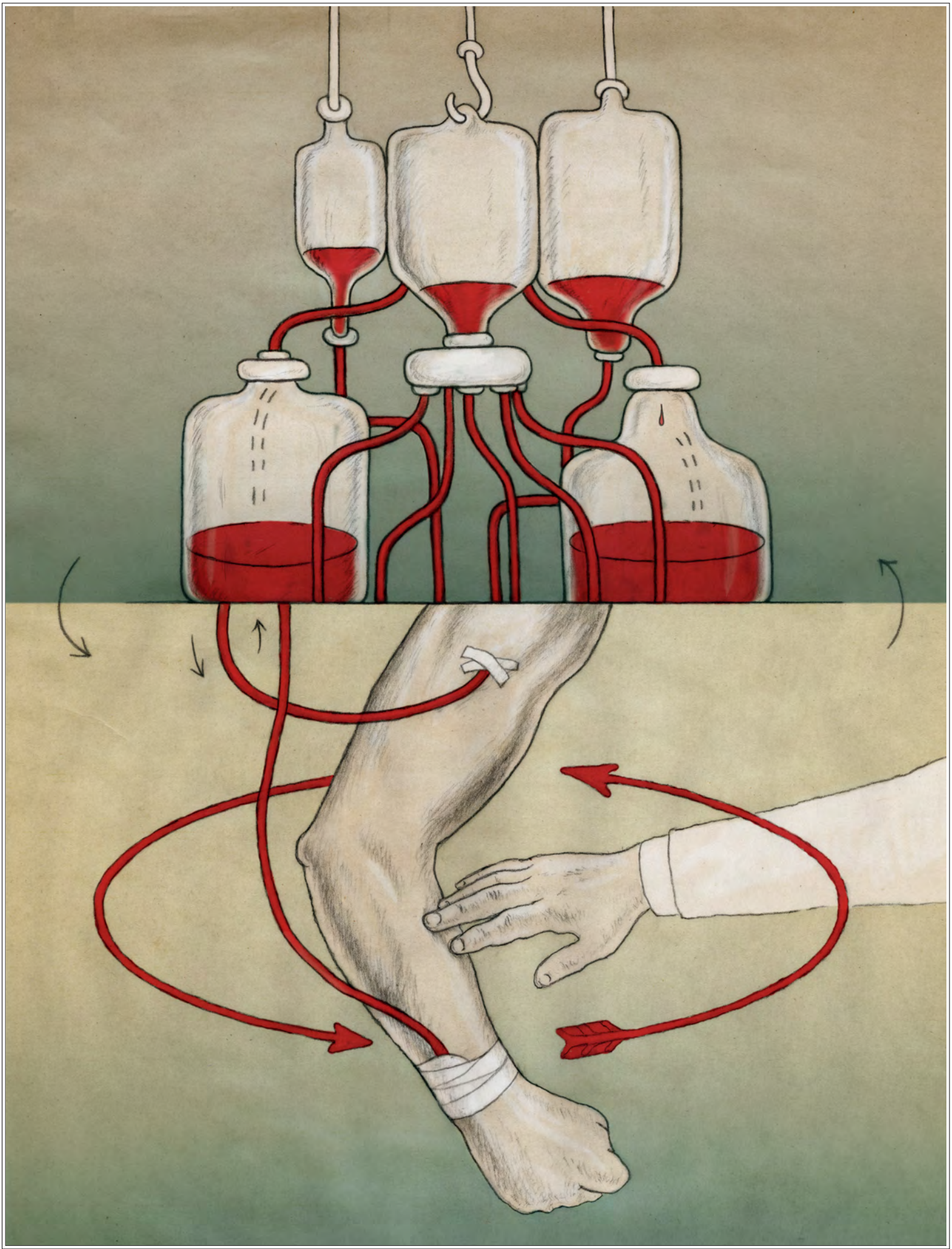
against THE FLOW

WHAT'S BEHIND THE DECLINE IN BLOOD TRANSFUSIONS?

One day in 2011, an ambulance pulled up to the Stanford emergency room and paramedics unloaded a man in his 30s who had crashed his motorcycle. He was in critical condition: Tests showed dangerously low blood pressure, indicating that around 40 percent of his blood was lost. And an ultrasound revealed that the blood was collecting in his belly, suggesting that one or more of his abdominal organs was the source of the blood loss. • Paul Maggio, MD, a trauma surgeon and co-director of critical care medicine at Stanford Hospital & Clinics, sped the patient into the operating room. But he made sure that the technicians prepping his operating room took the time to set up one key piece of equipment, called an intraoperative cell salvage device, which is now commonly used in trauma cases. As the patient lay on the operating table and Maggio made the first cuts into his abdomen, suction devices slurped up the loose blood, directing it away from the surgery site through tubes. But instead of leading to a container bound for disposal, the tubes led to the salvage device. • The ATM-sized machine spun the blood to separate its components, cleaned it of any debris that had been suctioned up from the abdomen and sent it back out into fresh bags. From there, the blood was shunted right back to the patient's body, through intravenous tubes poking into his veins. The cell salvage device has been around for decades, but only recently has evidence emerged that autotransfusion — giving patients their own blood instead of blood from donors — leads to better surgery outcomes. As a result, the use of the machines has gone from extremely rare to commonplace. Today, hospitals that have the machines use them in many scheduled abdominal and heart surgeries and routinely in trauma cases involving massive bleeding.

By Sarah C.P. Williams

ILLUSTRATION BY JONATHON ROSEN



"Autotransfusing this patient spared him from getting more banked donor blood and from all the risks associated with it," says Maggio of the motorcycle crash victim. He turned out to have an injury to his spleen, which Maggio repaired. In all, around 2 liters of blood were collected from the patient's abdomen, processed through the salvage device, and transfused back into his body.

Blood transfusions involve routing a needle into one of a patient's veins — most often in an arm — and attaching a thin tube to the needle. Blood flows through the tube directly into the patient's blood vessels. Ten years ago, a patient like Maggio's would most likely have had a transfusion of blood donated by volunteers at the Stanford Blood Center. But over the past decade, a growing body of research has revealed that in hospitals around the world, donated blood is used more often, and in larger quantities, than is needed to help patients — both in operating rooms and hospital wards.

Some of the research has been conducted by physicians working with patients who refuse donated blood on religious grounds; other findings have come from the front lines of the war in Afghanistan, where blood is hard to transport; and some studies have been inspired simply by the rising cost of blood and a desire to save resources. Some findings are new, and others, like studies by Stanford's Tim Goodnough, MD, a hematologist and the director of transfusion services, are years old but only recently being noticed. The takeaway message from all is the same: While blood is precious and continues to save lives, its use can be minimized and fine-tuned to optimize patients' health and reduce costs.

The American Medical Association brought attention to the subject last fall at its national summit on the overuse of five medical treatments. Blood transfusions were on the list (along with heart stents, ear tubes, antibiotics and inducing birth in pregnant women).

"From the clinical standpoint, I'm not really thinking about resources or cost," says Maggio, who's also an assistant professor of surgery. "I'm thinking about giving the patient the best care." Donated blood carries risks, albeit very slight, of infection and setting off an immune reaction. But research is also showing that even when these drastic outcomes are avoided, there's something else about donated blood — which scientists don't fully understand — that could slow recovery time or increase complications.

While autotransfusion for trauma patients is growing, and guidelines for blood transfusions are changing in response to this new research, altering the protocols that doctors have been using for so many years is a slow process.

CHANGING THE ROUTINE

At Stanford, it took an innovative new program that used alerts on doctors' computer systems to enforce fewer blood transfusions. But the push paid off: Blood use in the operating rooms, emergency rooms and hospital wards of both Stanford and the Lucile Packard Children's Hospital has declined by 10 percent in just a few years. At Packard Children's alone, 460 transfusions and $165,000 were saved in one year, according to a pilot study conducted Feb. 1, 2009, through Jan. 31, 2010.

"I think we're probably still giving too much blood in some of these situations," says Maggio. "But we hope that physicians are becoming better informed about when to give blood."

People most often need blood transfusions when they're in one of three situations: They lose blood from a major surgery that's been scheduled for weeks or months; they lose blood in a way that their body won't be able to replace, such as a blood cancer that shuts down the body's ability to make blood cells; or they lose blood during a more sudden trauma — either an external wound or internal bleeding.

"For that first group of patients, scheduled for elective surgery, if you can plan ahead, you should be able to avoid using blood," says Goodnough, a professor of pathology and of medicine. In those patients, drugs can boost a patient's own blood production ahead of surgery, blood can be collected from a patient ahead of time to re-infuse later, precautions can be taken to prevent sudden blood loss, or autotransfusion machines like the cell salvage device can be set up. "Where we still need a national blood inventory is for patients who

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>
> PATRICIA FORD, MD
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can't plan ahead," says Goodnough.

In the cases where physicians continue to give blood when it might not be needed, it's often because they can't imagine not doing everything they can to help a patient — and blood has always been viewed as having far more benefits than risks in almost any population of patients. But now, that risk-benefit analysis is changing.

"There's this idea ingrained in the culture of medicine that people will die if they don't have a certain level of blood, that blood is the ultimate lifesaver," says Patricia Ford, MD, founder and director of Pennsylvania Hospital's Center for Bloodless Medicine and Surgery at Penn Medicine. "And that's true in some specific situations, but for most patients in most situations it's just not true." Ford's center is one of the oldest and largest in the country that specializes in treating patients without donated blood; dozens of others have been created over the past decades but mostly at a smaller scale.

GOING BLOODLESS

Every year, Ford treats or operates on around 700 Jehovah's Witnesses, whose religion prohibits transfusions of blood that is not one's own. Since 1996, she has been fine-tuning ways to give these patients the best care as well as ways to apply these techniques to the broader population.

"Many physicians I talked to at the beginning had this misperception that a lot of patients just can't survive without receiving blood," says Ford. "I may have even thought that myself to some degree. But what I rapidly learned was you can care for these patients by just applying some easy strategies."

In fact, a study published in August 2012 by researchers at the Cleveland Clinic concluded that Jehovah's Witness patients recovered better from heart surgery than patients who received blood transfusions. It's the longest study conducted on such patients — the researchers followed them for up to 20 years. The Jehovah's Witness patients had higher five-year survival rates, fewer heart attacks following the surgery and fewer complications including sepsis and renal failure. The better outcomes might not have been due to the absence of transfusions but to differences in care received — the patients were more likely to be treated for low blood levels before surgery by receiving iron supplements and vitamins, and every patient's surgery included use of an intraoperative cell salvage device. The findings suggest that these methods employed for bloodless surgeries could help patients beyond the Jehovah's Witness community.

At Pennsylvania Hospital, Ford has discovered that, for scheduled surgeries, one of the best ways to avoid the need for blood transfusions is to test patients' levels of hemoglobin — the protein in red blood cells that carries oxygen — well before their surgery. If the levels are low, then the patient can take vitamin K and iron supplements, which help the body produce more blood cells and help red blood cells more efficiently carry oxygen throughout the body. The practice of testing for low red blood cell levels, or anemia, is now beginning to spread from specialized clinics like Ford's to other hospitals around the country.

"Testing for anemia was just not on people's radar screens, because they knew that they could always give the patient blood," says Ford. Now, many doctors consider testing a patient's blood cell levels just as important as testing their heart and lung health before surgery. This shift is supported by studies such as an October 2012 analysis in the *Annals of Thoracic Surgery* of the outcomes of more than 17,000 heart surgeries, which found an increase in stroke, death during surgery and death after surgery when patients were anemic before surgery.

At Stanford, standard pre-surgery tests include blood counts for patients who are expected to lose large amounts of blood, says Goodnough. If anemia is suggested by the results, clinicians aim to manage the condition before surgery.

At Penn, Ford also emphasizes the conservation of blood during surgery, often by using an intraoperative cell salvage device. Patients can also donate blood in the weeks leading up to a scheduled surgery and their own saved blood — called an autologous donation — can be used for a transfusion if necessary. In the 1980s, Goodnough studied the usefulness of autologous donations in different patient population groups and pushed for its broader usage. It's now considered a mainstream way of reducing the need for donated blood. "It sounds like a mundane concept now, but it was quite progressive when we first started looking at it," says Goodnough.

Among Ford's lessons with the Jehovah's Witnesses, she says that perhaps her most important has been that there's no magic hemoglobin number that tells doctors when a patient will start exhibiting signs of anemia. Typically, doctors consider hemoglobin above 12 to be normal, and hemoglobin below 7 or 8 to indicate the need for a blood transfusion. But Ford and a growing number of other doctors think those numbers could be pushed down further, a change that would require new studies for many to adapt.

"It's not unusual for me to see a patient who has a hemoglobin of 5 and they look as healthy as anyone walking down the street," says Ford. Of course, there also can be patients who become sick with much higher hemoglobin levels, but Ford would like to see more doctors treating blood levels based on symptoms, not a number. Goodnough agrees: "It's really hard to demonstrate at what level of hemoglobin a transfusion will help a patient," he says. "And we're increasingly seeing that for most patients, hemoglobin has to be

exceptionally low to have effects." But it depends more on the patient's health and risk factors, he says. There's no one-size-fits-all solution.

APPLYING LESSONS

Beyond learning from Jehovah's Witness patients who receive no donated blood during surgeries, the past decade has seen the first controlled trials in the broader population to test whether limiting blood transfusions — though not eliminating them entirely — affects outcomes. The first large trial to test whether allowing patients to have lower levels of hemoglobin was harmful was called Transfusion Requirements in Critical Care and the results were published in 1998. Before then, transfusing any critically ill patient with hemoglobin levels under 10 grams per deciliter was considered appropriate — even necessary — treatment. But the trial looked at the outcome of 800 patients in intensive care units and found that there was no difference in patients' health over 30 days if the transfusion trigger was 7 instead of 10. Moreover, the amount of blood used by an ICU was halved when the trigger was lowered. But the findings applied only to a specific patient population.

"What was happening in the community is that everyone was focusing on this one initial study but it was done on ICU patients only," says Jeffrey Carson, MD, of Robert Wood Johnson Medical School. "We figured those results really needed to be replicated in other patient populations."

So Carson and his colleagues launched a new study, following more than 2,000 surgical patients who had hemoglobin levels less than 10 after hip surgery and had accompanying cardiovascular disease, making them a higher-risk population. Once again, they found that neither death nor complication rates increased with a more restrictive transfusion strategy. The results were published in the *New England Journal of Medicine* in 2011. In Carson's trial, one-third the amount of blood was used in hospitals when the transfusion trigger was dropped from 10 to 7.

But more studies are still needed. "The question is, how low can you go?" Carson says. If 6.5, or even 6, is as good a trigger as 7, blood is still being transfused unnecessarily.

At Stanford and Lucile Packard Children's Hospital, physicians including Goodnough spearheaded that next step — enforcing less blood use — by creating a unique method of nudging doctors to change their ways.

An analysis at Stanford revealed that more than two-thirds of patients with hemoglobin levels over 8 grams per deciliter were receiving blood transfusions. "It led us to believe we were heavily overutilizing blood," says Goodnough.

Now, if a Stanford doctor tries to order a blood transfusion for a patient with hemoglobin levels over 8, a pop-up alert appears on the computer, reminding the doctor of the latest guidelines on when to transfuse blood (the AABB published guidelines in July 2012 recommending transfusion only below a hemoglobin level of 7 for stable patients), and asks questions about the doctor's reason for ordering the transfusion. The doctor ends up cancelling the order 40 percent of the time.

"The system helped people think twice," says Goodnough.

For those 60 percent of incidents in which doctors continue to give blood to patients with a hemoglobin level above 8, the reasoning is occasionally based on a patient's symptoms — if they don't have stable vital signs, for instance, there is evidence that a transfusion could help them. But in many cases, it's simply physician preference; doctors want to stick to the protocols they have been using for years, even though they may be outdated.

Nationwide there's been a dramatic decrease in blood usage, says Susan Galel, MD, director of clinical operations at the Stanford Blood Center. Some of it is attributed to the economic downturn combined with the rising cost of blood — hospitals can save money by buying less blood — and some of it to more effective blood management and efforts like Stanford's computer system.

In a May 2012 *Anesthesiology* article, Goodnough quoted Richard Benjamin, the chief medical officer for the American Red Cross, as stating in a personal communication that national blood usage had declined 3 percent each of the previous two years, for a cumulative decline of almost 7 percent. The details are not public at this time.

Whatever the motivation for the decrease in blood use, and whatever the pace of the decline, the outcome of using less blood is conserved resources, saved money and — based on the recent studies — improved patient health.

CASES OF TRAUMA

In some emergency situations, though, patients will always need blood transfusions. Despite years of research, no safe substitutes for real human blood have been developed that can help patients in cases of blood loss. Substitutes that showed promise in the 1990s failed in clinical trials after leading to increases in mortality rates and adverse outcomes such as heart attacks, and exciting early prospects have led to disappointment time after time. As recently as the early 2000s, the compound PolyHeme was generating excitement and being tested in phase-3 clinical trials. But the trials were halted in 2006, citing an increase in patient deaths when relying on the blood substitute, and temporarily, at least, closing the door on artificial blood. So today, doctors continue to depend on donated blood from blood banks when they're dealing with major emergency blood loss.

Now if a Stanford doctor tries to order a blood transfusion for a patient with hemoglobin levels over 8, a pop-up alert appears on the computer. "The system helps people think twice."

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STANFORD HEMATOLOGIST, DIRECTOR OF TRANSFUSION SERVICES
AND PROFESSOR OF PATHOLOGY AND OF MEDICINE

Even in these trauma situations, however, where it's clear that the need for blood is not going away any time soon, doctors continue to research the best ways to use blood products to help patients survive: When should blood be given? How much? What mixture of blood components should a transfusion consist of?

"What we're doing is coming up with massive transfusion protocols to help physicians administer blood products in the right ratios," says critical-care specialist Maggio.

While most blood transfusions — those that are discussed above — consist of red blood cells, there are other components of blood that may need to be replaced in patients suffering massive blood loss. So the mixture typically given to trauma patients has three ingredients: red blood cells, plasma (the liquid part of blood that contains not only water, but sugars, proteins, fats and salts) and platelets (fragments of cells that help blood clot).

And for patients who need these fine-tuned mixtures of blood, it's not always the case that less blood is better. Instead, it's a matter of recognizing when a patient does need massive amounts of blood and determining how it's best administered. In the past, Maggio says, a doctor's first priority when seeing a patient who had lost a large amount of blood was to provide a solution mimicking the fluid component of blood — not the blood cells. But recent studies have shown that for patients requiring large volume resuscitation, administering blood cells should be a higher priority than fluids. So Stanford has a new system to make that possible.

When a patient with major blood loss is seen in the emergency room, doctors can immediately activate the massive transfusion protocol, says Maggio. "A cooler of blood comes down to the ER containing six units of packed red blood cells, four units of fresh frozen plasma and one pack of platelets." This ratio of red blood cells, plasma and platelets approximates whole blood. Data from the military suggests that survival is improved in patients who received the components at ratios similar to blood, but studies have yet to show whether switching to whole blood, rather than mixing the components, shifts that benefit. "A lot of these changes to transfusion practices in trauma are actually based on military data coming out of Afghanistan and Iraq," says Maggio. "And we're now applying it to the civilian population."

At Stanford, trauma doctors are also adopting blood reuse protocols such as those that Ford uses at Penn. For major trauma patients, like the motorcycle crash victim he saw last year, the cell salvage device is critical, Maggio says. And it's routinely set up for every case of major trauma at Stanford. "For cases where I suspect there may be a large amount of blood loss, I also call ahead and make sure it's set up," Maggio explains. Once surgery has begun, it's too late to set up the device, since the majority of blood is cleaned out of the surgery site immediately after the first incision, he says.

And for many trauma patients, and others who need a transfusion in an emergency, it's still true that blood is a lifesaver. The more than 50,000 blood donations through Stanford Blood Center each year are key to saving many lives.

But for patients whose hemoglobin levels are borderline and appear healthy, doctors are thinking twice about whether the cost and risks of blood transfusions are worth it. "Physicians don't understand well the benefits of blood transfusion. We're pretty sure it saves lives but that's never been demonstrated for the FDA," says Goodnough. "There's never been a prospective trial demonstrating that blood saves lives."

Such a trial will likely never happen, at least in the full-blown sense, but the studies of Jehovah's Witnesses and the lack of ill effects from lowering the transfusion trigger point have made it clear that in some cases the human body can recover from low blood levels by relying on its own, natural mechanisms for blood replacement.

So when Goodnough sees patients in the hospital wards, he does what every doctor is trained to do: judge patients' health through not a single number or test, but by a combination of factors, including patients' own reports of how they feel. Hemoglobin levels are only one part of the puzzle as to how someone's body is operating, and transfusions of blood are only one possible course of action if symptoms do suggest low blood levels. **SM**

Contact Sarah C.P. Williams at medmag@stanford.edu

I awoke close to midnight. It was the middle of August, in 1992, and the windows were open in the room of the Paris hostel where I was staying. The air was warm and still. My chest felt moist with — sweat? I touched the substance with an index finger and pressed it to my thumb. It felt tacky. **Blood!**

I put on shorts and flip-flops and walked down a flight of stairs to the men's bathroom. There, I stood in front of a mirror and contemplated the thin, crimson paste that covered my chest. I ran a hand through it like finger paint, searching for the source. Had I scratched a mole? I was starting to feel nauseated. I opened a faucet and splashed water on my neck, shoulders and torso. I patted myself dry with a paper towel, which soon was covered in damp, pink blotches. Pale and sweating, I turned toward the door, grasped the handle and twisted it. Stepping into the hallway, I collapsed.

BLOOD, SWEAT AND FEARS

A COMMON PHOBIA'S ODD PATHOPHYSIOLOGY

By John Sanford

ILLUSTRATION BY MATTHEW WOODSON
PHOTOGRAPH BY ERIN KUNKEL

A specific phobia is an anxiety disorder in which the presence or anticipation of an object, animal or situation provokes intense and irrational fear. Approximately 12.5 percent of American adults will suffer from at least one such phobia at some period in their lives, according to the National Institute of Mental Health. Where I work, one of my colleagues suffers from a phobia of spiders. (She underwent therapy for the condition several years ago, which helped.) Another colleague has a phobia of riding in elevators and, whenever possible, will take the stairs. Yet another is phobic about driving over bridges.

A phobic reaction starts in the brain but instantly affects other parts of your physiology: Heart rate and blood pressure increase as the sympathetic nervous system activates the body's fight-or-flight response. Some people may sweat, tremble and feel their muscles tense and heart palpitate.

But blood phobia and its next of kin, injury phobia and injection phobia, are different. (*The Diagnostic and Statistical Manual of Mental Disorders* groups these phobias together as blood-injection-injury phobia, or BII.)

Observing blood seep from a wound, flow into a syringe or spatter on the ground, blood phobics initially will respond like other phobics — that is, their heart rate and blood pressure will increase. But then something else will happen: Their heart rate and blood pressure will suddenly drop, causing dizziness, sweatiness, tunnel vision, nausea, fainting or some combination of these symptoms. This is a vasovagal response. The vagus nerve, a component of the parasympathetic nervous system, meanders from the brain stem through the neck, chest and abdomen. It helps to control involuntary "rest and digest" functions, such as lowering heart rate and promoting the secretion of gastric juices. But when it overreacts — in response to hunger, dehydration, standing up quickly, standing too long, intense laughter, sudden fright, severe coughing, pain, vomiting and, of course blood, among other triggers — it causes a vasovagal response, which does not generally occur with other phobias.

Blood-injury-injection phobia is a fairly common psychiatric disorder: Studies estimate 3 to 4 percent of the population suffers from it. But why would the sight of blood, or for that matter the sight of being stuck by a hypodermic needle, trigger a physiological response that is so different — practically diametric — to that of other phobias? This is the mystery.

When I woke up, I was lying on my back on the tile floor of the hall outside the bathroom. My body felt heavy and relaxed. An oval ring of faces — fellow students on my study-abroad program — peered down at me. Someone told me my forehead was bleeding; it must have happened when I fell. I didn't feel like moving. I felt like sleeping on the floor. But I was bustled into a tiny car and driven to a nearby hospital, where I underwent a series of evaluations by a group of medical residents. No big deal, I told them, in amateurish French. I had just eaten poorly that day and was probably dehydrated, too. But the thought of the blood nagged me. I never figured out its source, but I was fairly certain it had played a role in my fainting episode.

A couple of years later, I confirmed my hypothesis after reaching beneath the kitchen sink at my parents' home in Santa Cruz, Calif., to take out the garbage. I sliced my finger on an unseen lid of a can nestled in the refuse. As blood dripped down my finger, I lay down on the living-room carpet, sweating through my clothes. Had I remained standing, I probably would have fainted. Since then, I have felt nauseated at the

sight of blood on several occasions and fainted on another. But what I have always found puzzling about my phobia is this: I'm not consciously afraid of blood; it just makes me feel sick.

So I was intrigued to learn that some researchers have hypothesized that disgust sensitivity may play a role in triggering the vasovagal response in blood phobics. But what little research has been done on the disgust-fainting relationship has yielded mixed results. And one of the most recent studies on the subject, based on a sample of 361 blood donors and published last year in the *Journal of Behavior Therapy and Experimental Psychiatry*, found no connection between disgust sensitivity and vasovagal symptoms.

Other researchers have suggested that fainting at the sight of blood may be the vestige of tonic immobility — playing dead — that is still observed in many animal species when confronted with specific fears. "This 'emotional fainting' could be a physiological activation of a specific evolutionary reflex rather than an acquired cultural phenomenon," according to a 2001 study in *Circulation*.

Still others have suggested that blood phobia bestowed an evolutionary advantage: If, while hunting mammoth, you accidentally stabbed your foot with the tip of your spear, low blood pressure may have reduced blood loss and ultimately increased your opportunity for future reproductive activities. Studies show that slightly more than 60 percent of blood phobics' first-degree relatives also have the phobia, suggesting there may be a genetic component to the disorder. (My brother has become dizzy and sweaty at the sight of blood, though he has never fainted.)

Yet blood phobia presumably would not — at least in modern times — provide much in the way of selective advantage. Emergency medical responders generally can reach you quickly and stanch bleeding. And if you faint, you can sustain a worse injury by falling. The more useful question, it seems, is how to stop from fainting in the first place.

WHAT I HAVE ALWAYS FOUND PUZZLING ABOUT MY PHOBIA IS THIS: I'M NOT CONSCIOUSLY AFRAID OF BLOOD; IT JUST MAKES ME FEEL SICK.

In the early 1980s, a Swedish psychologist named Lars-Göran Öst read a case study, published in the British journal *Behavioural Psychotherapy*, that intrigued him: The study's authors, Michael Kozak and George Montgomery of the University of Wisconsin-Madison, had instructed a 21-year-old woman with a history of fainting at the sight of injuries to tense her muscles as a way of coping with such visual stimuli. The tensing increased blood pressure and cerebral blood flow, preventing her from fainting. The authors noted that earlier studies had reported the use of leg exercises and "fantasy-provoked anger" to accomplish the same goal. Yet Kozak and Montgomery wrote that the value of such exertion "probably lies in its allowing prolonged exposure to the eliciting stimulus, thus allowing adaptive relearning to occur." In other words, they viewed the technique as a tool for assisting treatment rather than the main engine of treatment.

Öst and a colleague, Ulf Sterner, conducted a study in which blood phobics tensed their muscles in response to blood stimuli. The results, published in the paper "Applied Tension: A Specific Behavioral Method for Treatment of Blood Phobia," showed that the relatively short treatment sequence — five one-hour sessions — led to marked improvement. First, participants practiced tensing muscles in their arms, torso and legs for 10 to 15 seconds, until they began to feel their faces flush. Then they did this while observing slides and videos of blood and, later, while observing blood withdrawal. Finally, they used the applied tension technique while watching live thoracic surgery. At the end of the treatment sequence, the participants watched a 30-minute video of a thoracic operation. Every one was able to watch the entire film without fainting or, for that matter, experiencing any vasovagal reaction, the study says.

In 1991, Öst and some colleagues compared vari-

JOHN SANFORD

Blood phobic no more.

ous techniques for treating blood phobia: applied tension, in which participants tensed while exposed to blood stimuli; tension only; and exposure only. The results were dramatic: 90 percent of the applied-tension group and 80 percent of the tension-only group showed improvement, compared with just 40 percent of the exposure group. These findings indicated that the coping skill — tension — was the crucial component, the researchers wrote.

I called Öst at his home in Uppsala, Sweden. He is on the faculty of Stockholm University. "I was surprised at how effective applied tension was," he says. "Having worked earlier with other coping techniques, we supposed the patient would use the technique post-treatment, when they were watching the thoracic surgery film. We were astonished when more than half the patients in the applied-tension group said they hadn't used it while watching the film. When we asked why, they said they hadn't needed to. They said, 'If I had the symptoms, I knew I had an effective technique I could use.'"

He continues: "In some ways, it seems they got a boost of confidence by learning this technique and were no longer afraid that they would suffer the symptoms yet be unable to do anything about it."

Craig Barr Taylor, a professor of psychiatry at Stanford's medical school, has treated many phobics, including my colleague with the spider phobia. He is the director of the Stanford Hospital & Clinics anxiety disorders clinic, which is where I met him, in his office, last fall. He has a ring of white hair and a white mustache, and he looks relaxed and vaguely amused. I had arranged the meeting with him to undergo a session of applied-tension therapy. The blood-injection-injury phobics whom he had treated before were mainly patients who needed to give themselves shots, such as diabetics. "But I also really do see a public health benefit to this therapy," Taylor says. "Blood donation is important for society."

Treatment for most phobias, he explains, is done by gradually exposing people to the objects of their fears. For example, arachnophobes will first sit in a room with a plastic spider on the table. Then a dead daddy long-legs in a jar will be placed on the table. Then a live daddy long-legs in a jar. Then the patient will touch the jar with a ruler. And so on until the patient can actually hold a spider in his or her hand. Often the patient will perform deep breathing and other relaxation techniques during the exposure therapy. "When the brain looks at something it fears under conditions of perceived safety, it will habituate to that fear," Taylor says. "It's one of the most profound and important parts of our biology."

"SQUEEZE YOUR FEET AND YOUR LEGS, YOUR HANDS AND YOUR SHOULDERS AND CHEST UNTIL YOUR FACE FEELS FLUSHED. OK — BREATHE."

In applied-tension therapy, exposure is combined with the coping mechanism of tensing muscles. I practice the technique, and Taylor coaches me: "Squeeze your feet and your legs, your hands and your shoulders and chest until your face feels flushed," he says. "OK — breathe. Remember to breathe. Perfect. Now relax." We practice this several more times. He has to keep reminding me to breathe normally, which I find difficult to do while tightening my muscles at the same time. Soon I feel the itchy sensation of sweat forming at the top of my forehead.

Next, Taylor shows me an image, on his computer, of a dark-orange dot. It does not look like blood, but I look at it while tensing my muscles for 10 seconds. No problem. "We'll just see your reactions to these and how far you can go," Taylor says.

He tells me to close my eyes as he puts a new image on the screen of the computer. It is a red dot. I tense my muscles. No problem. And so it goes, until I am looking at blood dripping off the cuticle of a nail. Still, no problem. "I love treating phobics," Taylor says, grinning. "It's so wonderful to see people do these exercises and get better quickly. It's so effective."

The Stanford Blood Center on Hillview Avenue, near Foothill Expressway in Palo Alto, is housed in a modern concrete-and-glass building. I drive there a few days after practicing my applied-tension technique with Taylor. I meet training su-

pervisor Mary Hayes, RN, who has worked at the center for 14 years. She teaches nurses and medical assistants how to withdraw blood for donation.

The blood center, which also has locations in Menlo Park and Mountain View, supplies blood and blood components to seven hospitals in the region, helping an estimated 100,000 patients annually. To meet that need, it must collect 200 pints of blood a day.

"A lot of donors, when they are sitting in that chair, they'll look at you and they'll say, 'You know what? I really don't like needles,'" Hayes says. "And I'll look at them and I'll say, 'Honey, you're in the wrong spot.'"

Some experience a vasovagal response simply as a result of parting with a pint of blood, which lowers blood pressure. "You'll look at a donor and think, 'He wasn't that color a few seconds ago,'" she says.

Still, only a small number of blood donors actually suffer a vasovagal response. In such cases, the center's staff generally will tip back the donors' chairs to get their feet in the air and encourage blood flow to the head. "Usually, they recover within minutes," Hayes says. "It's very, very quick."

Drinking 16 ounces of water half an hour before donating blood can help prevent the vasovagal response; water increases sympathetic-nervous-system activation and blood pressure, Hayes says. She also says coughing, which increases cerebral blood flow, is a good coping mechanism.

I walk on to the floor of the blood-drawing area and sit down in a chair next to a middle-aged man. He smiles at me. I ask whether he would mind if I watch him donate blood, and I explain why. Not at all, he says. A few minutes later a needle is inserted into his arm and blood begins to flow into a slim tube. I begin tensing my feet, legs, arms and shoulders. I feel awkward staring at someone while turning red in the face, but I soldier on. I soon realize, after doing the exercise twice for about 10 seconds each time, that I'm not going to feel sick or faint. I relax my muscles and continue gazing at the blood.

I WATCH A GLOBULE OF BLOOD BEGIN TO FORM AND SLIDE DOWN MY FINGER. I TENSE MY MUSCLES AND CONCENTRATE ON THE BLOOD.

Later, I ask Öst, the Swedish psychologist, whether he thinks treating blood phobia was any easier than treating other kinds of phobias. "I don't think that it is possible to conclude that blood-injection-injury phobics, in general, are easier to treat than other kinds of specific phobics," he says.

Was I cured? I wasn't certain. I decide to give myself one final test.

I visit Taylor again, and this time I bring a box of lancets with me. Meeting in his office, I swab my middle finger with some alcohol. Taylor pulls the cap off the end of a lancet.

"Are you ready?" he asks.

"Yes," I say.

It is virtually painless; it feels more like an intense itch than the prick of a needle. I watch a globule of blood form and slide down my finger. I tense my muscles and concentrate on the blood. After about 10 seconds, I relax. I am fine.

"You are amazing," Taylor tells me. "Do you know what you just did? I'm so proud of you. If you can do that, you can do anything."

I wrap a bandage around my finger, thank him and walk out of the office. What surprises me most is the realization I have overcome a physiological response that, until recently, I was pretty sure was out of my control. It feels akin to suddenly discovering you can move an object with your mind. In the process, I tricked my brain into calmly entertaining the sight of blood.

The photo that accompanies this article was taken a couple of months after my last meeting with Taylor. Though I knew the plan for the photo was for me to hold a vial of blood, I didn't bother using applied tension before or during the shoot. I felt strangely nonchalant about the possibility of fainting or feeling sick, my confidence bolstered by all I had done before. **SM**

Contact John Sanford at jsanford@stanford.edu

in his blood

A DOCTOR DRIVEN BY HEMOPHILIA

Not many second-graders manage to clear the school with a single show-and-tell project. But 8-year-old Holbrook Kohrt had a knockout demonstration. Literally. • Kohrt, a hemophiliac, was showing his class how he had learned to give himself lifesaving transfusions of a blood-clotting factor that his body was unable to make naturally. Engrossed in the performance of what was for him a routine occurrence, he was startled by the reaction of others in the room. • "Halfway through, my teacher passed out, as did many of the other students," he says. Because his rural Pennsylvania school was both remote and minimally staffed, the entire school was dismissed for the afternoon. • Kohrt, now an assistant professor of medicine at Stanford with an MD and a PhD to his name, is keenly aware of the importance of healthy blood — mostly because he doesn't have any. He tells the show-and-tell story in a wry tone, acknowledging the inherent comedy in the scene. But it's a rare light-hearted moment in a childhood that was, by any measure, harrowing. As a child in the early '80s, he, like other hemophiliacs, was forced to rely on transfusions from apparently healthy donors to prevent bleeding to death from even minor injuries. But these treatments carried a significant risk of lethal infection. • "From when I was about

By Krista Conger

ILLUSTRATION BY JONATHON ROSEN

PHOTOGRAPH BY ERIN KUNKEL

10 until I was about 15 or 16, I was very aware that my risk of contracting HIV and other pathogens increased with each transfusion," recalls Kohrt. "I was also very aware, though, that without the transfusion, I would die. I watched some of my best friends become infected in this way, and saw them go through the process of dying from AIDS and the stigma the disease carried at that time. The whole experience was very shaping."

All told, about 80 percent of people with severe hemophilia during the early 1980s were infected with HIV, according to the National Hemophilia Foundation. Many of these people died as a result. In 1998, the federal government set up a system of restitution through the Ricky Ray Hemophilia Relief Fund Act for those affected by the slow or inadequate screening of the nation's blood supply.

Kohrt's story is a scrapbook of how treatments for a blood disease have gone from being nearly universally fatal to treatable with routine, safe injections of a recombinant form of the clotting factor. Recent advances in gene therapy, including an ongoing clinical trial at Stanford and elsewhere, have researchers cautiously optimistic that it may one day be possible to provide a permanent cure for patients like Kohrt.

It's also what's led Kohrt to a career in hematology and oncology, and a rare dual understanding of what it's like to be both a bedridden patient and a bedside caregiver. Kohrt has parlayed his experience into a burgeoning career as a physician-scientist with an intensely personal mission: to help patients with life-threatening conditions in any way he can.

"Holbrook has the unique ability to see clinical problems from the patient's perspective as well as a clinician's," says Ronald Levy, MD, director of Stanford's lymphoma program with whom Kohrt has worked to design new clinical trials for patients with that blood cancer. "He's acutely aware that he himself has been the beneficiary of this type of clinical research, and he's eager to bring similar advances to other patients who are suffering."

Hemophilia is firmly anchored in the annals of human history — a fact for which we can thank the British royal family. Queen Victoria passed the mutation that causes the blood disorder, which is carried on the X chromosome, to at least three of her eight children. Those children went on to intermarry with the royal and notable families of Europe and spread the disorder to many descendants, including Victoria's great-grandson Alexei Nikolaevich Romanov.

Hemophilia is a recessive trait, meaning that female carriers of just one defective copy are asymptomatic carriers of the disorder. These women have a 50 percent chance of passing the mutated gene to their children; boys like Kohrt who receive this copy will display symptoms because they have only one X chromosome. There are two main types of hemophilia, categorized by the gene that's disrupted, and the disorder can occur in varying degrees of severity. Kohrt has a severe form of what's known as hemophilia A; his gene for a clotting protein known as Factor 8 is completely non-functional.

But Kohrt's parents, Alan Kohrt, a pediatrician, and MaryLou Kidd, a nurse, knew nothing of Brook's (as they call him) genetic destiny when he was born in 1977. Kohrt's mutated Factor 8 gene had occurred spontaneously; they had no family history of hemophilia. So they were alarmed when their newborn son began to develop large, unexplained bruises all over his body and bled profusely after his circumcision.

"We experienced the same kind of shock and denial when he was diagnosed that all parents feel: This can't be happening to our child," recalls Alan Kohrt, MD, who now chairs the department of pediatrics at the University of Tennessee College of Medicine in Chattanooga and is the senior medical director of the

Children's Hospital at Erlanger. At the time, the family was living in a remote area of Paupack Township in Pennsylvania, where Alan Kohrt was working as part of his enrollment in the National Health Service Corps.

"The most difficult thing to accept was that Brook didn't just have hemophilia, he had severe hemophilia," says the elder Kohrt. "This changed everything for our family, from planning where to go to vacation to learning how to deal with him as an infant crying in the night. Was he hungry, or was there something more serious, like a bleed, happening? And things became even more challenging when Brook became a toddler and started crawling and falling."

Until relatively recently, most people with severe hemophilia died young — sometimes as infants. The best treatment was preventive, and patients sought to avoid any injury or trauma that could cause life-threatening internal or cerebral bleeds. Many sufferers experience spontaneous bleeding into the joints that can cause debilitating pain, swelling and lasting damage. Kohrt wore a helmet to protect himself from injury until he was about 7 years old, and frequently used a splint after a joint bleed. He quickly became a spokesperson for the condition.

"Brook was always a trouper," says Alan Kohrt. "He'd explain to the other kindergartners about his helmet and his condition. After he was born, his mother went to work for the local branch of the Red Cross and in middle school Brook was often featured in ads explaining the benefit of donating blood." At the time, blood, or blood components, from healthy people was the only source of the clotting factors missing in hemophilia patients.

In 1840, physicians at St. George's Hospital Medical School performed the first successful whole-blood transfusion on a person with hemophilia. Whole, healthy blood contains minute amounts of the clotting factors made by the liver of the unaffected donor. This type of transfusion can be slow, dangerous and painful, however, even if the blood types of the donor and recipient are carefully matched. In the late 1950s, physicians began to use fresh, frozen blood plasma — the pale yellow liquid that remains behind after blood cells are removed by centrifugation — which eliminated many of the unpleasant side effects in the recipient. But neither whole blood nor plasma contains a concentration of clotting factors sufficient to completely prevent bleeding, and physicians had to transfuse large volumes for any effect.

In 1977, however, there were other options for Kohrt and his family: a powder called cryoprecipitate, which is collected from the plasma of between one and four blood donors, or purified clotting factor isolated in large quantities from the pooled plasma of hundreds or thousands of donors.

Cryoprecipitate was discovered accidentally in 1964 when Stanford researcher Judith Pool, PhD, tested the composition of the residue left behind in a bag of thawed plasma. It had a high concentration of Factor 8, and it allowed physicians to treat patients with much smaller volumes. In the late 1960s, physicians and researchers had learned to isolate from large batches of plasma purified clotting factors, which were even more convenient to use.

These advances freed for the first time patients and their family members to administer appropriate treatment at home.

"Before this, or if a parent didn't know how to transfuse their child, the family would have to go into the hospital or clinic as often as every other day," says Kohrt. "But when I was about 6 years old, my parents taught me how to give myself infusions. Other families in our small town might have meat or groceries delivered to their homes; we had blood-delivery trucks pulling up filled with giant coolers of cryoprecipitate."

His parents' choice of cryoprecipitate over the purified factors was deliberate.

"We were doing everything we could to make sure that the product Brook received was the safest possible choice," says Alan Kohrt. "We stayed with cryoprecipitate for as long as possible, in part because that comes from one donor, or a limited number of donors. And we treated him only when he had a bleed, instead of giving it on a regular basis."

His parents would keep the cryoprecipitate as a powder

> "OTHER FAMILIES IN OUR SMALL TOWN MIGHT HAVE MEAT OR GROCERIES DELIVERED TO THEIR HOMES; WE HAD BLOOD-DELIVERY TRUCKS PULLING UP ... ."

HOLBROOK KOHRT

Life with hemophilia leads him to seek cures for serious disease.


Eppendorf
J.T.Baker

in the freezer until Kohrt experienced a bleed. As an infant, Kohrt's parents injected him with about 10 to 30 milliliters of the cryoprecipitate-containing solution — a process that could take as long as an hour. As he grew, the volume of the injection grew to around 100 milliliters and Kohrt began treating himself. Eventually Kohrt, who by then was experiencing chronic joint pain and problems, had to accept regular, prophylactic therapy to head off bleeds before they occurred.

"Basically the treatment involved taking in a lot of unpurified blood product," says Kohrt. He relied on cryoprecipitate, which contained multiple blood components other than the Factor 8 clotting factor, and as a result eventually triggered severe allergies. But when he switched to the purified, concentrated form of the clotting factor, the risk of infection was much higher because it was purified from the blood of many more people.

Although the cryoprecipitate and purified clotting factor were lifesaving for Kohrt and others with hemophilia, both carried an unavoidable risk of exposure to blood-borne diseases. By the early 1980s it was clear that hemophilia patients across the nation were contracting hepatitis C and HIV from the pooled plasma, and Kohrt and his parents knew they were playing a deadly game of roulette.

"There was always that apprehension," says Alan Kohrt. "We never knew if that day's treatment was going to be contaminated. But we tried to give him as normal a childhood as possible. I don't know how much of how we all handled it was denial, and how much was us simply praying he didn't get it."

The uncertainty lasted until the mid-1980s, when physi-

fixing hemophilia

REPLACING BAD GENES WITH GOOD

Think about the last time you bled from an injury: While you were cursing and looking for a Band-Aid, the very blood oozing from your wound was also forming a clot to keep you safe. That is, unless you had hemophilia. In that case, a faulty gene for one of the 12 main clotting proteins means your blood would have kept running. • For decades, scientists have pursued the dream of gene therapy for hemophilia, seeking to replace the relevant faulty gene to get a long-term fix. The research appears to be starting to pay off. • Stanford's Mark Kay, MD, PhD, has long been on the front lines of the hemophilia gene-therapy effort. His lab conducted some of the first experiments, starting in the early '90s, on gene therapy for hemophilia B, which is caused by a faulty Factor 9. Though not the most common type of hemophilia (that would be hemophilia A, caused by a defective Factor 8), they chose it partly because the Factor 9 gene is smaller and easier to work with.

In experiments in mice and dogs with hemophilia, he and his colleagues showed that a human virus called adeno-associated virus could be used to insert copies of Factor 9 gene into the animals' cells and reduce or eliminate bleeding. Subsequent tests on humans proved encouraging at first, yet disappointing when the patients mounted an immune response against the viral proteins. Though the death of a patient in a different gene therapy trial, at the University of Pennsylvania, was a severe blow to the entire field, some gene therapy trials continued.

Recently Kay, a professor of pediatrics and of genetics, worked with a team of international collaborators to conduct a trial on six patients in the United Kingdom with hemophilia B using a different version of the virus. The new virus, which was isolated from monkeys, is thought to be less likely to cause an immune reaction in humans.

"It looks promising," says Kay, who conceived of the new vector, conducted early studies and helped design the trial. "Since then, a number of other patients have been treated and, although some do develop a transient immune response, it's been well-controlled with short courses of oral steroids."

Four of the six patients began to produce enough clotting factor after the gene therapy that they no longer needed additional treatment with injected Factor 9. (The other two were able to reduce the amount of external Factor 9 they used.) The results of the trial were published in the *New England Journal of Medicine* in December 2011. Kay and collaborators are now recruiting patients for the next phase of the trial, in which they increase the dose of the virus. Kay's lab is also continuing to experiment with ways to make the virus more tolerable to the immune system.

"I FEEL LIKE MY EXPERIENCES HAVE PREPARED ME TO PROVIDE SOME LEVEL OF EMPATHY FOR MY PATIENTS WHO ARE NEWLY DIAGNOSED WITH CANCER."

cians began to heat the plasma to kill viral contaminants. And in March of 1985, blood banks across the country implemented new screening techniques that vastly improved the safety of the nation's blood supply. *[To learn about Stanford's pioneering role, see page 18.]* In 1984 researchers cloned the gene for Factor 8, and in 1992, the Food and Drug Administration approved the use of what's called a recombinant form of Factor 8. This recombinant form is made by specially engineered hamster cells under laboratory conditions, and eliminates any exposure to the blood of other people.

These changes didn't come soon enough for many of Kohrt's friends, however. As an adolescent, he attended a yearly, weeklong summer camp outside of Philadelphia for children with hemophilia. The camp had hundreds of attendees, and Kohrt made many close friends by teaching his peers how to perform their own transfusions, practicing on oranges and other thick-skinned fruits. As the years passed, however, attendance dwindled.

"About 80 percent of these kids got HIV," says Kohrt. "As a result, there are about 50 percent fewer hemophiliacs alive today than there would have been without HIV. That was a horrible time. It was incredibly difficult at a young age to see all those people who were not as lucky as I was."

Kohrt switched to the recombinant form of Factor 8 as soon as possible, but he didn't escape those early years of uncertainty unscathed. When he was 13 he contracted a severe case of hepatitis C and was hospitalized for six weeks with nearly full liver failure. His immune response rallied and eradicated the virus — an outcome that happens in only about 20 percent of patients with active hepatitis C.

Kohrt's experiences as a patient with hepatitis sparked an interest into how clinicians might jumpstart a patient's immune system to fight other diseases such as cancer and fueled his entrance into medical school, then research. Today Kohrt, together with lymphoma program director Levy, is focused on several ongoing clinical trials for patients with lymphoma. In 1997 the FDA approved the use of an antibody called rituximab developed in Levy's lab for these patients. Now Levy, a professor of medicine, and Kohrt are designing ways to help the antibody work even better.

"Essentially, we're working on developing a second antibody that, in combination with rituximab, can help the immune system respond more vigorously to the cancer," says Levy. "In animals the results are very synergistic and quite remarkable. We hope that it will do as well in people."

Not one to do things halfway, Kohrt crafted his own PhD program focused on clinical trial design, and the treatment is now being tested in several small groups of patients.

"I feel like my experiences have prepared me to provide some level of empathy for my patients who are newly diagnosed with cancer," says Kohrt. "I can really feel how scared they can be because I remember what it was like to be in that situation. What I'm doing now, all of it, is fueled by my personal background with hemophilia. I want to give the benefit of this type of translational research to other people. That is the fuel to my fire and my inspiration. Without recombinant Factor 8, I would likely not be here today."

"Learning how you can help other people is the best gift you can receive in life," says Alan Kohrt. "That's the one thing that's going to give you the most back. Brook has been able to focus on this idea and say, 'This is what I want to do.' He's always been that kind of person, and I think he was truly meant to do the work that he is doing."

It's not known exactly why Kohrt remained uninfected. Research conducted by the Centers for Disease Control on him and others who escaped HIV didn't turn up any molecular cause, like an underlying resistance to the virus, for his good fortune.

"Essentially I just got really, really lucky," says Kohrt. "What it really underscores for me is that, in some parts of your life, things are under your control, and in others they are not. Initially there is a very high level of fear when you realize that the outcome is out of your hands. You have to choose whether you're going to perseverate on that and feel that fear every day, or if you're going to hope and move forward." **SM**

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BETTER SCREENING,
TREATMENTS OFFER HOPE FOR KIDS WITH IMMUNE DISORDER

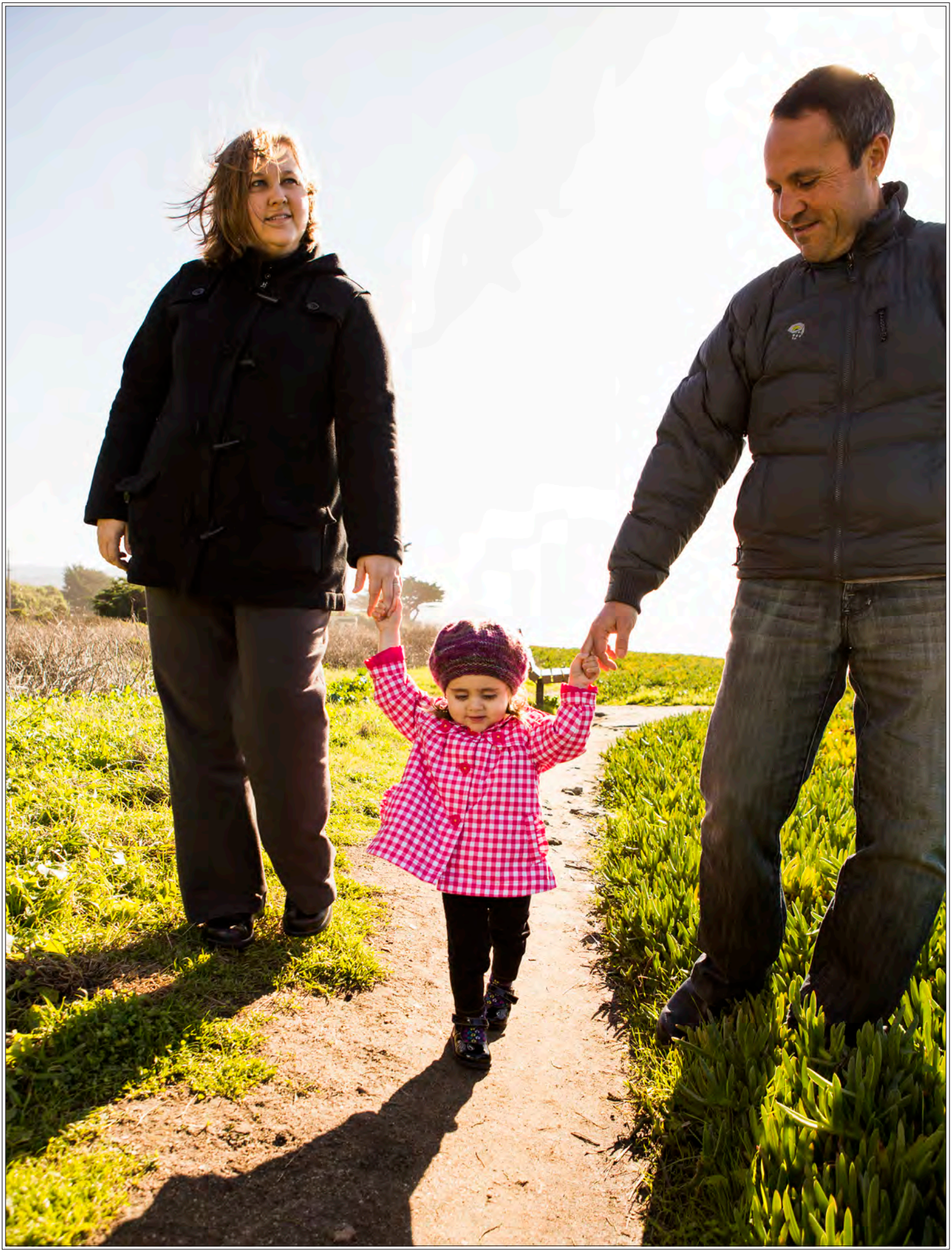
BUBBLE girl

For most of Isabella Messina's first year of life, people who wanted to see her had to squirt their hands with sanitizing gel, pull open the heavy door of the Bass Center for Childhood Cancer and Blood Diseases at Lucile Packard Children's Hospital, and walk across a strip of sticky flooring that took dirt off their shoes. Isabella's visitors stopped at the unit's scrub sinks for a vigorous two-minute hand washing, then progressed down a much-mopped floor through fluorescent-lit hallways equipped with negative-pressure ventilation to keep out germs. At the door of her room, they donned gloves, shoe booties, face masks and full-length, long-sleeved disposable gowns. When they finally entered the small room that was Isabella's entire world, her doctors, nurses and family members looked oddly similar, distinguishable only by the small rectangles of face visible around their eyes. • The person who looked back at them — a baby with light brown hair and a keen smile — was too young to ask why she was confined to a hospital room, too little to understand that she had been born with almost no immune system. But she was quick to locate her favorite eyes, the large, liquid-crystal-blue pair that belonged to her mom, Kim, and the dancing brown eyes of her dad, Giovanni. • For their only child, Kim McFall and Giovanni Messina had eyes full of smiles. But when they left Isabella's room, worry overtook their expressions. Isabella had been diagnosed at three

By Erin Digitale

PHOTOGRAPH BY ERIN KUNKEL

RIGHT: ISABELLA MESSINA AND HER PARENTS
A little walk is a big deal for this family.



weeks of age with a rare variant of severe combined immunodeficiency, the disorder known colloquially as "bubble boy disease" after a SCID patient whose confinement to a sterile environment was dramatized in the 1976 film *The Boy in the Plastic Bubble*. For her parents, Isabella's diagnosis felt both lucky and painful. Because the disease was caught so quickly, Isabella was cocooned in the hospital, protected from run-of-the-mill infections that kill many SCID patients before their first birthdays. Early diagnosis also provided her with a much better shot at a successful treatment. However, to go home, she needed her immune system repaired via a stem cell transplant, a procedure with no guarantee of success.

Hard as it is to fathom given the uncertainty of Isabella's situation, blood disease experts anticipate a hopeful new era of research and treatment breakthroughs for all forms of SCID, including Omenn syndrome, Isabella's diagnosis. One reason is a newborn-screening test for SCID that was rolled out across California in August 2010 and is gradually being introduced in other states around the country. Another is improvement in the stem cell transplants used to treat SCID. Originally developed for patients with blood cancers, the procedures, which were previously called bone marrow transplants, replace all or part of a patient's malfunctioning immune system with that of a healthy donor. But the cancer-oriented protocols carry the risk of severe side effects, including fatal complications. Scientists want to tailor the transplant procedures so they are less harsh and more specific to non-malignant diseases, including genetic anemias such as sickle cell disease, several hereditary metabolic diseases and the various forms of SCID.

"I've taken care of five kids total in my career with Omenn syndrome, and only one of the previous four is still alive," says Kenneth Weinberg, MD, one of Isabella's stem cell transplant doctors at Packard Children's, who has worked in the field for three decades. "I'm hoping Isabella will make it two out of five."

BEFORE ISABELLA'S BIRTH in December 2010, Messina and McFall lived a pleasantly ordinary life in a small town on the California coast. Messina worked days at a preschool and nights at a restaurant; McFall ran the local yarn store with her grandmother. They could see the ocean from their kitchen window.

In the first weeks of Isabella's life, they were plunged into a medical world where "ordinary" vanished. As a newborn, Isabella failed to gain weight and developed a severe rash. Fortunately, her pediatrician immediately referred the family to Packard Children's, where an immunologist diagnosed Omenn syndrome, a disease so rare that most doctors wouldn't recognize it. (All forms of SCID together affect perhaps one person in 100,000; Omenn syndrome cases are a small fraction of these.)

McFall was at Isabella's bedside with Messina's mother, who was visiting from Italy, when the doctors delivered the diagnosis. "I remember the looks on their faces when they said, 'We think she has severe combined immunodeficiency, Omenn syndrome specifically,'" McFall says, pressing her fingers under her eyes to slow the tears produced by the memory. "I said, 'What does that mean?' They said the only cure was a bone marrow transplant. I remember thinking, 'What are you talking about?' It's shocking — you don't absorb it right away."

McFall and Messina were further surprised to learn that Omenn syndrome is an autosomal recessive genetic disease, meaning affected children inherit a mutated copy of the relevant gene from each parent. The chance that McFall, who grew up in the United States, and her husband, who emigrated from Italy as an adult, could both be carriers was so miniscule that it has left them searching for meaning behind the disease.

"There has to be a reason," McFall says. She treasures a photo of Isabella holding a stethoscope — one of many

"They said
the only cure was a bone marrow transplant.
I remember thinking, 'What are you talking about?'
It's shocking — you don't absorb it right away."

from Isabella's long hospitalization, when taking photos of their baby was one of the only normal-feeling activities her parents had available to them — and says half-seriously that she hopes her daughter will grow up to be a physician who makes groundbreaking scientific discoveries that help other children. "It's hard to accept that there's no reason, that it's just the way it is."

"As long as she's OK in the end," Messina adds. "We look for the outcome."

But the outcome is uncertain. And although they express their feelings about the diagnosis differently — McFall is more talkative and anxious, Messina quietly optimistic — it wears on both of them that their daughter is now 2 years old and, still, no one can reassure them that she'll ever be cured.

IN CLASSIC SCID, the body fails to make T cells, white blood cells that perform many important immune functions. Normally, T cells destroy virus-infected and tumor cells; remember and eradicate pathogens the body has previously fought off; assist other types of immune cells; and shut down the immune response at the end of an immune reaction. Without any T cells, most SCID patients succumb to pneumonia or viral infections in infancy.

Omenn syndrome patients make a small number of T cells but they are abnormal and malfunction. Instead of protecting the body, they attack healthy tissue, causing the rashes and digestive problems Isabella experienced as a newborn.

The only treatment is a stem cell transplant to supply healthy bone marrow that can form normal white blood cells. The transplants, originally developed to treat blood cancers such as leukemia and lymphoma, are now offered to individuals with a variety of hereditary metabolic diseases and blood disorders, such as sickle cell anemia. Unlike adults who usually receive transplants for cancer, about one-half of children who could benefit from a transplant have non-malignant, usually genetic, diseases. But in the past, few Omenn syndrome or SCID patients were diagnosed in time for a transplant to help.

"I've gotten plenty of phone calls about sick or dying 6-month-olds for whom, too late, someone figured out they have SCID," says Weinberg, who is the Anne T. and Robert M. Bass Professor in Pediatric Cancer and Blood Diseases at the School of Medicine in addition to his position at Packard Children's. Late-diagnosed patients often have such severe viral infections that they cannot tolerate the chemotherapy needed to prepare for a stem cell transplant. Weinberg hopes newborn screening will eliminate late diagnoses. As of January 2013, nine states including California screen all new babies for SCID and an additional nine states either screen for SCID in select populations or are working to implement universal SCID screening. "The goal in the past was always approached as, 'Let's educate pediatricians to recognize SCID so they refer kids earlier,'" Weinberg says. "But the disease is so rare that you could educate a pediatrician and they might never see it in their entire career. Universal newborn screening will save lives by allowing earlier treatment before these babies become ill."

ALTHOUGH EARLY DIAGNOSIS was an important factor in saving Isabella's life, it was only the first step in a protracted medical journey. McFall and Messina began spending large chunks of each day at Packard Children's, and after Isabella started chemotherapy, one of them stayed with her every night. Messina also quit his preschool job; he couldn't risk catching germs from his charges that he might pass on to Isabella.

"They told us, 'This will be a long haul; you have to pace yourself,'" McFall recalls. Isabella's stem cell transplant would require several months' hospitalization to give time for the donor's stem cells to take root and grow.

"The day of transplant is sort of like conception day for the new immune system," Weinberg explains, adding that normal immune-system development in utero takes approximately six months.

To begin treatment, Isabella's physicians used immune-suppressing drugs to bring her rogue T cells under control. Then, they waited for her to grow old enough to receive the chemotherapy drugs that "condition" the patient's bone marrow before a stem cell transplant. The chemotherapy conditioning has two goals: It creates physical space in the bone marrow for donor stem cells, and it suppresses the patient's immune function to prevent rejection of the new cells.

"Babies handle the drugs differently than older children or adults, so the doses have to be monitored very carefully," Weinberg says, noting that the drugs, which were designed for cancer treatment, carry some risk of organ damage in infants. To reduce the risk, Isabella's chemotherapy was delayed until she was 16 weeks old, and the drug regimen was modified to take her vulnerable age into account.

The conditioning drugs are unnecessarily harsh for infants with SCID, Weinberg notes, but doctors lack other treatment options. Weinberg and his research colleagues are conducting two clinical trials to test gentler alternatives.

CONTINUES ON PAGE 52

a nobel experience

BRIAN KOBILKA GETS THE ROYAL TREATMENT

Dear friends and family,
Seasons greetings from the Kobilkas and best wishes for a prosperous and fruitful New Year!
Thus begins the Kobilka family's annual Christmas letter, an unusually eventful one this year.
In addition to the accomplishments of the two adult children —
Megan running two 50-mile races and Jason taking up adult ice hockey in a San Jose league —
there was also an engagement announcement for Megan (photo of the gorgeous ring included)
and an announcement of Jason's new software start-up plans.
But Dad managed to beat out even Megan's engagement for top billing:
Huge news this year dropped on us in the form of an early morning phone call (2:30 a.m.!) from Sweden in October,
writes Jason, the letter writer this year, in the first paragraph.
The Swedish Royal Academy of Sciences decided that this year, Brian Kobilka would share
the 2012 Nobel Prize in Chemistry with his erstwhile mentor Bob Lefkowitz (a professor at Duke University),
in recognition of their extensive and invaluable body of work with GPCRs.

By Tracie White

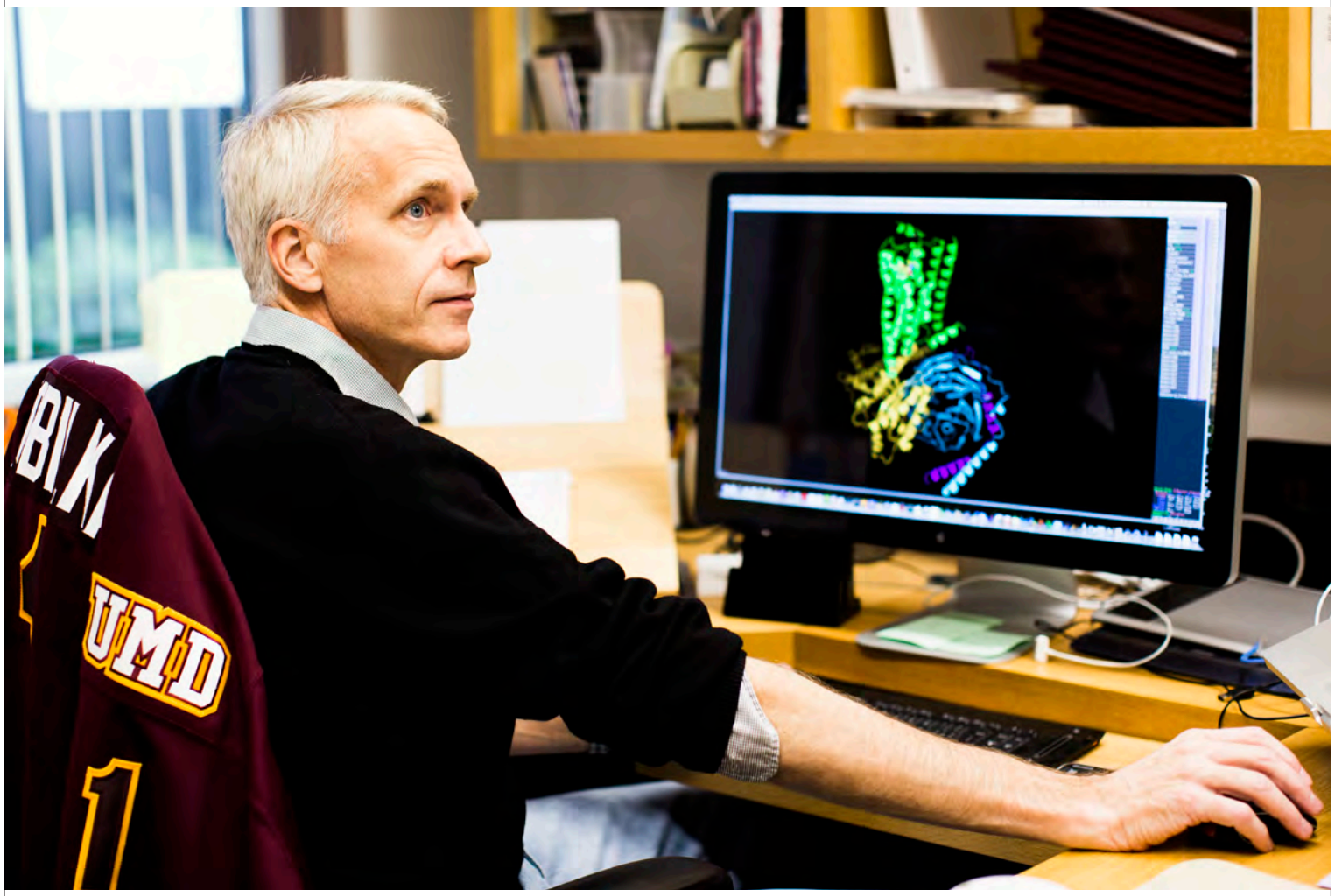
PHOTOGRAPH BY ERIN KUNKEL

It was quite a Christmas letter yet it barely touched on the highlights of the whirlwind three months beginning very early on Oct. 10, 2012, when Brian Kobilka, MD, a 57-year-old physician-turned-dogged-researcher, finally picked up the phone in the dark of his Palo Alto bedroom. (He and his wife, Tong Sun Kobilka, assumed the first attempt to call them was a wrong number and ignored it.) The award led to $600,000 prize winnings and VIP treatment including meeting President Obama and hobnobbing with Supreme Court justices before going to Stockholm where they were escorted in a BMW to banquets, and wined and dined with Swedish royalty.

For the Kobilkas — a down-to-earth California family for whom visits to the haberdashery to be fitted for tails and buying ball gowns are rarely on the "to do" list — it was a sudden and dazzling introduction to the world of scientific celebrity. "Surreal" is the word that Tong Sun, also a physician and scientist, most often uses, a "never-in her-wildest-dreams" kind of thing. "All the time you are thinking, 'This is surreal,'" says Tong Sun, who has helped run her husband's lab since college days. This time she's referring to meeting President Obama at the White House along with the other American Nobel laureates in November. "The President was just a foot away from us. No one said a word; all these brilliant Nobel laureates were tongue-tied. I was the only one who blurted out, 'So Mr. President, when are you coming to visit Stanford?' Then you hear that voice: 'I will visit. I love Stanford!'"

Here her eyes pop, and she laughs.

And all that was before they ever stepped on the plane to Sweden to accept the award.



BRIAN KOBILKA

On Kobilka's display is a model of one of the body's most important proteins. Discovering this structure won Kobilka the Nobel.

Brian and Tong Sun, accompanied by Megan, departed for Stockholm on Dec. 3, arriving the next day. During the flight, Brian was constantly reworking his Nobel lecture. He took the responsibility very seriously, feeling a bit nervous, he says. His goal: to summarize two decades of his work that led to the awarding of the Nobel — in under 30 minutes. He remembers little of the days leading up to the lecture except for his preparation, which stretched to about 30 hours all told.

Four days after arriving, he stepped onto the stage in Stockholm University's Aula Magna, an arena-style lecture hall, nervous but prepared, facing a crowd of hundreds.

"I'd like to thank the Nobel committee for this great honor," he said, standing at a podium, a giant screen behind him on the stage showing the first of a series of slides on the structural basis of G-protein-coupled receptor signaling.

"What I'd like to do is give you a brief tour through my lab's efforts ... at understanding this really interesting signaling process," Kobilka said into the microphone. "I'll provide a brief overview of the noncrystallographic approaches to understand structure, then efforts to obtain crystal, then the mechanistic insights we've obtained from these structures."

Kobilka won the Nobel for his work on understanding the structure and function of G-protein-coupled receptors, or GPCRs, a large protein family of receptors that sense molecules outside the cell and convey chemical messages from those molecules into the cell's interior. They act as molecular switches. Roughly 800 different GPCRs have been identified to date, making them one of the largest families of human proteins. They regulate the beating of our hearts, the workings of our brains and nearly every other physiological process. About 40 percent of all medications also target these receptors.

In 2011, Kobilka and his team were the first to obtain a three-dimensional image of the exact moment a G-protein-coupled receptor clasped its signaling molecule while simultaneously kicking off a cascade of hundreds of reactions inside the cell. To do so, the lab relied on a technique called X-ray crystallography to generate an image that the Nobel committee would eventually call "a molecular masterpiece." Such knowledge, it's hoped, will lead to the design of better drugs to activate or inhibit the receptors.

"We knew that this was really exciting work," says Søren Rasmussen, PhD, assistant professor at the University of Copenhagen and one of two postdocs formerly in Kobilka's lab who were invited by Brian to join the celebrations in Stockholm. "We also knew it was risky. But the feeling was more like it was just a matter of time before Brian would succeed."

Kobilka wrapped up his lecture with a photo of his colleagues grinning after generating that long-sought image. As always, he finished his lecture with thanks to his collaborators, his fellow scientists and especially his wife, all vital to the success of the research. "In conclusion we've learned a lot about this interaction. There is still a lot we don't know. .... There is still a lot of work to do in the future." But, first, there would be a little time to celebrate.

"More than
a week of receptions, lectures and audiences
with the Swedish royal family left my parents exhausted,
itching to get back to work, but ultimately elated."

Kobilka family Christmas letter, continued:

Our family and several of my dad's key collaborators had the privilege of joining the Nobel entourage during the awards ceremony and banquet in Stockholm this December. More than a week of receptions, lectures and audiences with the Swedish royal family left my parents exhausted, itching to get back to work, but ultimately elated. My mother, who has also been instrumental in my dad's success, also enjoyed her much-deserved share of the limelight, and was seated next to Prince Daniel at the royal banquet. ...

While Brian may have difficulty remembering, his wife has no problem relating the VIP treatment that started the minute they arrived in Sweden.

"Stockholm from the air looked beautiful with a blanket of sparkling snow," Tong Sun wrote in an email about flying into the city. "We were met at the exit door by the secretary general of the National Academy of Sciences. There was a separate stairway for us to walk down to the tarmac where the car was parked. Brian was assigned a BMW with a driver by the name of Stefan Lindman. He took us to the VIP area

of Arlanda airport where we waited until they collected our luggage. (This is how we should always travel!) Stefan drove us to the Grand Hotel where we were met by the managing director and taken directly to our suite. It is a huge suite overlooking the bay; the bedroom has a sitting and a dining area and it has a connecting study and of course a huge bathroom."

Day two, Brian had a fitting for his tux, then finished polishing his lecture. Day three, their son, Jason, and his girl-

TONG SUN AND BRIAN KOBILKA AT THE NOBEL BANQUET.

Right: The Nobel diploma

friend arrived. There was a get-together with the laureates and their families in the Nobel Museum. The physics laureate from Colorado was held up in Frankfurt because of the weather; the literature laureate's arrival was delayed by bad weather in Beijing. But they all eventually made it.

"It was a nice and laid-back gathering," Tong Sun wrote.

The celebrity treatment continued the entire week — interviews with journalists on public Swedish TV, private tours of museums and castles, sitting for portraits, dinners, receptions with ambassadors. The couple most enjoyed having their entire family together, along with one of Brian's earliest collaborators at Stanford, Bill Weiss, PhD, professor of structural biology, the two former postdocs and other research partners.

Still, the focus of the week centered on the ceremony awarding the medal and diploma, a grand affair filled with much pomp and circumstance.

The Nobel ceremony is based on a long and formal tradition. Since 1901, the prizes have been presented to the laureates at ceremonies on the same date, Dec. 10, the anniversary of inventor and industrialist Alfred Nobel's death. The ceremony, as is also traditional, is held at the Stockholm Concert

Hall, which is followed by a banquet for about 1,300 people. The Nobel laureates and the Swedish royal family are guests of honor for both events.

It's a white tie and tails affair for men, long evening gowns for women. This December, the entrance of the royal family, bejeweled and wearing crowns, was announced by a rolling of the drums and a banging of cymbals, and then the laureates marched in. Mozart played in the background.

Kobilka was looking both nervous and proud among the other laureates. "I now ask you to step forward and receive your awards from the king," the laureates were told. When it was Kobilka's turn, the announcer stated: "He didn't believe it was real until after speaking with five people on the phone with Swedish accents. It was definitely real."

The camera panned to the Kobilka family, beaming from the audience. And after the awards were bestowed, the royal family and the laureates marched off stage to the singing of the Swedish national anthem.

"It's a tradition that has gone on for Nobel laureates for the past 100 years," says Rasmussen, one of those beaming in the audience. "You feel like you are part of research history."

Finally, the partying began.

The banquet, a lavish affair, was held in the gigantic Blue Hall of City Hall, which was filled with long, Hogwarts-style banquet tables. Rasmussen remembers feasting on pheasant and poached pear, almond-potato purée and black cherry sorbet, and that it was amazing. The Crown Princess Victoria — a press favorite — looked glamorous in a glittering green gown. Brian, seated next to the princess, was caught on camera often, as was Tong Sun seated next to the princess's husband, Prince Daniel.

"Both are very nice people," Tong Sun says. "Prince Daniel was a commoner until he married the princess."

For Brian, it was the party after the party, the post-banquet affair, that he enjoyed most, finally able to relax. His 14 invited guests, research collaborators, friends and family, congregated in their own room, watched the dancing, marveled at the entertainment and, well, talked about science. "We are scientists, so, yeah, we probably talked about work," Rasmussen says.

"I really enjoyed the chance to celebrate with friends and family," Brian says. "We had a room to ourselves and could go out into the party to enjoy the music and food and entertainment. The acrobats were amazing, scaling the windows and walls. No photographers were allowed. We could just relax and enjoy."

The trip ended with the family back home in Palo Alto — with Christmas and a wedding still to plan.

"I'm just a little unused to all of this," says Brian, at home in his comfortable kitchen, his hands shoved deep in his jean pockets. He'd just returned from walking his son's big, white dog, Satchel. Already, he's back to worrying about getting back the results of grant applications and being behind in his research.

Winning the Nobel, while an amazing accomplishment, does not mean the end of worrying about funding, he says. One of the first things he did after hearing of the award was to join other laureates in signing a petition sent to Obama stressing the importance of funding basic science.

He has hurdled his own financial struggles along the path to his Nobel, his main funding source drying up in 2003. But when his lab began to struggle financially, even going into the red, he never once considered quitting. Instead, he did much of the hands-on research himself, worried that he might ruin the careers of his postdocs by setting them to work on "impossible" achievements.

"When things weren't going well, and we weren't getting anywhere, we'd pre-celebrate," Kobilka remembers. Tong Sun would throw a "pre-celebration" party — pizza and beer or coffee and doughnuts in the lab.

It was nice to finally get the post-celebration party.

"We had a room to ourselves and could go out into the party… . The acrobats were amazing, scaling the windows and walls. No photographers were allowed. We could just relax and enjoy."

The Kobilka family Christmas letter, continued:

The Swedish media were all up in my dad's business as well, even sending a small crew to California to follow and film his day-to-day life. The whole experience left him a bit dazed, like a shy, lanky deer in headlights.

All the pomp and circumstance haven't slowed the research down at all either. … We all feel very blessed, and we hope that 2012 has brought you all the same kind of fortune.

Tong Sun, Brian, Megan, Jason, Satchel and Gus (10-pound mini-dachshund Gus and 100-pound mutt Satchel.) SM

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"It certainly was satisfying to know that the test was successful. The patients at Stanford were protected. The hospital was one of the few in the country that wasn't sued," says Engleman, who was called as an expert witness in several lawsuits.

The cost of the screening test amounted to $10 to $14 per unit, and though others had warned that laboratory testing would scare away some donors and lead to blood shortages, that was never the case at Stanford, Galel says.

The story was different in San Francisco. Though self-exclusion eliminated some 86 percent of the risk, later analysis showed that at least 1 percent of those transfused — or at least 2,000 recipients — became infected with HIV, Busch says. That was "vastly different" from the earlier one-in-a-million estimates, he notes in a paper published in October 2010 in the journal *Transfusion*. The San Francisco blood bank would face some 50 lawsuits, which it successfully defended.

In retrospect, he says his blood center was wrong about the hepatitis B antibody test, which would have picked up significantly more infected donors than originally believed — between one-third and one-half of the HIV-positive donors.

Paul Volberding, MD, director of the AIDS Research Institute at UCSF and one of the pioneers in the epidemic, says Irwin and other blood banks can't be faulted for their actions, which were based on what very little was known at the time.

"My own position was that the blood banks were doing what they could, not knowing what was going on, given that blood is a precious thing," Volberding says. "You could have shut down the whole blood system and eliminated AIDS, but then people would have died of not having blood. Or you could have instituted broad tests that may or may not have reduced HIV but rejected units that were perfectly safe."

But Engleman is still defiant, believing that blood banks acted irresponsibly. "I felt the blood-banking system had let the public down," he says. "I felt the blood banks went against science and rational behavior because they refused to use our test or other tests, like the hepatitis B test."

It was not until May 1984 that the existence of HIV, first isolated in 1983, was officially confirmed in a series of reports in *Science* magazine. Margaret Heckler, former secretary of the Department of Health and Human Services, then famously declared that a blood test would become available within six months and a vaccine ready for testing within two years. But it would be almost a year — March 1985 — before the FDA approved the first assay to detect HIV, and most U.S. blood banks waited until then to adopt the first official HIV test. An effective vaccine has yet to be developed.

In the interim, between the critical period of 1983 and 1985, it's estimated that at least 20,000 people nationwide, and possibly as many as 29,000, became infected with HIV through blood transfusion.

Since then, HIV tests have been significantly refined. With the early assays, there was an estimated 56-day lag between the time of infection and the detection of antibodies. Later tests reduced the window to three weeks. Today, with use of nucleic acid tests, which detect sequences of specific HIV genes, the window has been reduced to nine days, Galel says.

The risk now of receiving HIV-tainted blood is estimated to be about one in 1.5 million. And in this age of highly effective screening, the FDA continues to prohibit gay men from donating blood — an exclusion that remains controversial.

The AIDS experience ushered in a new era of tight controls over the blood-banking industry. The Institute of Medicine issued a detailed analysis of the crisis in 1995, criticizing blood banks and federal agencies for a "failure of leadership and inadequate institutional decision-making." It recommended sweeping changes, including new federal oversight and surveillance. Engleman also testified twice before Congress, which directed the FDA to overhaul its regulatory process for the industry.

"I think the whole AIDS experience completely transformed how the FDA looks at blood safety," Galel says. "This showed that an infectious agent could be in the population and be transmitted for years without anybody being aware of it."

But she says the FDA may have gone too far in its regulatory zeal. For one thing, Stanford could not do today what it did back in 1983 — introduce a test without regulatory approval, she notes. And that has proved frustrating and problematic at times. For instance, a parasite known as *Babesia*, which causes a malaria-type disease, has infiltrated blood supplies on the East Coast, with more than 100 reported cases of infection through transfusion.

Though some blood banks would like to screen for *Babesia*, they cannot do so until a test has undergone clinical trials, which are now under way, and has been approved by the FDA.

"Times have changed to make it very hard to respond in real time to a newly recognized threat," Galel says.

Despite today's rigorous and costly screening programs for a wide range of agents, it is theoretically still possible for something dangerous to slip through, Engleman says. "But if you look at the bigger picture, blood is much safer today than it has ever been before." **SM**

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One trial for genetic diseases, begun several months after Isabella received her conditioning, uses non-cancer drugs to reduce the doses of cancer drugs. A second trial, funded by a $20 million grant from the California Institute for Regenerative Medicine to Judith Shizuru, MD, PhD, an associate professor of medicine, will substitute antibodies for conditioning drugs. The antibodies recognize a molecular marker on the surface of blood-forming stem cells and tag the cells for destruction. After a waiting period to allow all the antibodies to be cleared from the body, patients will receive infusions of highly purified donor stem cells, rather than the unpurified infusions of both blood and bone marrow now used. Shizuru has found that the method works in a mouse model of SCID and has few side effects. Her team plans to begin enrolling children in the human study in the winter of 2014.

A third study that will launch at Stanford and Packard Children's later this year is intended to speed the stem-cell transplant process after conditioning is complete. "We're supplementing stem cells with cells that are like teenage lymphocytes — not fully grown but not newborns, either," Weinberg says. He and Janice Brown, MD, associate professor of medicine, have found that giving these cells, called common lymphoid progenitor cells, to mice undergoing transplant quickly restores their immune systems and protects them from early infections. The new study will test the cells in children with leukemia. If the cells safely speed transplants in that context, they may later be added to the treatment regimens of infants with SCID.

Another approach being developed at Stanford will use stem cells from patients' own bone marrow. Matthew Porteus, MD, associate professor of pediatrics and another of Isabella's stem cell transplant doctors, wants to correct the SCID-causing genetic mutations in the stem cells. These "corrected" cells could be transplanted without concern for rejection. Porteus recently received a National Institutes of Health grant to develop this approach for SCID's two most common forms.

Most of the nascent science, promising as it is, came too late to help Isabella. Nevertheless, she received her first infusion of stem cells — supplied by an anonymous donor — on April 18, 2011.

Then came the most difficult and uncertain part of Isabella's treatment: waiting. Throughout much of 2011, Isabella's physicians monitored her T cell counts while McFall and Messina waited for good news. The hospital routine no longer seemed foreign — they were used to the gloves, gowns, booties and masks; used to washing their hands over and over; used to spending a little time each day with their face masks off so that Isabella could see their mouths moving as they spoke, an important sensory input for language development; used to the regular parade of doctors and nurses through Isabella's room; used to the fact that, for now, pictures and videos of the outside world had to be substituted for Isabella's ability to experience it directly.

And they were heartened by their baby's cheerfulness — she grinned and gurgled at them like any other infant, and her development progressed on close to a typical schedule. They dressed her up in adorable outfits for holidays and showed her off to her caregivers. When he visited the family, Weinberg took joy in seeing how both parents doted on Isabella, commenting especially on Messina's close bond with the baby. "When he looks at her, if it was a cartoon, there would be a big balloon saying 'Love!' overhead," Weinberg says. "It's how every child dreams of being seen by their parent."

Soon after the first stem cell infusion, Isabella's T cell counts climbed, but after a few months, they leveled out and then began to fall. As the summer wore on and Isabella's T cell counts did not get better, everyone grew more concerned.

In August 2011, Isabella's medical team realized her own malfunctioning T cells were re-taking her immune system and decided to give a second dose of stem cells from the same donor. She received a targeted form of conditioning to attempt to wipe out her T cells while allowing her donor's stem cells to remain intact. Weinberg crossed his fingers and hoped this would work. His only other surviving Omenn syndrome patient had undergone two failed stem cell transplants before a third transplant finally succeeded; that child spent more than two years in the hospital. He wanted a better outcome for Isabella.

After the second infusion of donor cells, the medical team periodically measured how much of Isabella's immune system came from her donor compared with her own cells. Unlike a blood cancer patient, Isabella did not need to have her native immune system eradicated, but she needed a reasonable supply of healthy T-cell-producing stem cells from her donor. The hard part was that no one was sure how many donor stem cells would be enough to allow her to live safely in the outside world.

At first, the test results were so dis-

couraging that Isabella was scheduled for a third transplant procedure in October 2011, and McFall and Messina were told to expect her hospital stay to extend into the spring of 2012. But shortly before the third transplant was to occur, Isabella's test results jumped.

Suddenly, she was hitting milestones that allowed her to start emerging from her germ-free cocoon. In one of the happiest moments, her doctors told McFall and Messina that they could stop wearing gowns, gloves, booties and masks in her room. "We were able to feel her baby skin with our bare hands and give her kisses for the first time in nine months," McFall says. "That was a good day."

Then, in mid-October, Isabella was declared healthy enough to transfer to the Ronald McDonald House near the hospital as the first phase of her transition home. McFall and Messina couldn't quite believe it.

"We didn't pack a single thing in advance," McFall says of the family's Oct. 23 move out of the hospital. "We left the hospital room at 9 o'clock that night."

By Thanksgiving 2011, Isabella was well enough to go with McFall and Messina to a small family party at McFall's mom's house in San Jose, Calif. In December 2011, after a two-month stay, the family left the Ronald McDonald House and headed home.

TODAY, ABOUT 90 percent of the stem cells in Isabella's bone marrow are still her own; just 10 percent come from the donor. For a leukemia or lymphoma patient, a stem cell transplant with this outcome would be a failure; in blood cancer, cure requires total replacement of the patient's blood-forming system. But with her diagnosis, Isabella's situation may be a resounding success. She's making a steady supply of functional T cells.

The question is whether that will continue indefinitely. In the past, some children with classic SCID received transplants that left them with many of their donor's healthy T cells but almost no donor stem cells; these children often ran out of T cells after a few decades and required second transplants.

"I'm optimistic that won't happen with Isabella; she has stem cells from the donor and is continuing to make T cells, so she's conceivably stable," Weinberg says. "I fully expect she'll attend preschool and kindergarten like everyone else, and I expect her to come home with colds like everyone else."

At home, though she has slight speech and motor delays, Isabella is thriving — running, climbing, chattering in both English and Italian, and enjoying a typical toddler's assortment of books, toys, trips to the park and strolls through the neighborhood with her parents. One day in the fall of 2012, as a visitor sat at her kitchen table, she jabbered happily to everyone present, then settled on the floor to entertain herself by threading a shoelace between her toes.

McFall and Messina still worry about taking Isabella to crowded public places, but they have cautiously tried a few expeditions to restaurants and the grocery store. They were encouraged recently when Isabella didn't catch a cold they both had. And they are gradually expanding Isabella's contact with other kids — she'll soon take a parent-child gymnastics class for toddlers, an activity that would have been unthinkable a few short months ago.

In an email, reflecting on her family's medical journey, McFall says:

"A woman made a comment in a store the other day about how it would be nice to keep them babies forever, and I had a funny reaction to that statement. I think it's because I want to get as far away from that period, which was her infancy, as possible. I look more forward to the future, and 'getting on with it.'" **SM**

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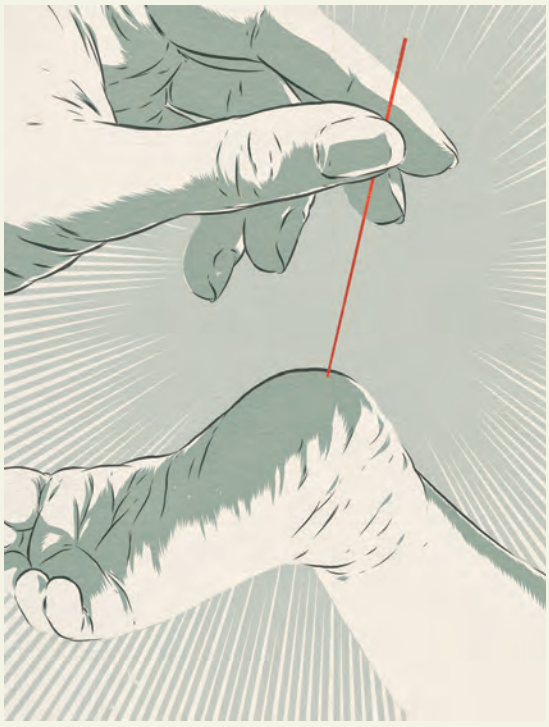
HEEL STICKS

WILL TESTS FOR NEWBORNS GO BIG?

It's a ritual of modern birth: Soon after delivery, blood is collected from new babies' heels, blotted onto filter paper and tested for life-threatening diseases. Newborn blood-spot screening began in the United States in 1966, with surveillance for a single disease, and has expanded enormously. Thirty-one disorders are now recommended by the federal government's screening committee, and many states, including California, screen for even more. But that expansion is tiny compared to what's on the horizon.

Within the next decade, whole-genome sequencing, which records every letter of the genetic code, will likely become sufficiently fast, accurate and cheap to compete with current screening methods. Today, newborn screening relies largely on mass spectroscopy, a technology that measures specific metabolic products in the blood. It's a needle-in-the-haystack approach that looks for markers of specific diseases. Whole-genome sequencing, in contrast, could test the whole haystack. The idea carries a tantalizing possibility of catching or predicting far more diseases than current screening methods, and, in a best-case scenario, alleviating much human suffering.



MATTHEW WOODSON

But screening newborns' genomes would raise a bushel of ethical questions, says Stanford bioethics expert Hank Greely, JD, a law professor and director of the Center for Law and the Biosciences. Already, a few of the screening tests performed in some states give ambiguous results, leaving parents wondering if their children are actually sick.

"If we move to whole-genome sequencing, we'll be going down this road at supersonic speeds, and it's a winding road," Greely says. "But there are strong forces in favor of new technology. It will be hard to resist the lure of getting the whole genome for the same price as testing for 30 to 50 diseases."

The biggest ethical questions revolve around interpreting the data. Individual genetic variations, coupled with our still-sketchy understanding of the human genome, mean each screen would produce thousands of puzzling data points. How much of that information would families need? How often would it be re-interpreted in light of new science? How would we ensure it wasn't used to "treat" infants for genetic variations that would never lead to illness? No one knows.

Privacy concerns also loom: How would genetic data, once collected, be secured? What if the data revealed uncomfortable surprises, such as genetic-disease predispositions among parents or siblings, or awkward revelations about the identity of an infant's father?

Some newborn screening experts are skeptical about whether whole-genome screening will be adopted, even as the technology improves.

"We're looking to detect known disease," says Fred Lorey, PhD, chief of program and policy for the Genetic Disease Screening Program at the California Department of Public Health and a member of the federal committee that evaluates diseases for screening. The committee recently rejected single-disease tests that share the ambiguities whole-genome screens would produce, Lorey says. The proposed tests poorly predicted which children would get sick, or the diseases lacked effective treatments. "I don't see newborn screening, at least in the near future, ever going to tests that show mere risk factors," Lorey says.

Still, Greely's not relaxing, suggesting that newborn screening experts start recommending how to address the ethical challenges. He concludes, "I think that if price comes down and accuracy goes up, political and social dynamics will make it impossible for us to turn this down." — ERIN DIGITALE

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Spotting the evidence

CAT COATS AND HUMAN HEALTH

How did the cheetah get its … stripes? • "Until now, there's been no obvious biological explanation for cheetah spots or the stripes on tigers, zebras or even the ordinary house cat," says Stanford geneticist Greg Barsh, MD, PhD. "How do periodic patterns like stripes and spots in mammals arise? It's kind of surprising how little is known."

Barsh and his colleagues, including Christopher Kaelin, PhD, compared specific gene sequences among feral cats and wild and captive cheetahs. They found that the same biological mechanism is responsible for both the elegant stripes on the tabby cat and the cheetah's normally dappled coat. Dramatic changes to the normal patterns occur when this pathway is disrupted: The resulting house cat has swirled patches of color rather than orderly stripes, and the normally spotted cheetah sports thick, dark lines down its back.

"Mutation of a single gene, called Taqpep, causes stripes to become blotches, and spots to become stripes," says Barsh, an emeritus professor of genetics and of pediatrics at Stanford and an investigator at the HudsonAlpha Institute for Biotechnology, in Huntsville, Ala. The research was published in *Science*.

Taqpep encodes a protein normally found in the cell membrane, but that can also diffuse outside the cell. This ability to float freely and interact with other molecules in the extracellular soup is a key component of a principle called reaction diffusion proposed by the famous computer scientist Alan Turing, PhD, in 1952 as a way to explain how periodic patterns (like stripes and spots) can arise out of randomness.

Previous work in Barsh's lab has shown that coat-color genes are involved in many other important biological pathways. They've been linked to brain degeneration, anemia and bone marrow failure — all things we humans would dearly like to avoid.

So the next time your fractious feline deigns to let you run your hand down his back, take a minute to marvel at his unique coat pattern and its links to Africa, computer science and human health. And if you really want to play with fire, whisper in his ear how sweet he is and how helpful he's been to science. Then back away quickly. — KRISTA CONGER

GREG BARSH