

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

Winter 2019

special report

A GLOBAL PURPOSE

Education, research and care

Where are they?
Advancing women
in health care leadership

Neglected no more
Zimbabwe's youngest
ENT patients

The deadly bite
Controlling disease spread
by mosquitoes

Cleaner air
One brick at a time in Bangladesh

The doctor who led
the World Bank
A conversation with Jim Yong Kim

plus

Make it stop
Ending chronic pain

Dying to heal
Insights into cellular suicide could
improve disease treatments



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A BETTER WAY TO RESUSCITATE

STANFORD-INDIA BIODESIGN FELLOWS INVENT A DEVICE THAT HELPS NEWBORNS BREATHE ON THEIR OWN

In the United States, resuscitating a baby who suffers from birth asphyxia is relatively simple. When a newborn fails to breathe, one clinician holds a respirator mask to the baby's face while another person squeezes a ventilation bag, pushing air into the baby's lungs. But in low- and middle-income countries such as India, where staff is more limited, resuscitation is not so straightforward. An individual clinician commonly resuscitates the baby alone, using one hand to perform a triple maneuver of a jaw thrust, chin lift and neck tilt, sealing the respirator mask around the baby's mouth, and using the other hand to squeeze the bag.

According to the World Health Organization, birth asphyxia causes about a quarter of the 2.5 million newborn deaths each year.

"In the absence of adequate training, much of the air during resuscitation may leak out, causing the baby to suffocate," said Avijit Bansal, MD, a pulmonologist from India.

Recognizing a problem, in 2012 Bansal and biomedical engineer Ayesha Chaudhary, PhD, co-founded Windmill Health, a medical device company in New Delhi. They developed NeoBreathe, a foot-operated resuscitator that frees one of the operator's hands, cuts down on air leakage and significantly improves ventilation. With the freed hand, the operator can multitask more efficiently in that first life-saving minute of a baby's life.



The idea for the device was sparked in 2011, when Bansal and Chaudhary met through a Stanford Byers Center for Biodesign Stanford-India fellowship and realized they both wanted to improve the treatment of birth asphyxia. Founded in 2000, the Stanford biodesign center aims to provide knowledge, skills and mentoring for people seeking to become health technology innovators.

Through the program, four fellows from India spent six months at Stanford University, studying biodesign innovation and working on team projects, and six months at the All India Institute of Medical Science in New Delhi, zeroing

in on unmet health care problems and developing new technologies to solve them.

The fellowship gave Bansal and Chaudhary the skills to design and develop their device. After extensive feedback from product users, several design cycles and thorough testing, the machine was commercially launched in December 2016. The device is now being used in 20 out of the 36 states in India, as well as in Kenya, South Africa, Nigeria and Mali.

Other technologies that have come out of Stanford Biodesign's India program include Sohum, an affordable device used to screen newborns for hearing defects, and HiCARE LIMO, a cardboard splint that helps caregivers temporarily immobilize injured limbs.

The company plans to introduce NeoBreathe in other countries that need it, including Peru, Chile and Argentina, said Bansal.

"We have created a new way of performing an age-old procedure. It is helping save lives, and people are taking notice," said Bansal. "This is just the beginning for us." — HELEN SANTORO

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letter from the dean

We share this planet with billions of people, a rich panoply of cultures, languages, beliefs and interests. Yet amid this diversity, we also share a universal yearning: to enjoy healthy lives.

This issue of *Stanford Medicine* magazine explores people, places and programs that illuminate how tightly we are bound to each other, even when separated by thousands of miles, and how dedicated physicians and researchers can make a real difference for individuals, communities, nations and, eventually, all of us.

Any focus on global health must address equality and the complex interplay of the social determinants of health, including education, poverty and pollution.

One powerful example is the story behind Stanford's efforts to increase the number of health leaders who are women by hosting the first annual Women Leaders in Global Health Conference. The lack of gender equity at the highest levels of health care leadership is as much a problem here as it is internationally. By working together, women from different continents are beginning to connect and receive the training and mentorship they need to effect change on an institutional level.

Similarly, in an interview, Jim Yong Kim, the first physician to lead the World Bank, argues forcefully that investing in health and education is one of the most powerful ways to reduce poverty, citing evidence that better outcomes in both correlate more strongly with economic growth than we previously thought. That's one reason I'm so passionate about health care and higher education. They're the means to a better life — for everyone.

Not only does health affect poverty, but poverty also affects health, and so do a host of other factors, from the environment to social support. A focus on these social determinants is a cornerstone of Stanford Medicine's precision health vision. In the fascinating profile of epidemiologist Stephen Luby, we see the ways in which he is coming to understand, and seeking to reduce, the health effects of the carbon-monoxide-spewing brick kilns in Bangladesh. In an article about mosquito trackers, we learn the stunning fact that there's a statistically significant overlap between dengue infections and homicide risk.

Through rotations in social medicine and work with homeless populations, global health residents at Stanford explore how socioeconomic, environmental and behavioral factors work together to contribute to health and disease. During their training, residents discover what is common among us. As Andrew Chang put it poignantly, "Practicing medicine overseas makes you realize that, in many ways, people are all the same. Fear, regret, anger, sadness — these things are universal. When someone starts crying, you hold their hand."

Worldwide, we are all fighting against the many forces that make us sick — sexism, pollution, crime — and regardless of where we call home, all of us are, in a very real way, neighbors. Read on to learn more about how Stanford Medicine is improving health globally — and locally.

Sincerely,

Lloyd Minor, MD

Carl and Elizabeth Naumann Dean of the School of Medicine
Professor of Otolaryngology-Head & Neck Surgery



upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD MEDICINE

cracking tough cases

A GROUP OF SLEUTHING doctors has diagnosed 132 previously unknown diseases in patients whose ailments had gone unnamed for years.

"We do this Sherlock Holmes-like detective work-up by carefully observing, gathering information and asking pointed questions, but we're also pairing that with the most advanced genomic technologies to try to solve their case," said Euan Ashley, MD, professor of medicine and a physician in the Undiagnosed Diseases Network, which the National Institutes of Health expanded from an existing program in 2014.

The group has diagnosed roughly 35 percent of the 382 ailments they have analyzed, according to a study by scientists at Stanford and other research centers.

"Some of these patients had been waiting decades to put a name to their illness" and are relieved to finally know



what they're up against, said Ashley, lead author of the study published Oct. 11 in *The New England Journal of Medicine*.

Having a diagnosis led to new actions — such as different therapies, testing and family screening — in 80 percent of the cases diagnosed, he said.

Senior author Kimberly Splinter, associate director of research operations for the network's coordinating center and a genetic counselor at Harvard Medical School, said the group hopes the work will "provide a compelling case for adopting some of the network's diagnostic approaches" when treating rare conditions.

The father factor

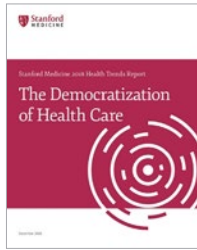
CHILDREN of older dads are at higher risk of having health problems at birth, research suggests.

"We tend to look at maternal factors in evaluating associated birth risks, but this study shows that having a healthy baby is a team sport," said Michael Eisenberg, MD, a Stanford Health Care urologist, associate professor and senior author of a study published Nov. 1 in the *British Medical Journal*.

Data from more than 40 million births showed that newborns of older-than-35 dads had more health risks.

Newborns of dads under 35 needed intensive care about 6 percent of the time. Babies of older-than-45 dads needed it 8 to 10 percent of the time.

Almost 6 percent of teens prescribed opioids by dental providers were diagnosed with opioid abuse in the next year. More at <https://stan.md/2RPWafQ>



New Health Trends Report

A PROLIFERATION OF DATA is driving more democratization in health care, according to Stanford Medicine's second annual *Health Trends Report*, published in December.

Building on 2017 findings about the changing role of data in medicine, the report explores how using and sharing data will transform research, medical practice and the role patients play in their care.

With the dramatic expansion of health care data, new technologies and industry players are taking medical knowledge from a human scale to a digital scale.

"Whole realms of expertise, previously siloed, are beginning to open up to more people in more places than ever before," said Lloyd Minor, MD, dean of the School of Medicine.

The report evaluated existing research and publicly available data on health care sector trends, combined with insights from Stanford faculty and external health care experts. It identifies three pillars of influence:

- Intelligent computing — improved analytics in the artificial intelligence market will improve insights and provide a more precise, efficient, personalized and accessible health care system.
- Sharing — free-flowing information between stakeholders (patients, clinicians, insurers and technology providers) will ensure that the full benefit of collaboration is realized.
- Data security — a balance must be struck between innovation and safeguarding patient security, privacy and safety.

Find the full report at <http://med.stanford.edu/school/leadership/dean/health-trends.html>.

inner origami

IMAGINING THE INDIVIDUAL FATES of embryonic stem cells is like envisioning what will become of a class of kindergartners: It's not obvious who will be a poet, a math whiz or a class clown.

Now, scientists studying therapies for a blistering skin disease believe they have narrowed down how proteins responsible for helping stem cells become distinct tissue types — like muscles, skin or nerves — team up to spark the process.

Their findings emerged during research on how stem cells develop into cells called keratinocytes to form sheets of skin. Replicating the process could help repair open wounds in people with epidermolysis bullosa, a genetic condition caused by mutations in the keratin protein that helps bind cells to form skin tissue. If tissue doesn't bind properly, it falls apart and easily blisters from friction.

During the study, researchers identified a key regulatory hierarchy whereby proteins called morphogens control the origamiliike folding and unfolding of the cell's DNA. The process brings master regulators called transcription factors in contact with the set of genes necessary for skin development.

"For the first time, we were able to see how morphogens and master transcriptional regulators work together to make specific cell types," said dermatologist Anthony Oro, MD, PhD, the Eugene and Gloria Bauer Professor. "We've always wondered how a transcription factor required for the production of vastly different cell types knows which genes to make into proteins in which situation."

Now they know that morphogens help the master transcription factors hook up to the right targets and that specific cell development is not random.

"We can work to harness and accelerate this process to generate all kinds of transplantable tissues," said Oro, senior author of a paper describing the research published Nov. 5 in *Nature Genetics*.



ILLUSTRATIONS: CHRISTIAN NORTHEAST; PHOTO AT RIGHT, LUCILE PACKARD CHILDREN'S HOSPITAL STANFORD



boning up

DEER HAVE THE RARE ABILITY TO GROW ANTLERS, with males (and, among reindeer and caribou, females) sprouting a new pair every spring and shedding the pair in winter. During the summer months, antlers can grow as much as 2 centimeters a day.

When Peter Yang, PhD, associate professor of orthopedic surgery, heard about that rapid growing cycle during a vacation in Alaska, he wondered whether specific genes were responsible. To find out, he and research colleagues traveled to a deer farm in California to collect samples of antler tissue, which is primarily made up of skeletal stem cells, then used a variety of techniques to decipher the genetics behind antler growth. That research identified two genes — *uhrf1* and *s100a10* — that drive the antler's quick bone production, according to a study published Oct. 30 in the *Journal of Stem Cell Research & Therapy*.

The researchers hope that knowing the genetics behind the fast bone growth and mineralization in antler regeneration can provide insight into treating fractures and bone diseases such as osteoporosis in humans. "Antler regeneration is a unique phenomenon that, to me, is worth studying just out of pure curiosity, but lo and behold, it may have some really interesting applications for human health," Yang said.

NEW CHILDREN'S HEALTH LEADER



PAUL KING BECAME THE NEW president and CEO of Lucile Packard Children's Hospital Stanford and Stanford Children's Health in January. He succeeded Dennis Lund, MD, who served as interim CEO of Stanford Children's Health beginning in March 2018 following the retirement of Christopher Dawes, who had led the organization since 2000.

King has worked in health care for more than 30 years, most recently as executive director of the University of Michigan Health System's C.S. Mott Children's Hospital and Von Voigtlander Women's Hospital.

"As we plan for the continued growth of Stanford Children's Health and expansion of innovation across the entire continuum of care, Paul's distinguished record of accomplishment and dedication to the critically important role of pediatric and obstetric care will undoubtedly help us achieve our vision of precision health at Stanford Medicine," said Lloyd Minor, MD, dean of the School of Medicine.

Heart-healthy mutations

AN ANALYSIS OF GENETIC and other health data from thousands of U.S. military veterans is helping scientists find clues for treating heart disease and diabetes.

The study of 297,626 veterans zeroed in on three mutations associated with improved cholesterol levels but with other benefits: A mutation in the *PDE3B* gene protected against heart disease, a *PCSK9* mutation protected against heart disease and abdominal aortic aneurysm, and an *ANGPTL4* mutation reduced Type 2 diabetes risk.

The mutation in *PDE3B* is

intriguing, said senior author Tim Assimes, MD, PhD, because there's an inexpensive drug on the market — cilostazol — that mimics its effects on cholesterol levels. It could be a candidate for treating heart disease, he said, though more research is needed.

"We've been misled before by drugs that had effects on cholesterol, but they turned out to be cosmetic," he said. "Better cholesterol profiles can look great, but if the drug doesn't affect the outcome you're aiming for, which is heart attack in this case, then it's useless."

Assimes, an associate professor of cardiovascular medicine, conducted the study, published Oct. 1 in *Nature Genetics*, with colleagues at Stanford and the Veterans Affairs Palo Alto Health Care System.

No longer

A ZIMBABWEAN CLINIC'S AIM IS TO VANQUISH DIRE EAR, NOSE AND THROAT DISEASES IN CHILDREN

Peter Koltai, MD, first met 3-year-old Paige Bunjira in May while visiting with a renowned Zimbabwean stone sculptor whose work he admires. Koltai, professor of otolaryngology and of pediatrics at Stanford Medicine, has often visited Zimbabwe as an adviser in the establishment of an ear, nose and throat clinic for children in Harare, the nation's capital.

This time, Koltai was traveling with his wife, Rita, and they had just purchased a piece from Locardia Ndandarika, one of the country's first woman sculptors. While sharing tea with Ndandarika, multiple generations of family members joined them, including Paige, who is Ndandarika's great-granddaughter.

When an aunt realized Koltai's medical specialty, she told him, "You know, our Paige seems to have lost her voice."

That got Koltai's attention. After hearing more, he suspected that Paige had recurrent respiratory papillomatosis, a disease caused by the human papilloma virus, or HPV, which results in small, wartlike growths, typically on the vocal cords — as in Paige's case. So he contacted his friend and the man he had aided in setting up the clinic, Clemence Chidziva, MD, a surgeon and professor of otolaryngology at the University of Zimbabwe, who quickly got in touch with the family and arranged the evaluation.

Paige underwent her first procedure to have the growths removed the next month at the pediatric otolaryngology clinic at Harare Children's Hospital that Chidziva helped open in

BY TRACIE WHITE

PHOTOGRAPH BY BRIAN SMALE

neglected

PETER KOLTAI HELPED CREATE THE
FIRST PEDIATRIC EAR,
NOSE AND THROAT CLINIC IN
ZIMBABWE. HIS LOVE
OF ZIMBABWEAN SCULPTURE
CONNECTED HIM WITH A YOUNG
PATIENT WHO NEEDED
CARE THERE.



'By the time they get to us, they can't sleep, they're not growing, their breath is raspy and they are struggling to get in air.'

March 2017. It was the first such clinic in Zimbabwe and only the second in Africa; the first was in neighboring South Africa.

In a country of more than 17 million people, there are only 10 otolaryngologists, also known as ear, nose and throat surgeons. Many consider the subspecialty of pediatric ENT a luxury because of Zimbabwe's other unmet health care needs. But Chidziva knew the effects of malnutrition, poor medical care and uncontrolled infection on his young ENT patients. He also knew that these problems reached far beyond Zimbabwe into other parts of Africa and the developing world.

Now, thousands of new patients a year make daylong trips by bus to be treated for long-neglected conditions, and the clinic's founders envision it as a training ground for African otolaryngologists and health care workers who seek to increase their knowledge in the care of these vexing and sometimes serious problems.

"This was a bold dream for a full-scale clinic with audiology and speech therapy services, as well as two operating rooms with a recovery room and beds for overnight care," said Koltai, whom Chidziva recruited almost five years ago as a volunteer adviser and participant for the project. "Now we believe that this new clinic can be used as a model to be duplicated in other regions of Africa."

THE PROBLEM

The children's hospital is part of Harare Central Hospital, which also includes an adult hospital, maternity hospital and psychiatric hospital. Conditions are difficult.

Prior to the opening of the new clinic, Chidziva's pediatric ENT patients received care at the adult hospital. When Koltai first traveled to Zimbabwe to advise Chidziva, he stayed in the background, listening and learning about the problems he and Chidziva's staff were going to try to fix.

"I saw the fragility of this medical system," Koltai said. "The lack of supplies, questionable water and electricity, the marginal cleanliness outside of critical areas in the hospital. There were no fiber-optic capabilities — that is, medical equipment used for internal examination of the body — and no record keeping for patients. But I also saw the dedication of these doctors, who were working under conditions we

would find almost intolerable at Stanford."

The types of ENT problems that Chidziva routinely treated — and that Koltai would eventually assist with during his repeated visits to Harare over subsequent years — were far more serious than the general population understands, Chidziva said.

There's a common misperception in Zimbabwe that ENT problems in children are trivial: Parents think that continually running noses, constant snoring and painful ear infections are just a way of life.

But the list of serious problems is long: tuberculosis ear infections with perforated eardrums and often deafness; HIV-associated epiglottitis; obstructed airways; malignant thyroid tumors; congenital neck masses; ingested button-cell batteries; leeches that crawl into the ears of babies left to play in the grass, causing uncontrollable bleeding.

"Many of these things are no longer problems in the modern world, but big problems in the developing world," said Titus Dzungodza, MD, who was the first graduate of the otolaryngology residency Chidziva started, and the clinic's initial director. He is now spending an extra year of training in Australia to become certified as a pediatric otolaryngologist. He will be the first pediatric otolaryngologist in Zimbabwe when he returns to lead the clinic in July.

One of the most serious and common medical problems treated by the Zimbabwean physicians is the recurrent respiratory papillomatosis from which Paige suffers. The HPV virus can pass from mothers to babies during pregnancy or childbirth. The disorder causes growths in the upper respiratory tract that, though not painful, can limit breathing, damage the vocal cords and become life-threatening. The condition is often misdiagnosed in its early stages as asthma, which delays treatment. Children first become hoarse, then lose their voices, as Paige did, and often stop talking altogether. If the growths aren't removed, they threaten to block respiration completely and the children struggle to breathe.

"By the time they get to us, they can't sleep, they're not growing, their breath is raspy and they are struggling to get in air," Dzungodza said. "Usually they're about 3 years old when they first show up, then they return maybe three to five times for surgery as the warts keep growing back. It's a challenge for us, especially when much of the equipment we had been using was quite archaic."

A shared mission

LEARNING TOGETHER THROUGH STANFORD-ZIMBABWE HEALTH CARE PARTNERSHIPS

For 11 months of her Stanford Medicine pathology residency, Megan Fitzpatrick, MD, lived in a tiny rural village in Zimbabwe. There on a fellowship starting in 2016, she conducted medical research at a hospital that was a five-hour drive on dirt roads outside the capital city of Harare.

Her work aimed to prevent cervical cancer, a major contributor to the deaths of the country's women. To optimize prevention efforts, she collected vaginal swabs from local women to study subtypes of the human papillomavirus, which causes cervical cancer. She also held workshops to train community health workers on how to explain cervical cancer to the women there.

Fitzpatrick is one among many Stanford students, scientists, physicians, surgeons and global health experts who have traveled to sub-Saharan African countries to learn and to help developing countries advance their medical education systems. Partnerships between Stanford researchers and the University of Zimbabwe stretch back to the 1980s and provide learning opportunities for both.

During her time in Zimbabwe, Fitzpatrick was able to join a conference on interesting cases with University of Zimbabwe pathology residents. "I saw cases of things we don't often see here, such as schistosomiasis, a parasite that mimics cervical cancer," she said.

Michele Barry, MD, the medical school's senior associate dean for global health and the director of Stanford's Center for Innovation in Global Health, began working in 1988 in Zimbabwe, formerly known as Rhodesia, soon after it gained its independence from the British. Her goal was to help rebuild the medical education system following the bloody civil war that drove medical professionals away. After its independence, the country experienced decades of political instability and corruption.

"There was a brain drain; many left for South Africa," said Barry. "But we continued and built relationships that have lasted."

Clemence Chidziva, MD, an ENT surgeon and professor of otolaryngology at the University of Zimbabwe, came to Stanford in 2015 for a monthlong exchange program to learn how to set up a clinical research program. That year, he

also recruited Peter Koltai, MD, a professor of otolaryngology at Stanford, to help create a pediatric otolaryngology training program at the University of Zimbabwe and establish an ENT clinic for children, which opened in March 2017.

"We were not doing any clinical research," Chidziva said of the time before the collaboration. "Now, we have publications coming out of our clinic. We've established a record-keeping method necessary for conducting research."

Crucial support for Stanford's efforts in Zimbabwe came from the President's Emergency Plan for AIDS Relief and the National Institutes of Health, which provided a \$10 million grant to improve education and research in Africa. The funds enabled Stanford, the University of Zimbabwe and dozens of other institutions to train future Zimbabwean educators, improve technology at the Zimbabwean medical school, develop faculty medical specialists and mentor future researchers.

The NIH initiative, which ended in 2015, sparked numerous Stanford efforts in Zimbabwe that continue today, including Koltai's work to help build the clinic; HIV/AIDS research by David Katzenstein, MD, professor emeritus of infectious disease; and surgical training by Sherry Wren, MD, professor of surgery.

In 2012, Wren established a general surgical rotation project that brought Stanford residents to Zimbabwe and Zimbabwean residents to Stanford. In 2015, she and Zimbabwean medical student Annete Bongiwe Moyo (who has since graduated) launched Zimbabwe's first mentorship group and surgical skills training program for female medical students.

Stanford's global health center recently received a new NIH grant to help the University of Zimbabwe College of Health Sciences build teams of health care providers from a wide range of professions.

Wren, whose work in Zimbabwe has branched out into other African nations, said working in Zimbabwe provides valuable insights for Stanford residents, who have trained in a high-tech environment with the most current medical devices on hand and experts nearby to help.

"It's important for our residents to see how to deliver surgical care in a resource-limited environment," Wren said.



ANNETE BONGIWE MOYO HELPED LAUNCH ZIMBABWE'S FIRST SURGICAL TRAINING PROGRAM FOR FEMALE MEDICAL STUDENTS.

COURTESY OF SHERRY WREN

Shortly after the clinic opened, Dzongodza treated an 8-year-old girl who was gasping for breath when she arrived at the clinic, after having traveled all day with her mother by bus from a rural village hundreds of miles away to reach the nearest hospital.

She was rushed into emergency surgery on that spring evening for what would be her eighth procedure to remove the viral warts from her larynx. As a toddler, she was misdiagnosed with asthma and had arrived at the hospital the first time when she was 3, struggling to breathe. This time, though, she was initially seen at the new clinic, with staff better trained to treat children, and had surgery at the children's hospital with new equipment designed for use with children.

"All the surgeons on the unit had met her one way or the other over the years," Dzongodza said. "Often, the senior colleagues would dig into their pockets to get her bus fare for the next journey back to the hospital."

THE CLINIC

To make his vision of starting a clinic a reality, Chidziva started by raising funds for construction from the Christian Blind Mission International, a charity committed to improving conditions of those living in some of the poorest communities in the world. Next, he invited Koltai to join his team. Koltai's prior experience in establishing the pediatric ENT programs at the Albany Medical College and the Cleveland Clinic, and leading the pediatric otolaryngology program at Stanford as its director for 10 years, proved invaluable, Chidziva said.

"Clemence had a vision, and I bought into it," Koltai said. "This project resonated with my goals of seeing the footprint of pediatric otolaryngology spread far and wide. I would supply some of the knowledge and know-how, and Clemence supplied the leadership."

Recognizing the need for specific tools and instruments for a pediatric otolaryngology unit, Koltai has since spent endless hours scanning eBay to scrounge up reusable medical equipment at affordable prices. He shipped two decommissioned surgical microscopes from Lucile Packard Children's Hospital Stanford to Harare and has been key in plans for the delivery of an ultrasound machine as well as other instruments. The Jenks family of Menlo Park, who had supported

Peter's work, together with his Zimbabwean counterparts, helping to stock the clinic with instruments and develop a training program for the surgeons, was a terrific example of an equity partnership.

Koltai's research work in the past, helped fund the eBay purchases and shipping costs. Early on, he secured funding from Stanford's Department of Otolaryngology-Head and Neck Surgery to fly two senior resident physicians to Stanford for a month of study. This has become an annual observership with continued funding from the otolaryngology department and accommodations provided by the Koltais in their home. Stanford's Center for Innovation in Global Health provided seed funding for Koltai's first trip to Zimbabwe, along with continued financial and moral support.

"Peter's work, together with his Zimbabwean counterparts, helping to stock the clinic with instruments and develop a training program for the surgeons, was a terrific example of an equity partnership," said the center's director Michele Barry, MD. "Having worked on and off in Zimbabwe for almost 30 years, I can tell you that this accomplishment was no small feat."

Koltai has returned repeatedly to Harare to teach advanced surgical techniques, hold seminars and set up a record-keeping system for patients in the new clinic. The record keeping will be essential for Chidziva's long-range plan of creating a training ground at the clinic for future pediatric ENT surgeons, along with a research program to better understand the otolaryngologic needs of African children and develop data suitable for publication to help advance academic appointments at the University of Zimbabwe. The first research project on the docket, he said, will be a clinical trial to identify the subtypes of HPV responsible for papillomatosis in Zimbabwe. "We feel that with scientific evidence to support us, we can get our government to change to a vaccine that is effective against the HPV subtypes responsible for this disease," Chidziva said.

Still, the clinic remains a work in progress. Plans are moving ahead to open an outpatient surgicenter adjacent to the clinic. The surgicenter would have two operating theaters dedicated to treating children with ENT problems. Fundraising has been amped up to fill gaps in care caused by the tripling of the patient load following the opening of the clinic. Constant funding shortfalls mean that much of the equipment considered essential at Stanford, such as MRI or CT machines, remains out of reach in Harare.

"When we created this clinic, we did it to improve care



COURTESY OF PETER KOLTAI AND YOLANDA BUNJIRA

FROM TOP: CLEMENCE CHIDZIVA, AT LEFT, IS WITH TITUS DZONGODZA, WHO IS RECORDING A LARYNGOSCOPY CONDUCTED BY PETER KOLTAI, TREATMENTS AT THE CLINIC HAVE BROUGHT BACK PAIGE BUNJIRA'S VOICE; DZONGODZA WITH A PATIENT SHORTLY AFTER THE CLINIC OPENED.

for our patients,” Chidziva said. “But within the first year of opening, we saw 3,500 patients, three times the average caseload. The struggle now continues to get them all onto an operating table in time.”

THE FUTURE

Last May, the team organized the first international symposium to advance pediatric otolaryngology to be held in Africa.

Called PENTAfrica and held in Zimbabwe, it was attended by otolaryngologists and other health care professionals from Africa, Europe, and North and South America. The event launched the organizers’ plan to use the children’s clinic as a model to provide education, expertise and greater access to care across the continent.

“We’re hoping our new clinic will plant a seed in each and every country in Africa,” said Chidziva. After Dzungodza returns from Australia, fully trained in pediatric otolaryngology, and the clinic’s operating wings open in July, Chidziva plans to invite ENTs to observe Dzungodza in his work so they can better understand the needs of pediatric patients and how they might be able to replicate the clinic’s model.

Still, such immediate needs as tracking down equipment and even navigating for hospital space for surgeries continue to challenge their ability to ensure treatment for children like Paige. The virus is especially aggressive in young children, including Paige, who needed a second surgery in November and a third in December. Then, a 40-day doctors’ strike left the clinic’s senior registrar, Erasmus Muganda, scrambling for two days — amid a flurry of communications with Chidziva and Koltai — to find a space to operate.

Koltai said he will do what he can to help the clinic build capacity to treat children like Paige, and he marvels at how his connection with the art of sculpture brought her into the clinic’s fold. A lifelong artist, Koltai provides medical illustrations for his own publications and recently began formal training in painting. “What inspires me about Paige is how serendipity has tied together my work in both the medical as well as the sculpture communities,” Koltai said. “My life’s work has revolved around taking care of kids and making art; the yin and yang of my being. Somehow this story has the scent of fate.” **SM**

— Contact Tracie White at traciew@stanford.edu



THE
M O S Q U I T O
T R A C K E R S

APPREHENDING
THE INSECTS
SPREADING DENGUE,
CHIKUNGUNYA
AND ZIKA

In 2016, Stanford infectious disease expert Desiree LaBeaud, MD, sent teams of schoolchildren to hunt for mosquito larvae and pupae around their homes in coastal Kenya.

In particular, they were looking for immature *Aedes aegypti* mosquitoes.

“The kids would say, ‘We found tons. They’re in all these piles of trash at the end of every block,’” said LaBeaud, associate professor of pediatrics at the School of Medicine.

LaBeaud remembers thinking, “Oh, God, now what are we going to do?”

The black-and-white-striped mosquitoes don’t spread malaria, the most famous mosquito-borne disease, but they spread several others, including dengue, chikungunya and Zika, which cause millions of human infections annually throughout the world.

And they adore garbage. Unfortunately, the rural Kenyan communities lacked trash collection and recycling programs. Much of the accumulated litter consisted of discarded, open plastic containers that hold water, where more than 80 percent of the mosquito breeding was taking place, the children and scientists discovered.

For the past several years, LaBeaud’s team has been studying diseases spread by *Aedes aegypti* and working to reduce outbreaks around the world. Dengue kills about 20,000 people every year; Zika can cause pregnancy loss and serious birth defects; and chikungunya produces debilitating, long-term arthritis in many people. Drugs and vaccines against the viruses are lacking, so there is a pressing need to understand how mosquitoes and humans interact in order to predict and prevent outbreaks. This is what LaBeaud has set out to do.

BY ERIN DIGITALE

ILLUSTRATION BY JASON HOLLEY

LaBeaud, trained as a pediatric infectious disease specialist, said the work requires her to be “half ecologist, half anthropologist.” A variety of factors — such as trash collection practices, household water sources and neighborhood violence levels — can all influence local risk for the viruses in the developing world, her team is learning.

Mosquito-borne illnesses are transmitted by intimate chains of insects and humans: An infected mosquito bites a person, who gets sick and is bitten by other mosquitoes, which get infected and bite more people. Most people recover eventually, but the mosquitoes don't; an infected insect is thought to keep spreading disease until it dies.

VIRUSES ON THE MOVE

LaBeaud's interest in mosquito-borne diseases began on a 2002 trip

to Laos. She had recently finished medical school and was completing pediatrics training at Rainbow Babies & Children's Hospital in Cleveland, where her residency program included an international health track with rotations in developing countries. Her two-month rotation to Southeast Asia overlapped with monsoon season and a large dengue outbreak.

“I treated a lot of children with dengue and saw a lot of children die from dengue,” said LaBeaud. Although many people make a full recovery, dengue hits hard in vulnerable populations, including babies and kids. It can cause life-threatening hemorrhagic fever — with low blood platelet levels and bleeding — as well as dangerous drops in blood pressure. “It's terrible to have to say, ‘I'm sorry, I can't help,’ especially being a pediatrician,” she said.

The suffering of her young Laotian patients motivated LaBeaud to study outbreaks of neglected tropical diseases. After her residency, her pediatric infectious disease fellowship took her to Kenya, where she fell in love with the complexity of figuring out how mosquitoes, people and insect-borne viruses interact. “These viruses have both sneaky, insidious transmission and large, overwhelming outbreaks,” she said.

LaBeaud soon learned that insect-borne viruses were on the move. Before 1970, severe dengue had been documented in nine countries. Today it's in more than 100 countries, putting more than 40 percent of the world's population at risk. Chikungunya used to be found only in Africa, Asia and India, but is now being reported in Europe and throughout the Americas. Zika has also become more widespread in recent years, causing a health emergency upon its 2015 arrival in Brazil, for example, where nearly 3,000 infants whose mothers were infected during pregnancy were born with



microcephaly and other severe birth defects.

Vaccines for dengue, chikungunya and Zika are in development, but complexities of the viral biology and limited financial support for the research have slowed the work. LaBeaud realized that helping to illustrate the scope of the diseases might improve funding and could assist public health officials in targeting mosquito control efforts.

A woman with dark, wavy hair and a red smile stands in a field of tall, brownish grass. She is wearing a dark green cable-knit jacket, grey riding pants, and red and orange boots. She is standing on a wooden post. In the background, there is a calm river reflecting the sky, and a line of trees on the horizon under a clear blue sky.

DESIREE
LABEAUD
STUDIES HOW
MOSQUITOES,
PEOPLE AND
VIRUSES
INTERACT.

HIDDEN OUTBREAKS

In their early stages, both dengue and chikungunya resemble malaria, a parasitic mosquito-borne disease that is widespread in many developing countries. Like malaria, dengue and chikungunya cause high fevers, headaches, chills and muscle aches — and be-

cause there are no cheap, accurate, rapid diagnostic tests, in some regions anyone who shows up at a health clinic with these symptoms is automatically diagnosed with malaria.

Since 2014, LaBeaud's team has been using polymerase chain reaction blood tests to look for genetic material from the dengue and chikungunya viruses and the malaria parasite in blood samples from children treated for fever at

Kenyan health clinics. The scientists' early data confirm their suspicions that dengue and chikungunya have been hiding in plain sight.

"In some of our communities, 98 percent of the children have a bit of malaria DNA running through their veins," LaBeaud said, noting that up to 40 percent of the children with a fever-related illness have dengue or chikungunya viruses in their blood. Around a third of Kenyan kids who are sick with fevers actually have viral infections, she estimates. "That's huge news," she said. "Before this research, the Kenyan ministry of health didn't recognize that dengue and chikungunya were endemic in the country."

Identifying why children get sick is essential to effectively preventing outbreaks. In the past, mosquito-control

what they'd find. They knew that *Aedes* mosquitoes like to breed in containers. In the rural region where the study was conducted, near Kenya's Indian Ocean coastline, people keep large household water containers on hand to protect themselves from the unreliability of local taps and wells. Because the mosquitoes don't fly very far — traveling within a radius of perhaps a few hundred yards over the course of their lives — the researchers figured that tracking their breeding sites with a house-to-house survey made sense.

"We went in thinking, 'It's going to be the prominent containers we know about, the big jerrycans that are 10 or 20 liters,'" Forsyth said. Instead, they discovered that 80 percent of mosquito breeding was happening in "containers of no purpose," many of which were trash. Other such

'PEOPLE DON'T RECOGNIZE THAT SPECIES AND ALL THE DIFFERENT

efforts in Kenya were targeted only at malaria-carrying *Anopheles* mosquitoes, which bite at night and breed in vegetated areas such as rice fields and swamps. But *Anopheles*-specific prevention measures, such as sleeping under insecticide-treated bed nets, don't offer protection from dengue and chikungunya, which are transmitted by mosquitoes that bite during the day. Instead, it's important to target *Aedes*' favorite habitat, water containers. In a paper published this year in the *American Journal of Tropical Medicine and Hygiene*, LaBeaud's team showed that children whose households used water storage containers — rather than getting water from a tap or well — were more likely to be infected by the viruses.

"People don't recognize that there are lots of different mosquito species and all the different mosquitoes have their own little mosquito behaviors," LaBeaud said.

PURPOSE MATTERS

Even when mosquitoes' behaviors are thought to be well-understood, close examination of their interactions with people can yield surprises.

When LaBeaud and graduate student Jenna Forsyth decided to involve Kenyan school children in mapping where *Aedes* mosquitoes were breeding, they thought they knew

containers were being kept in a family's yard "just in case they were needed."

"It turns out that a lot of the containers used for drinking and cooking don't sit around long enough for mosquitoes to breed," said Forsyth. When designing the next steps of the project, they realized they had to target those irregularly used containers. "It's meaningless if we just say, 'Dump out your buckets.'"

The researchers worked with local residents on taking actions that could reduce mosquito breeding, such as storing unused containers upside down. And they challenged 250 children involved in the study to see who could collect the most no-purpose containers. The kids collected 1,000 kilograms of plastic waste, consisting of more than 17,000 containers. They used 4,000 of the containers to sprout native tree seedlings, which were planted around their communities.

"We pivoted our study; the message really became about reducing and reusing plastics," Forsyth said. The team is repeating the study in an urban region of Kenya and has obtained funding to collaborate with faculty at the Technical University of Mombasa to study how local entrepreneurs can simultaneously reuse plastic waste and alleviate poverty.

"The project goal is to engage entrepreneurs to collect trash for profit, to set up something that will continue without us," said Amy Krystosik, PhD, a postdoctoral scholar

with the LaBeaud lab who has been collaborating on the project. “We want to use innovation to get the community excited, to incentivize them to clean up the environment and protect their own health.”

FEEDING ON VIOLENCE

But sometimes the barriers to lowering disease risk have a completely different shape. Krystosik was a graduate student working in Cali, Colombia, when community members told her that local violence might be increasing the spread of mosquito-borne disease.

Cali, a city of 2.4 million, is among the most violent in the world, with homicide regularly ranking as one of its top

homicide risk. Homicides clustered in the central-eastern portion of the city, where dengue risk was also highest. The biggest surprise was that the statistical association persisted after controlling for poverty, itself a widely recognized risk factor for mosquito-borne disease.

“Everybody assumed disease risk would be in direct relation to socioeconomic status, but we found, independently, that violence was still a predictor of higher burdens of dengue,” Krystosik said.

Knowing more about the link between violence and mosquito-borne disease could help public health officials better predict outbreaks of disease and gauge the broader health benefit of communities becoming more peaceful. Right now, the combination of local violence and mosquito-borne disease is “a double burden on the population,” she added.

THERE ARE LOTS OF DIFFERENT MOSQUITO MOSQUITOES HAVE THEIR OWN LITTLE MOSQUITO BEHAVIORS.'

two causes of death. And Cali’s slums are full of mosquito habitat: Located near lagoons and rivers, they lack basic infrastructure and flood during the rainy season. People throw trash in the waterways, making them even more appealing to container-breeding *Aedes* mosquitoes.

When Krystosik, then a PhD student at Kent State University, proposed surveying the slums for mosquitoes in 2014, Colombian public health experts told her it would be tricky. She’d have to get help from locals to navigate “invisible borders” between territories controlled by competing gangs. The city’s public health efforts had already been hampered by gang violence; city workers couldn’t check the function of local drains or set up mosquito-control methods that required them to go out into the community.

“I thought, ‘That’s crazy! We have methods to use for vector control, yet we can’t provide these services to communities that need them most,’” Krystosik said.

Her interest piqued, she began a project that continued when she moved to LaBeaud’s lab as a postdoctoral scholar in 2017. Using 2014-2016 data on homicides and cases of dengue, chikungunya and Zika, she mapped the overlap between community violence and illness in space and time.

The findings, published in 2018 in the *International Journal of Environmental Research and Public Health*, showed a statistically significant overlap between dengue infections and

“People are not going to be able to perform prevention and protect themselves from these viruses if they’re more interested in daily survival.”

USING CLIMATE DATA

On-the-ground mosquito hunts, as informative as they can be, are challenging to carry out on a large scale. So the research team recently took another approach for predicting where disease outbreaks could occur: building mathematical models that depend on climate data.

Ultimately, the team would like to be able to use remotely sensed data — from weather satellites for instance — to inform when and where mosquito-control strategies such as pesticides would be most effective.

“People don’t want to spray all the time; it’s expensive and labor-intensive,” said postdoctoral scholar Jamie Caldwell, PhD, who is leading the work in collaboration with LaBeaud; Erin Mordecai, PhD, assistant professor of biology at Stanford; and Eric Lambin, PhD, professor of earth system science and a senior fellow at the Stanford Woods Institute for the Environment. Targeting mosquito control to exactly when and where it’s needed could also reduce the chance that mosquitoes will become resistant to pesticides, as occurred

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A GLOBAL PURPOSE

education, research and care



a better brick

A QUEST TO SAVE LIVES BY CLEANING UP PRODUCTION
OF A UBIQUITOUS BUILDING MATERIAL

BY ROB JORDAN





BRICK PRODUCTION ON THE OUTSKIRTS OF DHAKA, BANGLADESH, FALLS TO SEASONAL WORKERS AND CAN BE DONE ONLY IN THE DRY WINTER SEASON. WORKERS, CLOCKWISE FROM TOP LEFT ON OPPOSITE PAGE, LINE UP RAW BRICKS TO DRY BEFORE FIRING, CARRY FIRED BRICKS TO TRANSPORT TRUCKS, STACK FIRED BRICKS, TAKE BUCKETS OF COAL POWDER TO KILNS FOR FUEL, SEPARATE FIRED BRICKS, AND REMOVE FIRED BRICKS FROM A KILN.

When Stephen Luby, MD, first arrived in Dhaka, Bangladesh, in 2004, he barely registered the hazy atmosphere. The 45-year-old epidemiologist from Nebraska had spent several years in Karachi, Pakistan, where soot-choked air was as predictable and intractable as open sewers and rutted roads. It didn't distract him then from his mission to save lives with modest, affordable health interventions, such as hand-washing training and directions to local clinics. It wasn't going to distract him now.



PHOTOS: [HTTP://INSTAGRAM.COM/NAVAISM](https://www.instagram.com/navaism)

Luby was focused on his new job with the U.S. Centers for Disease Control and Prevention, where he would be investigating emerging infections in a region considered a global hot spot. “I believed in what I was doing.”

As Luby, his wife, Jeni, and their four children moved into their U.S. embassy-furnished house in a quiet enclave of Dhaka, they found a rattling electrostatic air purifier the size of a small refrigerator.

“I thought, ‘Where is the data showing that thing has any effect?’” recalled Luby, now a professor of medicine at Stanford and director of research at the Center for Innovation in Global Health. “I turned it off. It stayed that way for eight years.”

Over time, though, Luby became aware of a catastrophic airborne health threat facing tens of millions of people, and a likely culprit was the production of a ubiquitous building material: the humble brick. The realization forced Luby to rethink basic medical assumptions, and to challenge development community dogma that was failing to address the issue.

Now, after more than eight years of research, analysis and on-the-ground negotiations, Luby is poised to launch a plan to transform the brick kiln sector in Bangladesh and, ultimately, across South Asia.

SILENT KILLER

Consistently ranked among the world's least livable cities, Dhaka is a cacophonous overflowing sprawl of more than 10 million people, with a population density of 44,500 per square kilometer. While other metrics of misery have declined in the face of the country's burgeoning economy, air pollution remains a scourge during the dry, winter months. Dhaka's air quality index, a representation of pollutant concentration over a specified period of time, hovers above 150 — a level considered unhealthy for all groups — but often spikes much higher between November and February.

“When you open the door to go out in the morning, there's a haze of smoke that hits your face,” said Alex Yu, MD, a post-doctoral scholar in infectious disease who works in Luby's Stanford lab. “You have a chronic low-grade cough. We call it Dhaka lung. People don't want to go out, but life has to go on.”

Still, when a Bangladeshi colleague of Luby's suggested they install air particulate sensors in Dhaka households as

It's different from a medical model that says let's wait until they get sick and treat them in clinic. We need to think, like a physician, about how we can treat the environment.

part of a 2011 influenza and pneumonia study, Luby was skeptical. “I was looking at it primarily through the lens of the pathogen — what organism was causing problems,” Luby said. “I was not attuned to air quality. I hadn't really thought about the science.”

The findings were stark: Air pollution had a huge impact on respiratory infections, but indoor air pollution — the focus of most related public health community efforts — wasn't the only culprit. It turned out that the most important determinant of indoor air quality was outdoor air quality. Surprised, Luby shifted his focus to the environment's effect on health.

“It's different from a medical model that says let's wait until they get sick and treat them in clinic,” he said. “We need to think, like a physician, about how we can treat the environment.”

Air pollution is among the largest contributors to mortality worldwide, hastening the deaths of more than 7 million people a year, according to the World Health Organization. Although the model-based WHO estimate is contested by some health experts, pollution's damaging impacts are clear. Microscopic particles of soot, ash and other pollutants can penetrate deep into lungs and bloodstreams. Resulting long-term inflammation and organ damage can lead to pneumonia, heart disease, strokes, premature births, early onset lower respiratory infection in children and a host of other ailments.

Luby realized that if he could determine what was driving the outdoor air pollution in Dhaka, he might be able to lift the curse of pneumonia, the leading killer of children under the age of 5 globally.

TO THE SOURCE

Once Luby began looking for a pollution source that might be causing such deadly infections, his research quickly led him to brick kilns. As Bangladesh's population and economy has grown, so has its need for building materials. In a land of few trees and minimal manufacturing capacity, bricks fit the bill. Primarily burning coal, thousands of kilns ringing Bangladeshi cities turn out about 25 billion bricks a year. It's a familiar story throughout South Asia. Brick kilns across the region have a global warming impact equivalent to that of all U.S. passenger cars.

In Bangladesh, a single brick kiln spews up to 53 tons of

carbon monoxide in one season, the annual equivalent of more than 180 passenger cars in the United States. The country's 5,000 or so kilns are responsible for about 40 percent of airborne particulate matter during winter (kilns operate only during rainless winter months so bricks can be left outside to dry). Perhaps unsurprisingly, hundreds of thousands of people who live downwind from kilns face an elevated risk of cardiovascular and respiratory disease, and tens of thousands of adults die from pollution-related illnesses each year, according to modeled estimates.

Research by Allison Sheris, a graduate student in Stanford's Emmett Interdisciplinary Program in Environment and Resources, suggests a correlation between spikes in airborne particulate matter and increased rates of pneumonia among children in Dhaka. Sensors reveal a strong signal of sulfate, a chemical common to coal burning, in the city's air.

"I had given brick kilns very little thought," Luby said. "Now, I can talk for days about kiln designs, technology, regulation, combustion. I can find specific data that substantiate the problem, then hold onto them like a bulldog."

But good data about the magnitude of the problem is hard to find. Yu and graduate student Nina Brooks are trying to fill that gap and quantify the adverse health effects that can be attributed to brick kilns. They are comparing rates of asthma, chronic obstructive pulmonary disease and other air-related illnesses in communities with and without kilns.

"This is about saving people's lives," Brooks said. "Human-generated waste is what's killing so many people — mostly poor people. It's preventable."

As research continued, Luby's team found mounting evidence that the global development community's approach to mitigating health effects of air pollution was systematically



STEPHEN LUBY SEES A WAY TO QUELL AN AIRBORNE HEALTH THREAT AFFECTING MILLIONS.

flawed. For years, funders poured hundreds of millions of dollars into improving people's health by targeting indoor air quality and advocating for cleaner-burning cookstoves. After more than three decades of promoting the stoves in Bangladesh, less than 2 percent of households were using them. To Luby, it was a self-perpetuating cycle of failure that had overlooked the key connection between outdoor and indoor air pollution. "Money comes available when an idea gets a certain amount of currency," Luby said. "People will do things because funding is available."

BRIAN SWALE

The pattern is familiar to people trying to solve health problems in the developing world. “The solutions that seem like they should be the most sustainable, effective and beneficial to people and the environment are not always feasible on the ground,” said Erin Mordecai, PhD, an assistant professor of biology who studies the ecology of infectious disease. “For example, improving access to clean, reliable, piped water would lift billions of people out of poverty, improve quality of life and reduce transmission of disease. But aid often focuses only on stopgap solutions like medicines and treatments once people are infected, which leave them vulnerable to reinfection after the initial treatment wears off or aid programs dry up.”

“It was clear people preferred their old cookstoves,” Luby said. “They cooked their chapatis better. I never thought it was going to be easy to change the way several thousand kilns make bricks, but I thought it’s got to be easier than changing the way 40 million households cook their meals.”

TEAMING UP

Luby was at a point where he was ready to lay the groundwork

for a plan of attack, which coincided with his 2012 hiring at Stanford, where he is also a senior fellow in the Stanford Woods Institute for the Environment.

To start, he gathered a team of Stanford researchers, including renowned political scientist Francis Fukuyama, PhD, and geophysicist Howard Zebker, PhD. Fukuyama, who, like Luby, is a senior fellow at the Freeman Spogli Institute for International Studies, helped Luby understand governance issues and formulate a politically effective message to incentivize kiln owners to switch to cleaner technologies. Zebker, a professor of electrical engineering and of geophysics, is an authority on developing space-borne radar systems and using remote sensing data to study earthquakes and other phenomena. He laid the groundwork for a satellite imaging program to pinpoint kiln locations, something that’s difficult to do using unreliable government records.

“This problem seems to be one in which you could have a huge payoff both locally and for the world as a whole if you could get to the proper solution,” Fukuyama said. “Most problems promise to improve life much less.”

Luby and his colleagues burned through iteration after iteration. “We definitely pursued some dead ends,” he said. Among the team’s biggest failures was a pollution-scrubbing

technology they spent months developing. At the invitation of a member of India’s parliament, Luby traveled across the state of Punjab to pitch the idea to industry leaders. Without an incentive to install the \$5,000 device, kiln owners balked.

Eventually, a game plan began to materialize. Luby and his team used the satellite data to start building a website that gives people information about nearby kilns, and teaches them how to nudge kiln owners toward making their operations more efficient and profitable. The site will help users pinpoint kilns that violate local ordinances and design standards, and join a larger discussion among public- and private-sector stakeholders.

Working with Greentech Knowledge Solutions, a Delhi-based leader in improving brick kiln efficiency, Luby’s team formulated affordable technology options, such as transitioning from a fixed chimney to a zigzag kiln, in which the flames from the kiln’s fire and a mechanized coal feeder circulate around the circumference of the kiln to take advantage of natural air drafts. The method improves combustion efficiency — a major incentive for kiln owners whose primary expense is coal — and reduces black carbon emissions by more than 80 percent.

The plan also includes a mechanism to provide loans for the cost-saving upgrades, a significant step for an industry that mostly operates in an informal economy. Seasonal and with few fixed assets, brick making is considered by the Bangladeshi government to be temporary, and therefore ineligible for government-backed bank loans.

“When we initiated this project, I saw that everyone, including the government and media, was blaming brick manufacturers for generating air pollution,” said Debashish Biswas, a Bangladeshi anthropologist working with Luby. “But thinking from the kiln owners’ perspective is important. Rather than impose changes on them, we need to identify the best viable strategy to solve the problem.”

By tracking emission reductions, the initiative could earn credits from global climate change funds. These credits, one for each ton of CO₂ kept from the atmosphere, could then be traded or sold to industrialized countries trying to meet emission reduction targets. The earnings could then be used to finance kiln upgrades and ongoing oversight of measures to meet efficiency and climate objectives.

“We’re doing something completely novel here,” Luby said.

The plan was in place, but Luby still lacked a key ingredient: a resourceful and influential partner to facilitate and oversee the initiative. The perfect candidate turned out to be nearby.

Founded in 1972 to help refugees after Bangladesh's war for independence from Pakistan, Building Resources Across Communities is the world's largest nongovernmental organization. Luby was familiar with its numerous, respected branches because he taught classes at the organization's school of health for several years.

With training from Greentech, the BRAC construction group could provide technical expertise to kiln owners on improving manufacturing practices, including support for construction and management upgrades. Its small-enterprise program could provide loans to kiln owners for upgrades, while ensuring adherence to standards and repayment. Its presence in tens of thousands of communities across Bangladesh made it an ideal partner.

Luby was mindful that the project's fate rested on his pitch, so he approached the director of BRAC, Fazle Abed, with trepidation. When they met, Abed held up his hand to signal his need to speak first. "I really appreciate what you've done for our school, and what you've done for Bangladesh," Abed told Luby. BRAC would join the effort.

"It struck me how much these big decisions are based on trust and relationship," Luby said.

The lesson is not lost on colleagues of Luby's, such as Desiree LaBeaud, MD, an associate professor of pediatrics at Stanford who has conducted extensive epidemiological field work in Kenya. "For the successes we have had, our trusted long-term relationships across sectors have been the driving force for sustainable improvements in our communities."

UNLIKELY ALLIES

There was just one major sticking point left. "As in many policy problem areas, the chief issue is to build a stakeholder coalition in favor of the kind of reforms that are necessary, and to find ways to get around those players who are opposed to change," Fukuyama said. "In the case of the brick kilns, it was assumed that the existing kiln owners would not accept the medical evidence that what they were doing was harmful."

Luby's anxiety over this possibility came to a head in January 2013. He had invited influential stakeholders, including representatives from government agencies, nongovernmental organizations and brick-dependent construction firms, to a dialogue in a Dhaka convention center aimed at gathering feedback on kilns' health hazards, as well as incentives for

'For the successes we have had, our trusted long-term relationships across sectors have been the driving force for sustainable improvements in our communities.'

change. Would the kiln owners come? If so, what would they say? Would they protest or demand major concessions? Jamil Hussain, vice president of Bangladesh's national brick manufacturing association, told Luby he likely would not show. He was wary of bad press and criticism for his already maligned industry.

Luby hired professional meeting facilitators and barred media coverage. Hussain showed up at the last minute. So far, so good. Luby braced himself for reaction to a colleague's presentation about the health impacts of kilns. There was a long moment of silence, then Hussain rose and asked to address the audience.

"I was at the edge of my seat," Luby said. "I thought this could be a shouting match. It could go off the rails."

Instead, Hussain told the crowd, "We don't dispute anything you just said. Brick kilns do damage the environment and human health. What I'm asking for is your help in solving this problem. I'd like you to help us so that people don't hate us."

Luby was stunned. And, now, instead of having to advocate for the project, he could focus on finding a solution.

Luby's concept, with its various incentives, had struck a chord for Hussain and other kiln owners wary of complicated and expensive pollution-reduction systems pushed by the central government. "If the new technology is economical and environment-friendly, if it's not harmful to our business, everyone should be interested," said Hussain. "This approach makes it possible for us to follow the regulations of the government and maintain our business. That's why we listened to Dr. Luby."

Working closely with kiln owners is another way Luby butts up against what he considers a systemic bias toward top-down solutions in the global development community. "We often get pushback," Luby said. "Why are you working with these guys? These guys don't wear ties. They're not educated." Luby's answer is simple: "These guys have 85 percent of the market. Why don't we work with the market leaders? They have a business model that works.' It pushes against this idea that we should leapfrog to the modern, that we should do it like we do in North Carolina or wherever."

Luby's team hopes to pilot various technological interventions at Bangladeshi kilns to generate results that would nudge kiln owners, government regulators and others toward change. He's seeking funding of \$4 million to \$8 million for pilots at about 10 Bangladeshi kilns this spring and at another

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A MOVEMENT TAKES OFF TO PUT MORE WOMEN
AT THE TOP IN MEDICINE

BY JODY BERGER

ILLUSTRATION BY SALLY DENG

cultivating women leaders

Michele Barry, MD, was sitting beside Wafaa El-Sadr, MD, at a conference on medical education in Nairobi in the summer of 2016. The two women — Barry, the senior associate dean for global health at the Stanford School of Medicine, and El-Sadr, the director of Columbia University's global health initiative — had known each other for years.

They listened as the medical school deans on stage discussed the future of medicine in Africa. When one man said that their countries would lead the world in progressive medical education, Barry shot a glance at El-Sadr.

“What is wrong with this picture?” Barry asked El-Sadr. Accustomed to seeing only white men speaking on similar panels in the United States, the two women had traveled around the world to find a panel composed of all black men in leadership and Francis Collins, MD, a white man who directs the U.S. National Institutes of Health.

Barry raised her hand to speak. “If you want to be the most progressive continent, look at who's on your podium,” she said. “You don't have a single woman. It behooves you to think about that.”

A few dozen women were scattered among the crowd of several hundred men. As Barry sat down, they stood and applauded. They understood that Barry's comments were a call to action that went beyond this panel. That realization — in that moment — became the catalyst for what has become an international movement to ensure that the decision-makers in global health look more like the population whose lives and well-being depend on their decisions.

In the United States and Canada, women lead just 1 in 6 medical schools, according to a 2018 survey by the Association of American Medical Colleges. And worldwide, women lead fewer than a third of health organizations, according to research by Global Health 50/50, an independent initiative housed within the University College London Centre for Gender and Global Health. For now, the people making critical decisions about how doctors are trained and how health care resources are allocated

mobile health van to connect medical professionals with victims of domestic violence who were unlikely to seek care in hospitals. She launched the first clinic devoted to refugee health in the Northeast. And she started one of the first overseas residency programs to introduce U.S. physicians-in-training to different cultural approaches to health care and strengthen medical settings globally. At Stanford, she created a residency track to prepare physicians to work in places with few resources.



around the world are disproportionately male.

Barry, the incoming chair of the Consortium of Universities for Global Health's board of directors and past president of the American Society of Tropical Medicine, wondered if the imbalances at the highest levels of leadership contributed to the imbalances in health outcomes. "There is no shortage of smart, educated and talented women working in global health," she said. "These women bring a different perspective than men, and their perspective is critical if we are going to improve health outcomes around the world."

For much of her career, Barry has focused on expanding access to health care. At Yale University, she created a

To Barry, the inequalities in health around the world demand attention and action. Why should people in one country suffer from a disease that is preventable, curable or at least manageable in another country?

After the conference in Nairobi, Barry began organizing the first women's leadership conference, in part with help from Collins, who provided a grant from the National Institutes of Health to get started.

Barry wanted people working for gender diversity in health care to share best practices, identify ways to collaborate, and inspire each other and the next generation of advocates. The Women Leaders in Global Health Conference was held for the first time at Stanford Oct. 12, 2017.

BUILDING THE NETWORK

PHYSICIANS, PROFESSORS AND REPRESENTATIVES FROM GOVERNMENT AND non-governmental organizations arrived on campus from 68 countries for the 2017 conference. Barry opened her Rolodex and leaned on her female colleagues to help her raise money and shape the conference's content. Women from 10 American universities and several foundations funded scholarships so women from low- and middle-income countries could attend. A group of women lawyers helped women from majority Muslim countries acquire visas so they could also make the trip, despite the travel ban President Donald Trump instituted earlier that year. Representatives from international organizations such as the World Health Organization, Women in Global Health and the United Nations Foundation helped structure the conference agenda.

The Bill and Melinda Gates Foundation awarded a grant to help fund the conference and sent a video greeting so Melinda Gates could speak to the more than 400 attendees. "This conference is about unraveling the complex, sometimes invisible systems that undervalue women," Gates said. "It's about building new platforms from which women can lead."

Women with experience leading teams at foundations,

position that was 20 percent academic and 80 percent administrative. She wondered sometimes if she had chosen career suicide because she had no time to pursue research, write grant applications or collaborate with other people.

"I was in leadership, but I was so isolated," she said. "I didn't have the connections that I wanted to have. Or the encouragement that I desperately needed. The conference at Stanford felt like an intervention because it suddenly plugged me back into a network of like-minded people."

Others were similarly inspired. At the final plenary session, women leaders from England, Rwanda and Peru stood one after another to offer up their home countries to host future conferences. Heidi Larson, PhD, director of the Vaccine Confidence Project at the London School of Hygiene and Tropical Medicine, called dibs on the 2018 conference. She spent a year organizing, planning and fundraising so she could expand the event, which took place over two days in November in London and included panels on political leadership, big data in global health and social entrepreneurship. It also offered more formal mentorship opportunities, including a breakfast where early career women could seek advice from groundbreakers like Joanne Liu, MD, interna-

'I was in leadership, but I was so isolated.'

I didn't have the connections that I wanted to have. Or the encouragement that I desperately needed.'

universities and the NIH spoke at the conference about why gender matters in the health workforce, how to become change agents and enlisting men in the effort to elevate women. Former U.S. Secretary of Health and Human Services Donna Shalala encouraged the crowd to reach higher. And Gary Darmstadt, MD, professor of pediatrics and associate dean for maternal and child health at Stanford, reminded the mostly female crowd that they weren't the only ones who would benefit from more diverse leadership. "Where you have greater gender equity, men's longevity improves, as does women's longevity," he said. "We have a lot to gain."

Rose Clarke Nanyonga, PhD, came from Uganda, where she is the vice chancellor of Clarke International University (formerly International Health Sciences University). Born in Uganda, she enrolled in college in the United States and stayed for graduate school. After earning her doctorate in nursing from Yale University, Nanyonga considered staying in the United States, where she'd have more career opportunities. Instead, she returned home and ultimately took a

tional president of Doctors Without Borders, and Patty Garcia, MD, the former minister of health in Peru.

"I had the most wonderful mentor," Garcia said, remembering her early training in the United States with King Holmes, MD, PhD, who directs the Department of Global Health at the University of Washington. "I learned so many things from him that I would never have thought about otherwise. Unfortunately, in countries like mine, and most low- and middle-income countries, we don't have that experience of mentorship."

More than 900 people attended the London conference, and thousands more watched online. The gathering offered small-group discussions that sparked immediate collaborations. In one session, an attendee from Somalia said she wanted to offer more training for nurses and midwives but found it difficult to hire outside instructors because of the continuing armed conflict in her country.

"Those nurses and midwives could be trained in the neighboring stable countries — Rwanda or Uganda or Kenya," thought Nanyonga, who was sitting a few rows back.

She offered her own campus as a possible training location. “I never would have known what was going on there, or that there was a solution that we can effectively implement, if not for this conference.” Now back home, they are discussing logistics to make it happen.

BUILDING THE FUTURE

THE FIRST TWO CONFERENCES GAVE BARRY, LARSON AND OTHER ORGANIZERS a sharper picture of what aspiring women leaders wanted and needed. At Stanford, Barry offered a pre-conference leadership skills-building workshop with Graduate School of Business faculty. The one-day course was open to 60 participants. More than

London conference, she co-founded Irish Doctors for the Environment and volunteered to write the group’s newsletter. “In London, the idea of a leader being and believing in something ‘greater than yourself’ came up several times,” she said. “Leaders also pass the microphone and allow others to obtain their voice.”

Barry wanted women around the world to find their voices. She wanted them to have all that the conferences provided — leadership training, a sense of community and inspiration — on a grander scale than was possible at a two-day event. Barry wanted something permanent and available on demand. As she contemplated this bigger initiative, she tapped Amie Batson, whose 25-year career included prominent roles at the World Bank, the World Health Organization and PATH, an interna-



‘THE CHALLENGES IN GLOBAL HEALTH ARE TOO BIG AND TOO COMPLEX TO LEAVE HALF THE TALENT SITTING ON THE SIDELINES,’ MICHELE BARRY SAYS OF THE DEARTH OF WOMEN LEADERS.

300 applied. In London, the mentoring breakfast was similarly oversubscribed.

Some conference attendees were inspired to action. After the Stanford conference, Aoife Kirk, MD, decided to enroll in a master’s program in public health so she could improve people’s health on a larger scale than she could as a physician. After the

tional nonprofit dedicated to entrepreneurship and innovation in global health. Along her career pathway, Batson saw the same imbalances among leaders in global health that concerned Barry.

“Women are a dramatically undervalued talent pool,” Batson said. “Too often, women with skills and talent reach the

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TOWARD A WORLD WITHOUT POVERTY

Former World Bank President Jim Yong Kim, MD, PhD, speaks knowingly of those marginalized by technology and the industrial economy. He spent his formative years in rural Iowa and many of his high school classmates have been swept aside by the colossal changes in the U.S. economy. An anthropologist and physician, the former president of Dartmouth College is a co-founder of Partners in Health, a legendary nonprofit global medical organization that fosters community-based health care in impoverished communities.

Before he was at its helm, Kim called for the World Bank to be abolished because its policies were failing the world's poor. Perhaps it took that perspective to understand how to deliver on the bank's promise to end extreme poverty in the world by 2030. When President Barack Obama appointed Kim in 2012, he said that it was "time for a development professional to lead the world's largest development agency." Kim was reappointed in 2016, but in January announced he was cutting his tenure short to become a partner and vice chairman of Global Infrastructure Partners, a New York-based private equity fund and global infrastructure investor. He took over the role on Feb. 1. World Bank leaders named CEO Kristalina Georgieva as interim president.

Stanford Medicine's executive editor, Paul Costello, conducted this interview via email before Kim left the World Bank. Though Kim resigned his position, we felt it was still important to hear his perspective because the changes he implemented could influence the bank's initiatives for years to come.

COSTELLO: Every person who walks through the door of the World Bank passes a large sign that says, "Our dream is a world free of poverty." How does improving health on a global scale fit into the dream of ending poverty?

KIM: When I joined the World Bank in July 2012, I decided that we should translate this dream into measurable goals. With input from our member countries, we committed to twin goals that drive all of the bank's work: ending extreme poverty by 2030, and boosting shared prosperity among the poorest 40 percent of people in every country. We also established that investing in people — through health and education — is one of the critical paths to reaching these



goals, along with supporting inclusive, sustainable economic growth and helping countries build resilience to crises and risks.

COSTELLO: You grew up in Muscatine, Iowa, a small rural town in the farmlands. How is your upbringing rooted in who you are today?

KIM: My Midwestern upbringing helps me understand the isolation we're seeing in some countries — and, even more clearly, why it's not the right solution to today's challenges. Many of the people I grew up with are still in Muscatine. Only 10 percent of my classmates went to college. Most left school and went to work at the local steel mill, on their family farms or in factories, believing that they had a secure job for life.

But the impact of globalization has swept through many places like my hometown, altering the fabric of society and the quality of life. Mechanization and new technologies have disrupted traditional industrial production and changed the nature of work.

This trend is not unique to the United States — it's affecting people around the world. In my view, we need more cooperation, greater economic integration and stronger partnerships than ever if we want the world economy to return to higher rates of inclusive, sustainable growth.

COSTELLO: In what ways is the World Bank influencing health around the globe?

KIM: World Bank leaders are focusing on how to help countries invest more, and more effectively, in their people. In October, the bank launched the Human Capital Index, which ranks countries in terms of the quality of their investment in health, education and social protection. The index is part of the Human Capital Project to help developing countries build strategies to improve outcomes in these areas.

Another priority has been helping countries and the international community understand the challenge of global health as a systems and delivery problem, rather than just a disease problem. In a health crisis such as Ebola or HIV, the largest challenge is setting up the delivery systems that protect people from the diseases of today and from the diseases of tomorrow. There's funding that can be channeled in that direction.

The World Bank can make a big difference by being really good at managing processes at a country level and at thinking about how to set up systems that deliver.

COSTELLO: The Human Capital Project is a somewhat new program of the World Bank, the notion being that investing in people will have a profound impact on economic vitality. Can you describe the program and how it's different from past initiatives? And why the term "human capital"?

KIM: Research shows that better outcomes in health and education are more powerfully correlated with economic growth than previously understood and can help drive poverty reduction all over the world. Human capital refers to the knowledge, skills and health that people accumulate over their lifetimes and bring to the economy.

Through the Human Capital Project, the World Bank is working with leading economists to shine a spotlight on how countries invest — and too often, don't invest enough — to build the human capital stock of the next generation.

COSTELLO: What's the connection between income growth in devel-

oping nations and improved public health?

KIM: Let's consider childhood stunting, which means that children younger than 5 are below height for their age because of such factors as chronic malnourishment and recurrent infections. The percentage of stunted children is staggering: 45 percent in Pakistan, 38 percent in India, 36 percent in Indonesia. And research shows that these children develop lower cognitive ability during their first 1,000 days of life. When they become adults, they'll be less able to compete in a more technology-driven economy.

Attacking this issue is critical for economic growth. For example, stunting makes Indonesia's per capita income 10.5 percent lower than it would be if no one in its workforce had been affected. The overall penalty for the East Asia and Pacific region is 7 percent of GDP; for Africa, it's 9 percent of GDP.

COSTELLO: You've cited a company called Zipline, where a group of rocket scientists use drones to deliver blood everywhere in Rwanda, as an example of a way to reduce costs and dramatically save lives. Are there other innovations on the global health front that are particularly exciting?

KIM: A recent World Bank partnership was established — working with Google, Amazon, Microsoft and such data providers as VanderSat — to develop an artificial intelligence model to help predict when and where a famine may occur.

Famine is a persistent issue in some of the poorest countries, but the larger problem is that responses to it come too late. The power of this innovative model is its ability to bring funding for humanitarian crises upstream, to prevent famines in the first place.

The World Bank also created the Pandemic Emergency Financing Facility to more quickly address global health threats. A \$450 million policy will automatically disburse funds to the poorest countries when an epidemic reaches a critical stage.

COSTELLO: What did you learn from the last Ebola crisis in West Africa that helped create this new funding mechanism?

KIM: For too long, the global community has suffered from a cycle of panic and neglect when it comes to pandemics by responding immediately to the crisis, then turning attention elsewhere once that crisis has abated.

With the 2014 Ebola crisis, we were unprepared to respond to an epidemic. The failure, over many years, to build effective health systems in every country meant that we weren't able to prevent terrible tragedies — the deaths of more than 11,000 people and economic losses of billions of dollars in Guinea, Liberia and Sierra Leone.

'My Midwestern upbringing helps me understand the isolation we're seeing in some countries — and, even more clearly, why it's not the right solution to today's challenges.'

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plus

EXPLORING THE REALMS OF MEDICINE AND HEALING

Hitting pain's off switch

FIGURING OUT WHY SOME PAIN BECOMES AGONIZING AND CHRONIC

By Nicoletta Lanese

ILLUSTRATION BY CHRISTIAN NORTHEAST

STACEY MORRIS REMEMBERS BEING ROUSED in the emergency room one summer night in 2008.

"I took too many pills," she told the hospital staff. "I don't know what I took."

Morris, whose name is changed for this article to protect her privacy, was kept overnight on a psychiatric hold because the doctors thought she may have attempted suicide. But that wasn't the case, she insists. Morris said she had accidentally overdosed on her prescribed medications for chronic pain, sent to the ER by a combination of gabapentin, Ambien and a small glass of wine. She was nearly a statistic, illustrative of a disturbing trend: More than 6,600 American women died of prescription painkiller overdose in 2010 — more than five times as many as in 1999. In 2016, women died from prescription opioid overdose at a rate of 4.3 per 100,000.

Six months before Morris' overdose, surgeons removed a spattering of calcium deposits from her right shoulder. A relentless ache flared up in their place. After seven prescriptions, countless medical appointments and that fateful trip to the ER, her pain was finally diagnosed as complex regional pain syndrome, or CRPS — a

condition in which pain festers in a limb long after an injury, causing swelling, discoloration and changes in sensation.

Pain specialist Vivianne Tawfik, MD, PhD, diagnosed Morris with the syndrome and has treated her at Stanford Hospital for the past five years. Tawfik's work helping patients like Morris man-



age their pain is increasingly important: More than 8 percent of American adults report being in severe pain every day, and pain medications rank as the second-most dispensed prescription. Overall, an estimated 1 in 3 American adults suffer from chronic pain, meaning it has persisted for longer than three months. Morris' pain syndrome is a relatively rare form of chronic pain, with about 55,000 newly diagnosed cases each year. The pain subsides for some and persists for years in others.

Tawfik aims to help her chronic pain patients with a variety of treatments, including physical therapy, sessions in pain psychology, pain-relieving drugs and procedures such as nerve block injections. But many of Tawfik's patients tick straight through that list and remain wracked with pain. They tote around packed pillboxes; swallow their empty promises of freedom from pain; and are left exhausted, foggy and constipated, rather than relieved. The stakes are even higher for women between the ages of 45 and 54, who have the highest risk of dying from a prescription painkiller overdose.

At the heart of the issue is a question that has plagued medicine for many years: Why does some pain dissipate after an injury has healed, while other pain hangs around long after the fact? If pain physicians knew that, they could prevent the onset of chronic pain, rather than trying to numb patients once it takes hold.

Tawfik, an assistant professor of anesthesiology, perioperative and pain medicine at Stanford School of Medicine, hopes to someday figure that out. In addition to caring for patients, she is studying the transition from normal, short-term pain to chronic pain, with mice as her subjects. Neuroscientists have known that cells called microglia amplify pain signals on their way to the brain. If this boost persists after

the painful injury has healed, it may lead to chronic pain. If this is the case, Tawfik hopes she might be able to alter the activity of microglia, tone down the incoming pain signals and turn off that prolonged pain.

Tawfik's challenge will be moving her research from mice to humans. Pain researchers have been under fire — often friendly fire — as some scientists increasingly argue that pain experiments in mice have little relevance in human disease. While pain signals move through mice and humans similarly, it's not possible to re-create the suite of emotional, psychological and physical aspects of human pain in a rodent.

Still, animal studies are irreplaceable pieces in the pain research jigsaw, Tawfik said. For patients like Morris, these studies offer some hope for relief. In the 10 years since Morris' shoulder surgery, her pain remains a moving target and a given in her daily existence. It has migrated to her left shoulder, and she compares the sensation to the pounding throb you feel after being hit with a hammer. It weighs down her body and mind like an invisible sandbag.

"I keep trying to find ways to be optimistic — that's the hard part," Morris said. "I don't want to think that I won't get better."

Tawfik is striving to improve upon pain studies of old and to achieve results in a field infamous for its shortcomings. Her largest ongoing study hints at a remedy for chronic pain.

TURNING UP THE VOLUME ON PAIN

THE SEED OF TAWFIK'S CURRENT RESEARCH TOOK root in the early 1990s. Before then, scientists assumed that neurons — the excitable messenger cells of the nervous system — were wholly responsible for relaying pain signals through the body. Neurons

send electrical signals down an output cable, known as an axon, which releases chemical messages to neighboring cells. Neurons are surrounded by cells that lack axons, called glia. Glia means "glue" in Greek, and glia were once thought to bind neurons together, providing them with insulation and structural support.

But as technologies were developed to better study glia, scientists found evidence that the cells are more than just brain stucco. Many neuroscientists dismissed the idea at first, but now years of extensive research have provided too much evidence to ignore.

Linda Watkins, PhD, a behavioral neuroscientist at the University of Colorado Boulder, was among those pioneering scientists who got glia into today's textbooks. Her early studies of influenza-related pain helped define the broader role for glia. "It turns out that all the symptoms of the flu are created

by glia," she said. "And pain is part of that." Though they have no axon or other direct line of communication with the brain or spinal cord, glia appear to contribute to that pain signal.

"You can think of them as turning up the volume on pain," Watkins said. "If they become activated, they start spewing out substances that make pain neurons go wild." For example, substances called proinflammatory cytokines call immune cells to assemble at an injury site and ignite inflammation to fight infection. Such chemicals make neurons more sensitive to incoming pain signals, influencing how intense pain feels down the line. After "turning up" pain for a certain length of time, glia can become prone to faster, stronger and longer activation, said Watkins.

Research suggests this prolonged

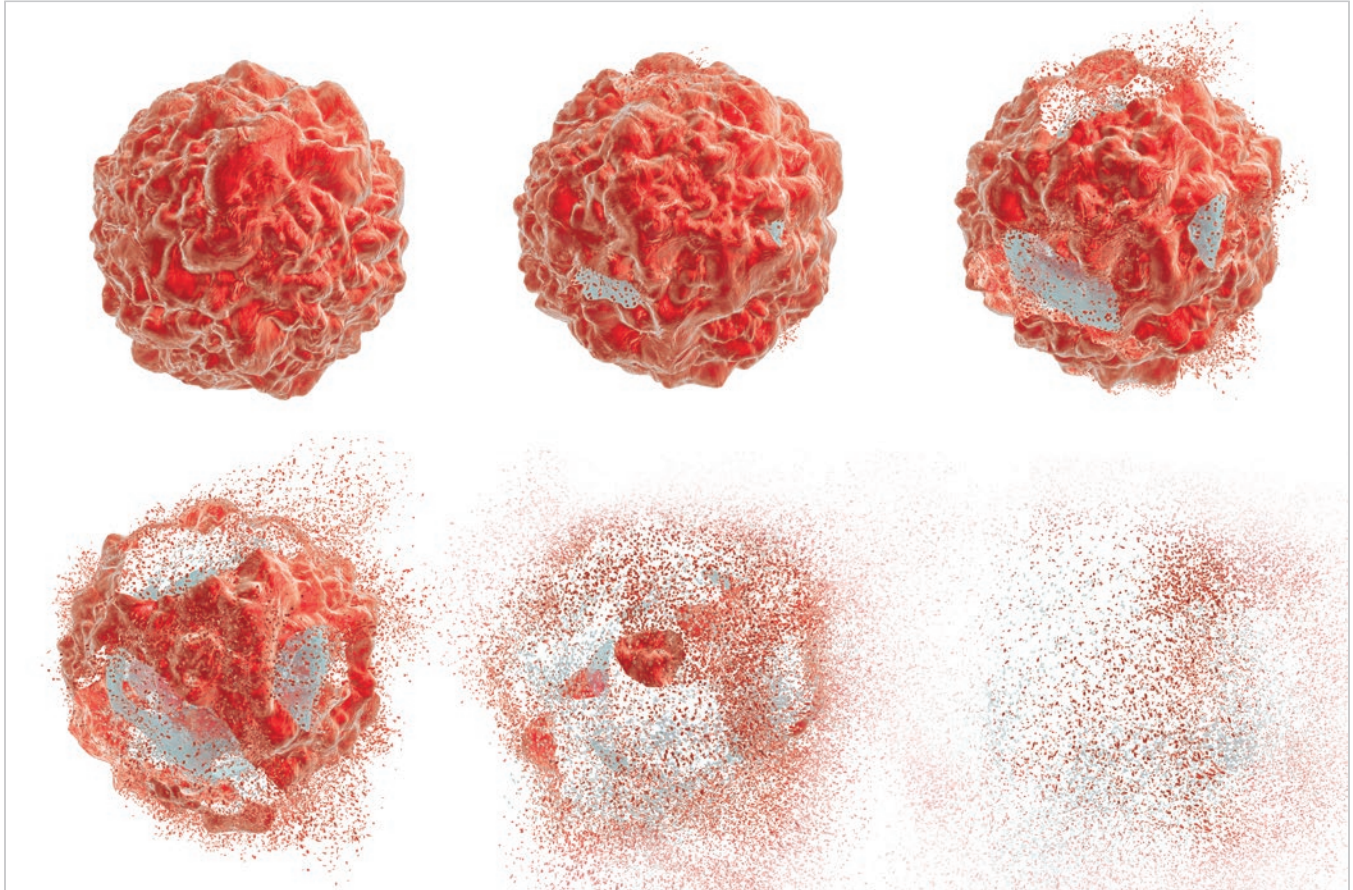
You can think of them as turning up the volume on pain. If they become activated, they start spewing out substances that make pain neurons go wild.

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How cells self-destruct

DISCOVERIES ABOUT THE WAYS CELLS DIE ARE INSPIRING NEW DISEASE TREATMENTS

By Hanae Armitage



A RECENTLY DISCOVERED FORM OF CELLULAR SUICIDE CALLED NECROPTOSIS PROTECTS AGAINST INFECTION AND CANCER BUT CAUSES ILLNESS WHEN IT OVERREACTS.

INSIDE EVERY SICK PERSON, THERE'S A MICROSCOPIC SCENE OF DESTRUCTION. VIRUSES, SIMPLE BUT NEFARIOUS LURKERS, commandeer healthy cells to breed infection that, unchecked, would overrun the body. But the body is equipped with weapons of its own. Like a bursting supernova, the infected cell can explode from the inside out. Its guts spew, and “alert molecules” are flung from the eruption, sending a message to neighboring cells: Danger is nigh.

The process is known as necroptosis, one of the more recently discovered forms of cell death, and it's crucial to foiling viral enemies.

The best understood form of cell death — a self-destruct routine called apoptosis — was identified in 1972. Since then, scientists have sleuthed out several more highly controlled cell suicide processes that protect the body from pathogenic threats. But, as with any complex process, there are flaws. Too little cell death can contribute to

diseases like cancer, while too much can promote autoimmune disease.

As scientists learn more about the chemical interactions inside cells that lead to cell death, some are using that knowledge for therapeutics by inducing cell suicide to kill tumor cells or repressing it to temper rheumatoid arthritis and multiple sclerosis.

“It's exciting to think about how we can induce cell death in the proper way to fend off or stunt illness,” said

Jan Carette, PhD, an associate professor of microbiology and immunology at Stanford who investigates cell death and whose most recent research has zeroed in on necroptosis. “But first we need to understand how these modes of death occur, how they differ and how they intersect. That’s what will drive therapeutics.”

IN THE BEGINNING, THERE WAS ONE

BEFORE APOPTOSIS WAS DISCOVERED, MANY SCIENTISTS believed that cells died only by accident or injury, expiring in a disorganized catastrophe. Observations of the tightly orchestrated molecular interactions that take place during apoptosis proved that wrong. The key to the process is a family of molecules called caspases, which act as shepherds of cell death and activate processes such as DNA degradation and the breakdown of organelles in the cell.

Like most other forms of cell death, apoptosis is a mediator of health. It’s switched on to rid the body of cells that are cancerous or infected, or of cells that don’t form properly, among other duties. But apoptosis is not exclusively for expunging dysfunctional cells; it’s also active during embryo development, sculpting fingers and toes from the paddlelike ends of our early extremities.

Once apoptosis was recognized, researchers lumped all other forms of cell death into a category they called “necrosis,” which was loosely comparable to a shoulder shrug: They knew cells could die in ways other than apoptosis, but what those were was still a mystery. Today, that catchall category has been spliced and spliced again, making room for a spectrum of microscopic deaths. [See the related story, “All the ways your cells can die,” on page 34.]

Necroptosis, the explosive response

to infection, is one of these relatively newly recognized types of cell death. Though it primarily plays out during infection, too little necroptosis has also been implicated in cancer, whereas too much instigates inflammation-based autoimmune diseases, such as irritable bowel syndrome and rheumatoid arthritis.

Necroptosis was discovered and named in 2005 when Junying Yuan, PhD, a seasoned cell-death scientist and professor of cell biology at Harvard University, experimentally disabled the apoptotic pathway in a cell. The cell was then put under lethal conditions and, much to the scientist’s surprise, it died by a process that looked nothing like apoptosis. Robbed of its original exit strategy, the cell had initiated a backup plan.

“The concept of another kind of programmed cell death was paradigm-shifting because, so far, apoptosis had owned the exclusive rights,” said Carette. Yuan’s discovery meant apoptosis was not the only type of cell death implicated in both the protection against and the perpetuation of disease.

In 2011, when Carette established his lab at Stanford, cell death was no-

‘We found it odd that human cells carry this potent molecule that, once activated, literally kills cells from within.’

where on his radar. Instead he was developing a new technology to pinpoint genes important for specific biological functions. “At that time, the necroptosis field was just starting — almost nothing was known about the pathway that leads to this potent form of death,” said Carette. While looking for biological functions to study, he and his lab members attended a talk about the necroptosis process and saw an opening.

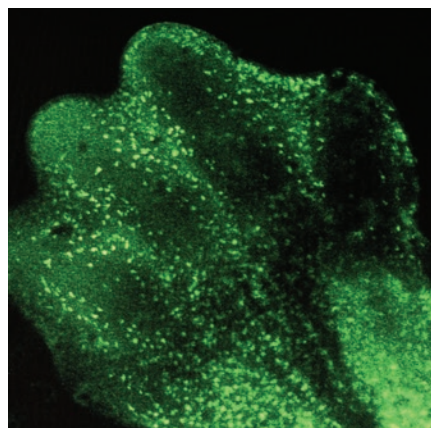
“When they described the pathway, there were all these question marks on their slides where the names of genes should have been,” said Carette. He and his lab members had a hunch that their technology could fill in those question marks. And so Carette’s new quest began.

BACK TO THE BASICS

NO MATTER WHETHER NECROPTOSIS IS ACTING as a defender against disease or as a perpetrator of illness, its underlying mechanism is the same. The killing blow is delivered when something Carette refers to as “the executioner protein” stirs from dormancy. This protein, formally known as MLKL, has a sort of Bruce Banner-turned-Hulk quality to it — docile when off duty, but extremely hostile when riled up.

“We found it odd that human cells carry this potent molecule that, once activated, literally kills cells from within,” said Carette. “So the question became, what keeps this weapon silent when there is no danger, and what prods it into ‘killer’ mode?”

The unleashing of MLKL is preceded by a whole cascade of signals and lock-and-key steps, many of which Carette and his team have helped discover. The protein then bores through



THE PAW OF A MOUSE EMBRYO IS PADDLE-SHAPED UNTIL A TYPE OF CELL DEATH CALLED APOPTOSIS OCCURS BETWEEN THE DIGITS TO FORM TOES.

the cell's covering and bursts out, exploding the cell like a water balloon speared by a needle from within. The cell's insides, including special signaling molecules, gush into the open. The signaling molecules' message to the cells they encounter: Gird yourself or prepare for death. Depending on the severity of infection or disease, those cells will follow suit and explode, perpetuating the cycle.

Just this past year, Carette and his group discovered a unique and critical detail about the activation of MLKL: It requires a code.

This "death code," as Carette coined it, consists of a string of specific molecules that latches onto MLKL in the final phase of activation to set it loose. Without it, MLKL is harmless.

"This is something that no one knew about, or really had even thought about before," said Cole Dovey, PhD, a postdoctoral scholar in Carette's lab. "We're really excited about the possibility of leveraging this information to develop targeted, precise therapies for certain diseases in which necropto-

sis is a main culprit." Dovey is hopeful that future work employing the "death code" might help tame inflammatory or autoimmune diseases by blocking the code from MLKL to prevent unprovoked necroptosis.

Already, pharmaceutical companies are beginning to capitalize on this idea, developing drugs that inhibit necroptosis to treat irritable bowel syndrome and rheumatoid arthritis. On the flip side, inducing necroptosis in diseased cells is an attractive tactic. While scientists have succeeded in triggering apoptosis in some cancers, many are now toying with necroptosis activation in the hopes that it can add to a growing arsenal of immune-based therapies.

All the ways your cells can die

SOME CELLS PUT ON QUITE a spectacle as they die, exploding in a dramatic burst. Others keep it tidy, quietly packing it in. And while it might seem like overkill for a body to have so many routes to do away with cells, the variety is crucial for the larger organism's well-being.

Until recent decades, scientists thought that cells all died in a haphazard fashion, which they called necrosis. But the great diversity in paths cell death can take has gradually become apparent. A quick look at what's been learned so far:

NECROSIS: If no known molecular routine switches on to cause the cell's destruction, it's typically termed death by necrosis. This is the spontaneous type of death that occurs with a cut to the skin, or from an injury or frostbite.

APOPTOSIS: This was the first actively regulated route to cell death discovered. In other words, scientists realized the death process some cells follow is an established course controlled by specific molecules. Apoptosis plays an important role in embryo development, it rids the body of cells no longer needed, and it acts as a defense mechanism against diseases such as cancer.

NECROPTOSIS: A cell undergoing necroptosis is not afraid to show it. In fact, a cell undergoing necroptosis as a result of an infection, for instance, erupts and scatters special molecules that alert neighboring cells to the threat. The process is carefully orchestrated by a string of molecules until finally an "executioner" protein drills through the cell's interior and into the open, causing the cell to rupture and die.

PYROPTOSIS: Like necroptosis, pyroptosis employs the detonate-and-alert-others-to-danger approach. The process occurs primarily in immune cells and is thought to be key for defending against microbes.

NETOSIS: Immune cells called neutrophils engage in NETosis to deploy little netlike structures, called neutrophil extracellular traps, to capture microbes that pose a threat to the body. However, the neutrophils themselves sometimes die in the process.

FERROPTOSIS: As "ferro" suggests, ferroptosis is iron dependent and occurs when the cell is deprived of a particular protein building block called cysteine. Cysteine is needed to make glutathione, a molecule that helps rid the cell of reactive oxygen species that are damaging. Without cysteine, the cell succumbs.

THE NEXT CELL DEATH

AS NECROPTOSIS CONTINUES TO EVOLVE IN ITS therapeutic utility, other programmed death pathways are coming into their own. The latest, ferroptosis, was discovered in 2012 by Scott Dixon, PhD, then a postdoctoral scholar, and his colleagues in the laboratory of Brent Stockwell, PhD, professor of biological science and chemistry, at Columbia University. How it works is still obscure.

"Ferroptosis just hasn't been on our radar that long," said Dixon, now an assistant professor of biology at Stanford. "Scientists have known about necroptosis for 13 years and apoptosis for more than 40, so there's been a lot more time for research to get underway."

After coming across other non-apoptotic cell deaths like necroptosis, scientists suspected there were more, and continued to search. That's how Dixon and Stockwell discovered ferroptosis, an iron-dependent demise unique from any found before.

Now Dixon investigates the drivers behind ferroptosis and the hand it plays in human disease. For now, scientists know that iron molecules help propel ferroptosis, and that it occurs when a particular protein building block, cysteine, and a compound called glutathione are dually low in the cell. Both cysteine and glutathione are critical to a process that wipes out destructive molecules called reactive oxygen species.

Overall, though, ferroptosis' role in health and disease is still opaque, which is in part because of some technical limitations. Both apoptosis and necroptosis exhibit molecular markers — evidence that a biological process has occurred or is present, like “signature” proteins or molecules that are unique to specific pathways. That's not the case when ferroptosis has been at work.

“Let's say you wanted to look at a post-mortem brain and see if ferroptosis contributed to that death. Right now, there's no way to inspect a section of the tissue to see if those cells indeed died through ferroptosis,” said Dixon. “There's just no marker. Not yet at least.”

So when they discovered ferroptosis, Dixon and his lab colleagues had to find a workaround to be able to spot ferroptosis in action.

“We knew how to induce ferroptosis in a dish, and we thought if we could find inhibitors of the process, we could track down where ferroptosis was biologically important,” Dixon explained. So they screened an enormous set of molecules for their ability to stop the new death pathway, and selected a handful that seemed to halt progress.

Dixon's lab at Stanford is still focused on the fundamentals, continuing to decipher ferroptosis' pathway, but scientists outside of his lab have been able to use the inhibitors he discovered to understand how ferroptosis fits into the bigger picture of health. “You can take these inhibitors and test them in different models of disease — stroke, Parkinson's, Alzheimer's and Huntington's, among others — in various organisms,” said Dixon. “And in many cases, it's turning out that the inhibitors we have found protect the models from cell death and subsequent damage.”

For Dixon and Carette, one of the next big questions is understanding exactly how the various microscopic deaths intertwine. There's already evidence to suggest that apoptosis and necroptosis somehow act as backup mechanisms for each other — if a pathogen thwarts necroptosis, apoptosis could theoretically pick up the slack.

“There are a few tentative reports that draw connections between ferro-

ptosis, necroptosis and apoptosis, but the data are scattered,” said Dixon. “Everyone is trying to forge those links, but I don't think anybody really knows yet. That's going to be the next frontier.” **SM**

— Contact Hanae Armitage at harmitag@stanford.edu

FEATURE

The mosquito trackers

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with DDT. Such targeting strategies, Caldwell said, would mean the pesticides' effects are more likely to last longer. “We'll get more bang for our buck in lots of ways,” she said.

In addition to improving the effectiveness of pesticide use, the models could help spur community education at the right time. There could be TV and radio ads, signs at doctors' offices or health clinics, and other outreach about what the mosquitoes look like and how to clean up possible habitats, LaBeaud said. Hospitals could also use climate prediction data to prepare for extra cases of illness, making sure they have supplies on hand to provide fluids to patients who become dehydrated, for instance.

“These diseases have really exponential spread, so anything you can do to prevent cases a few weeks before an outbreak can save a lot in terms of human health costs,” LaBeaud said.

Caldwell is building models that incorporate data on ambient temperature, humidity and rainfall, as well as non-climate factors such as degree of urbanization, land use and level of infrastructure. She's validating the models with data from Kenya and Ecuador, and testing to see whether remote data alone will be enough to drive accurate outbreak prediction there.

The models could also help predict where the diseases will go next.

“In many places, the climate is getting less suitable for malaria, but may be getting more suitable for dengue and chikungunya,” Caldwell said.

That includes the United States. In 2017, the U.S. Centers for Disease Control and Prevention reported 156 cases of chikungunya, including 32 in California, and 437 cases of dengue, with 130

in California. Those illnesses were confined to international travelers and don't seem to have spread to U.S. mosquitoes — yet. But *Aedes* mosquitoes are here; their presence has been recorded in 220 U.S. counties in 28 states, and the CDC estimates that their potential range “very likely” covers all the Southern states, much of the Midwest and Southwest, and nearly all of California. Local transmission of Zika was reported in parts of Florida and Texas in 2016 and 2017, and although no transmission was documented in the continental United States during 2018, Zika could return.

“Humans can get anywhere in the world in 24 hours, and so can these infections,” LaBeaud said. “They come in us. We go on vacation, the virus gets in our blood, we come home and, if the vectors are there, it's a perfect storm waiting to happen.

“We can no longer take a, ‘We are here in America, and the diseases stop at the border’ attitude,” she added. “Because of global travel and the way we're changing our planet, with climate change and extreme weather events, there's a lot of potential for these mosquito habitats to shift and spread and grow.” **SM**

— Contact Erin Digitale at digitale@stanford.edu

FEATURE

A better brick

CONTINUED FROM PAGE 23

30 to 45 kilns two years later. Eventually he'd like to see the industry transformed, which he estimates would cost \$30 million to \$80 million.

Luby's ready for an uphill battle. “Problem-defining research is most highly rewarded in academia,” he said. “One step that donors interested in a sustainable future can make is to fund solution-oriented research and reward leading researchers who engage in it.

“We know the problem,” Luby said. “People get rich by destroying the Earth or human health. If we can't figure out how to change that incentive system, we will destroy our future.” **SM**

— Contact Rob Jordan at rjordan@stanford.edu

FEATURE

Cultivating women leaders

CONTINUED FROM PAGE 27

middle levels of leadership and find their careers stall there. Global health leadership urgently needs more diversity to achieve better health impact.” Batson joined Barry as a volunteer, helping to shape the conferences and discussions about the future, and eventually signed on as the initiative’s senior adviser.

The two women assembled an international team to devise a strategy. Over time, they settled on a plan that calls for five hubs on five continents, physical locations where women can go for a few weeks of coaching and connection while each designs a project for her home community. Then, over the next 18 months, as each woman implemented her project, she would network with her cohort, mentors and coaches. The whole group would then reconvene at the training hub to share what they learned and what could be replicated in other communities. Barry, Batson and their team received a planning grant from the Gates Foundation to fund the initial stages of the initiative, and will apply for future grants to complete it.

The team also envisions a virtual gathering place where women from around the world can share stories, seek assistance and generally inspire one another and others to change the world. Between the training hubs and online organization, the plan calls for helping 5,000 women accelerate their leadership journeys. And for each one of them to push, pull or motivate other leaders on their journeys.

“When Wafaa and I were sitting at that conference looking at the all-male panel, I knew the picture had to change,” Barry said. “The challenges in global health are too big and too complex to leave half the talent sitting on the sidelines.”

Barry still receives weekly emails from women who attended the conference at Stanford. They write to say thanks and to let her know they’re ready to stand up, connect across boundaries and help solve those challenges. **SM**

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Q & A

Toward a world without poverty

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The Pandemic Emergency Financing Facility was born out of this experience. It allows the World Bank to disburse funds immediately to governments and responding agencies to support a surge in health care needs when there’s an outbreak. Providing financing within hours and days eliminates the potential that funding shortages will constrain a response, and it helps save lives and protect economies.

PEF made its first disbursement for an Ebola outbreak in the Democratic Republic of Congo in mid-2018, providing a \$12 million grant to support frontline response efforts.

COSTELLO: You co-founded Partners in Health as a Harvard student in 1987 and have worked in the global health arena for most of your life. The nonprofit has helped bring modern medicine to the world’s poor. What lessons learned from that did you transfer to the World Bank?

KIM: When Paul Farmer, Ophelia Dahl and I co-founded Partners in Health, we took as our creed a cardinal principle of Catholic liberation theology of “a preferential option for the poor.” That drove us to insist that *everyone* — even people with complex health problems, and especially the poorest and most vulnerable — deserves treatment.

I took that principle to the World Bank Group—a moral obligation to provide *everyone* in our client countries with opportunities to achieve their highest aspirations. All people have hopes and aspirations, and they deserve good health care, quality education and the chance to live with dignity. **SM**

PLUS

Hitting pain’s off switch

CONTINUED FROM PAGE 31

glial activation might push short-term pain over the edge so that it becomes chronic. But no one knows exactly how. By studying glial cells found only in the brain and

spinal cord, called microglia, Tawfik hopes to understand how these cells contribute to chronic pain and how to stop it.

MAKING DO WITH MICE

Pain is a complex interaction of physical, emotional and psychological factors, and scientists studying mice have yet to figure out how to ask a mouse how it’s feeling, emotionally. Researchers can only study painlike behavior and nociception — how the nervous system reacts to painful stimuli — in animals. For instance, a researcher may prod a mouse’s injured paw and note whether it pulls away and how quickly.

Compounding the problem, the vast majority of pain research has been done in male mice from the same genetic strain, even though chronic pain affects far more women than men.

Tawfik has tried to deal with these concerns by building an animal study that closely replicates what she sees in her patients, most of whom are women. Many of them first fracture a bone; then, after the cast comes off, the fracture pain lingers and develops into complex regional pain syndrome. Tawfik reproduces this scenario in her mouse experiments to study symptoms she sees in humans.

MANIPULATING MICROGLIA

In her Stanford lab, Tawfik is using genetic engineering technology to disable different genes along the pain pathway in mice that are bred to lack an essential microglial protein. She also is experimenting with disabling this component with an injectable drug to investigate how different levels of microglial activation correspond to the intensity of pain symptoms.

The classic symptom of complex regional pain syndrome is long-lasting pain that is stronger than expected given the injury that triggered it. Other symptoms include muscle tremors and weakness, brittle nails, slow-growing hair, swelling, redness

When
Morris walks
on pebbles
with bare feet,
it can
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walking
on jagged
shards
of glass.

or unexplained warmth in the affected limb. Those with the syndrome may become hypersensitive: A minor cut or bruise might cause severe pain while normally painless sensations, such as feeling clothing against their skin, can become excruciating. For instance, when Morris walks on pebbles with bare feet, it can feel as if she's walking on jagged shards of glass.

Tawfik studies these symptoms by observing whether her genetically altered mice are more sensitive to touch and heat after injury, or exhibit other symptoms that mimic those of her patients.

"If mice have some sort of injury, they tend to respond at a very low threshold," she said. The same goes for the mice's sensitivity to heat.

Tawfik also uses an imaging technology called positron emission tomography to scan the brains and spinal cords of her mice. She plans to use the same technology in human patients to take a snapshot of their own nervous systems. Tawfik uses the scanner to measure how active her mice's microglia are before and after injury. She hopes the scans will tell her whether injuries cause microglia to become more active in her mice, and how that activation might be paralleled in humans.

Tawfik has run six groups of mice through her experiments. Time and again, the same results have come back: Manipulating microglia, even temporarily or to a moderate degree, can completely change the trajectory of pain. By disabling or deleting 25 percent or more of a mouse's microglia, Tawfik can block their abnormally strong pain response before it takes hold. When she allows the mice's microglia to increase back to a normal level, they're still fine. It seems Tawfik may be flipping pain's off switch.

These are promising results, but the mechanisms that cause microglia to prolong pain remain a mystery. Tawfik wants to solve that so other scientists might develop medications to interfere with microglia and perhaps provide new treatments for chronic pain.

A PAIN-FREE TOMORROW

Such drugs could give patients like Morris a new lease on life. From the outside,

you'd never guess Morris was living with debilitating pain. Her fashionable outfits, sparkling nail polish and sleek, sandy hair seem incongruent with someone who's had an accidental drug overdose. If you overheard her joking at a coffee counter, asking for a unicorn drawn in her cappuccino foam, you wouldn't guess that years of relentless pain have left her clinically depressed.

"I can't even clean the dishes in my sink. I can't even put the toilet paper rolls in the bathroom, or make my bed in the morning, because I just don't want to do anything," she said, describing her worst days. "And that's so unlike me."

Morris said she has always had a "get-up-and-go" personality. She worked for years as a hospital marketing representative and raised two daughters who are now in college. She volunteers with local foster children at a Santa Cruz County nonprofit organization. In her free time, her ideal day would be filled with mountain biking, paddle boarding and canyoning, followed by beach volleyball at sunset. Tawfik notes that Morris remains extremely active — traveling, working and volunteering — in spite of her pain.

But none of this is possible without pain medications. Morris takes two tablets of the narcotic Vicodin two to three times a day, along with a nerve pain medication, Topamax, that makes her face twitch. That's in addition to injections twice a month of a nerve blocker — a medication that numbs the nerves in her neck to prevent the pain in her arm. She recently upped her Cymbalta prescription to treat her depression and nerve pain. The medications put her in a fog, make her drowsy, sap her motivation and disrupt her digestion.

On bad days, the pain still keeps her from her favorite activities and from her work with foster children.

"How can I be there for them when I'm not there myself?" Morris said.

In March of 2018, Watkins helped usher into human trials a glia-targeting drug that aims to interrupt the signals that glial cells use to turn up pain in patients with arthritis. It's already worked

in rats, dogs and horses, and Watkins hopes it will prove effective in people.

"The end goal would be that a patient comes into clinic, they get a scan and we can see that their microglia are activated," Tawfik said. "Then we can say, 'You're appropriate for treatment with this drug that modulates those cells.'"

Tawfik envisions a better future for her patients — one where she can offer them permanent escape from the pain that holds them hostage. **SM**

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GETTING REAL

MEDICAL RESIDENTS EXPERIENCE GLOBAL HEALTH NEEDS FIRSTHAND

In many parts of the world, rheumatic heart disease is part of history. “It’s the scarlet fever you read about in a Jane Austen novel,” said Stanford cardiology fellow Andrew Chang, MD. Globally, however, the disease still affects more than 30 million people, causing a quarter of all cases of heart failure. Often, it begins as an undiagnosed case of strep throat. Without a course of antibiotics, the infection can become rheumatic fever and damage heart valves until the heart can no longer pump effectively.

Chang traveled to Rwanda as a resident in Stanford’s global health track within the Department of Medicine. While there, he witnessed the punishing impact of the preventable disease. “It really shook me,” he said.



Cardiology fellow Andrew Chang says Stanford’s global health track for residents provided invaluable mentoring and opportunities for collaboration, research and community clinical work.

That, in some ways, was the point. Michele Barry, MD, Stanford’s senior associate dean for global health, created the track to give medical residents an understanding of overarching issues and the individual contributions they could make worldwide. Residents spend up to 18 weeks working with patients in clinics and conducting research either overseas, on an American Indian reservation or both. Global health faculty help residents identify their goals and acquire specific skills needed to achieve them.

Barry encouraged Chang to go to sub-Saharan Africa to work with Gene Bukhman, MD, PhD, the global cardiology director for Partners in Health, a nonprofit organization that works to improve health in impoverished communities. In Rwanda, Chang discussed difficult cases and research challenges with Bukhman. Most days, he cared for patients at the Centre Hospitalier de Kigali. During rounds and afterward, with no offices or team rooms to duck into, Chang stayed in the ward reviewing notes and answering questions. He felt connected to the community, with more time to talk to patients, often through translators or members of patients’ families. “Practicing medicine overseas makes you realize that, in many ways, people are all the same,” Chang said. “It’s the same base emotions. Fear, regret, anger, sadness — these things are universal. When someone starts crying, you hold their hand.”

While on Stanford’s campus, global health track residents complete rotations in internal medicine and in social medicine, working with homeless populations in and around San Jose. They take a two-week intensive course that explores the ethical, economic and legal issues of working overseas in resource-limited settings and attend a two-day retreat with Stephen Luby, MD, the director of research for Stanford Global Health.

While in his third year of residency, Chang traveled to Uganda to study women with rheumatic heart disease. A week before he left, though, he called Luby for last-minute coaching on all the complexities that come with conducting research, interviewing and analyzing data on 75 people. “That level of mentorship is what makes this program so powerful,” Chang said.

Global health residents have completed projects in Colombia, Ecuador and Zimbabwe. On campus, they’ve collaborated with faculty members in each of Stanford’s seven schools to hone their expertise in fields as varied as mathematical modeling, microbial genetics and the economics of health care legislation. They’ve gone on to work in global oncology, in tuberculosis diagnostics and at the intersection of big data and public policy.

Chang became chief resident before starting the fellowship in cardiology. Next, he plans to complete a PhD in epidemiology so he can focus on crafting policy to create population-level interventions that, he hopes, will make rheumatic heart disease history. — JODY BERGER

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HONEYBEE PROTEIN KEEPS CULTURED EMBRYONIC STEM CELLS YOUTHFUL

For worker honeybees intent on nurturing one of their own into the role of leader, it pays to treat her like a queen. And that means feeding her a steady diet of royal jelly, a gooey substance secreted by worker bees that promotes cell growth.

Now dermatologist Kevin Wang, MD, PhD, and plastic and reconstructive surgeon Derrick Wan, MD, have found that a protein in mammals that is similar to royalactin, the active ingredient in royal jelly, also affects embryonic stem cells in mice by suspending them in a state called pluripotency — an early stage of development before cells mature into specific types.

The discovery offers biomedical researchers new ways to work with pluripotent embryonic stem cells, which can become any cell in the body. Generally, researchers use inhibitor molecules to keep cells pluripotent until they want them to develop further. But with royalactin and its mammalian counterpart, no inhibitors were needed.

In folklore, royal jelly is bestowed with powerful regenerative properties. “It’s kind of like a super-medicine, particularly in Asia and Europe,” said Wang. Among bees, larvae are fed royal jelly the first few days after hatching. Worker larvae are quickly switched to a combination diet of royal jelly, honey and a pollen concoction known as “bee bread.” But bees destined to be queens are fed only royal jelly and grow much larger than workers.

In testing the impact of royalactin on embryonic stem cells of mice, Wang and Wan were

surprised that the protein worked as a kind of fountain of youth for mouse cells even though mammals don’t make royalactin.

So they looked for a mammalian equivalent of royalactin and discovered NHLRC3, a protein that is produced early in embryonic development in all mammals and is similar to royalactin in its effect on mouse embryonic stem cells. They renamed the protein Regina — Latin for queen.

“It’s fascinating. ... We’ve connected something mythical to something real,” Wang said. The study, published Dec. 4 in *Nature Communications*, reveals new pathways to pluripotency and suggests novel ways to keep stem cells in suspended animation until needed. Wang was the senior author, and Wan was the lead author.

They plan to investigate whether Regina has any effect on wound healing or tissue regeneration in mammals. — KRISTA CONGER



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