

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

Summer 2016

special report

**STRIVE, THRIVE
AND
TAKE FIVE**
The science of well-being

Healing from history

A new approach to preventing diabetes
in American Indians

No means no

Kenyan youth learn tactics to
reduce sexual violence

Unbroken

A conversation with Laura Hillenbrand

Stubbing it out

Ending America's love affair
with cigarettes

Broccoli BFF

Accidentally making friends
with healthy food

Ditto

The importance of replicating
experiments

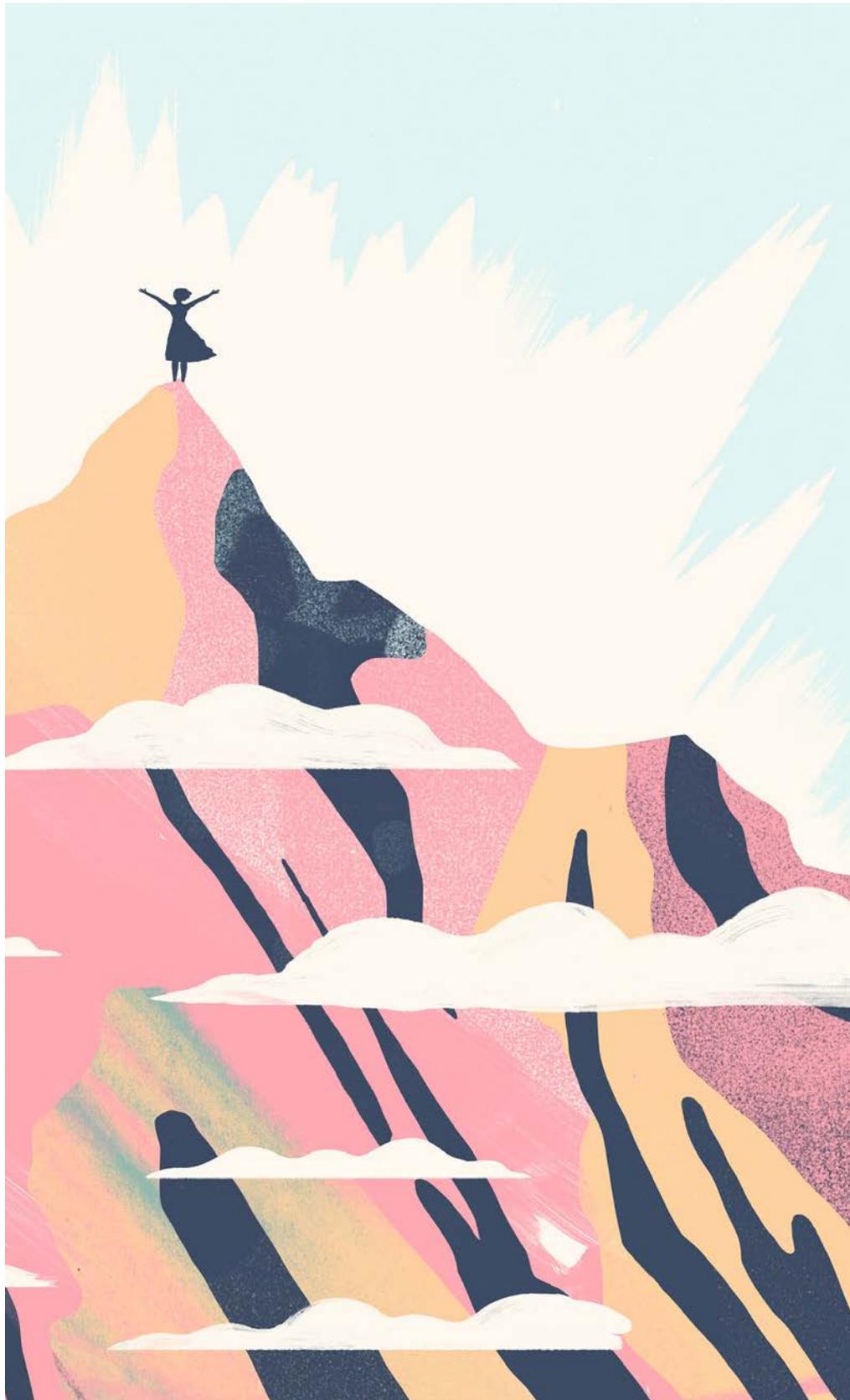
plus

Out of whack

The aging immune system

Will they pay?

A new litmus test for medical
innovation at Stanford Biodesign



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

Summer 2016



SCREEN TIME

AN EFFORT TO GET ATHLETES
TO PROTECT THEIR SKIN

To 20-year-old Erik Olson, the little pink lesion on his shoulder was no big deal. Probably just a pimple, he thought. But his girlfriend, Jessica Tonn, who first noticed it, was insistent he get it checked out. • It was the summer of 2012, and Olson and Tonn had just returned from a run — pretty much a daily event for the two Stanford track and field athletes. As usual, Olson was shirtless. By his own account, he had trained every day for six years without a shirt or sunscreen on his back. The blue-eyed blond would lather up his nose and ears to prevent a burn, but his deep mahogany back was his “street cred” in the distance-running community. He’d achieved that tan through relentless training. • A biopsy showed that Olson had melanoma, the deadliest form of skin cancer. Surgery removed the tumor, and examination of his lymph nodes showed it hadn’t yet metastasized. He knew he’d been fortunate, and when he returned to training, Olson was religious about wearing shirts and sunscreen.



Melanoma is rare for people in their 20s, but playing outdoor sports increases the risk. The average NCAA outdoor athlete spends four hours a day, 10 months per year practicing and competing in the sun. This intense, often year-round, training increases risk for sunburns, accelerated skin aging and skin cancer. Moreover, sweating increases the skin’s susceptibility to UV radiation damage.

Yet 43 percent of student-athletes report never using sunscreen, and only 8 percent use it daily, according to data gathered by Stanford’s SUNSPORT program — a joint effort of the Athletic Department, Dermatology Department and Cancer Institute.

How big is the risk from extensive sun exposure? SUNSPORT members are working to quantify it, and to take measures to reduce it.

The program, developed in 2012, conducts longitudinal research through annual surveys of Stanford’s nearly 900 student-athletes’ sun-exposure and skin-protection behaviors. SUNSPORT (Stanford University Network for Sun Protection, Organization, Research and Teamwork) also provides annual skin screening for athletes, educational talks to teams and in-depth presentations on sun damage and skin protection for coaches and athletic trainers.

“The education and treatment provided by our dermatologists make an impact, but we see student-athletes’ habits really change when they receive consistent reinforcement from coaches and athletic trainers,” says Susan Swetter, MD, professor of dermatology, director of

Stanford’s Pigmented Lesion and Melanoma Program, and a SUNSPORT founder.

“SUNSPORT is a part of our effort to support the well-being of Stanford’s student-athletes,” says Lindsay Donnelly, athletic trainer for the women’s softball and soccer teams.

And it seems to be working. The year after SUNSPORT launched, the Athletic Department exhausted its annual sunscreen stock and had to resupply.

The softball team now carries out a playful ritual before every practice — the “sunscreen toss-around.” One player grabs a bottle of sunscreen and applies it to her exposed arms, face and neck. When done, she flips it to the closest teammate, who repeats the process until the whole team is covered.

Associate professor of dermatology Kristin Nord, MD, spreads SUNSPORT’s message to the greater Stanford community, including summer youth athletic camps. “Stanford student-athletes are fantastic role models and we hope younger athletes will follow their example of healthy skin protection habits,” she says. — MICHAEL CLAEYS

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

SPECIAL REPORT

Strive, thrive and take five

THE SCIENCE OF WELL-BEING



How people soar
page 6

- 6 **Well now** *By Jennie Dusheck*
WHAT HUMANS NEED TO FLOURISH
- 10 **In the circle** *By Kathy Zonana*
AMERICAN INDIANS AND STANFORD RESEARCHERS COME TOGETHER ON DIABETES
- 16 **Can you repeat that?** *By Krista Conger*
THE CRISIS IN RESEARCH RELIABILITY
- 20 **Leaving frailty behind**
A CONVERSATION WITH LAURA HILLENBRAND
- 22 **Standing up to sexual assault** *By Laura Heaton*
RESEARCHERS SEEK TO TRANSFORM A GENERATION IN KENYA
- 30 **Cash flow** *By Stephanie Bruzzese*
WHEN ASSISTANCE PAYMENTS ARE LESS FREQUENT, PEOPLE MAKE WORSE FOOD CHOICES
- 32 **The end game** *By Ruthann Richter*
AIMING TO EXTINGUISH TOBACCO'S HARMS FOR GOOD
- 38 **Ulterior motivation** *By Erin Digitale*
THE POWER OF SERENDIPITOUSLY HEALTHY HABITS

Faster, better, cheaper
page 42



PLUS

- 42 **At what cost?** *By Amy Adams*
TEACHING INVENTORS TO MAKE HEALTH CARE BETTER AND CHEAPER
- 48 **Inflammation implication** *By Bruce Goldman*

Stealth health
page 38



DEPARTMENTS

- Letter from the dean 2
- Upfront 3
- Backstory 58



In modern health care, we're always playing catch-up. Once a disease occurs, we rush to intervene — curing the illness when we can, treating it when we can't. Then we wait for another disease to pop up.

At Stanford Medicine, we know there's a better way. Our vision for precision health is based on the simple idea that health care should be proactive and preventive, promoting health as much as it defeats disease. It starts with realizing that medical care plays only a small role in determining our health outcomes. It's our genes, behaviors, social status and environment that play the leading role in determining when, whether and how we get sick.

Yet the focus of medicine today is on the clinical signs and symptoms that we can easily see and measure, like an elevated blood-pressure reading or a patient's reports of fatigue. Rarely addressed are the factors that matter most and would yield rich insights into why the disease occurred in the first place. And the more we know about why, the more we will be able to tailor treatment for that disease and, best of all, predict and prevent other diseases altogether.

Creating a more proactive and preventive health-care system is a complex challenge that will require a whole new approach and level of innovation for the global medical community, but precision health is an idea whose time has come. In recent years, new tools and technologies have revolutionized our lives, from the way we work to how we play. Now it's time that we put these advances to work in promoting health and wellness.

Using data from electronic medical records, genomic sequences, biospecimen repositories, insurance records and wearable sensors, we are increasingly able to quantify the factors that affect our health and untangle the relationships among these factors. We can now answer such questions as: How does our behavior affect our genes? How do our genes affect our social status? How does our social status affect our behavior?

Understanding the complex interplay among the determinants of health is one of our precision health strategic priorities. To help us do this is a new \$11.5 million grant from the National Institutes of Health to establish the Stanford Precision Health for Ethnic and Racial Equity Center, or SPHERE. One of the center's initial projects, led by Professor Thomas Robinson, is to better understand how various factors — from genetics and behavior to socioeconomic and the environment — contribute to obesity in low-income Latino children in a nearby neighborhood.

Through quantifying the metabolic and biomolecular differences of these children and combining these findings with existing physical data, lifestyle surveys, family history and health information, the study will provide valuable insights into how best to prevent excessive weight gain for this vulnerable group. More broadly, we hope that this and other SPHERE projects will contribute to the elimination of pervasive health disparities.

By considering all the factors that determine health outcomes, precision health will allow us to spend less time treating disease as it appears and more time preventing that disease in the first place, giving us lives that are not only free of sickness but also long, happy and full. That's the future of health care.

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

upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD MEDICINE

Scaredy-rats

MOST ADULT HUMANS are risk-averse, preferring, say, a stable salary to a fluctuating freelance income. Most rats are too, preferring a constant dose of sugar water to one that ebbs and flows but still delivers the same amount of liquid over time. A minority of each species prefers risk.

It's a matter of brain chemistry, it appears. As rats were deciding which sugar-water lever to pull, Stanford researchers observed higher electrochemical activity in certain nerve cells in the brains of risk-averse rats than in those of risk-seeking rats. The cells, in the nucleus accumbens region of the brain, contained DR2, a category of dopamine receptors.

Stimulating the DR2 cells with laser light via an implanted optical fiber, the scientists were able to cause risk-seeking rats to behave in a risk-averse manner. Administering pramipexole, a dopamine-



stimulating drug for brain disorders that is known to cause risky behavior in humans, turned the risk-averse rats into risk seekers. Based on previous human-brain imaging studies and anatomical similarities between rats and people, "every indication is that these findings are relevant to humans," says Karl Deisseroth, MD, PhD, professor of bioengineering and of psychiatry and behavioral sciences.

Deisseroth is the senior author and former graduate student Kelly Zalocusky, PhD, is the lead author of the study, which appeared in March in *Nature*.

Children and adults in 130 countries are now using Foldscope, the \$1 paper-based microscope developed by assistant professor of bioengineering Manu Prakash, PhD. More at <http://stan.md/29sXUrk>.

New leader

STANFORD HEALTH CARE has appointed David Entwistle as president and CEO, effective July 5. He was previously the CEO at University of Utah Hospital & Clinics. Entwistle succeeds Mariann Byerwalter, who had served as interim president and CEO since January.

"David Entwistle is a proven leader who will collaborate effectively with Stanford Medicine physicians and with all our partners as we pursue the tremendous potential of the biomedical revolution in precision health to predict, prevent and treat disease as never before," says School of Medicine Dean Lloyd Minor, MD.

Only human

HERE'S THE THING about the pancreas: After death, the digestive organ essentially digests itself.

That has made it hard for researchers to study human pancreatic tissue. Studies of diabetes, the most common disorder of the pancreas, have had to rely on animal tissue.

But Stanford scientists have developed a nationwide network that allows the pancreas to be removed from organ donors and studied within a day and a half after death. Their recent study of tissue from this network highlights the importance of two genes linked to diabetes but not previously known to be active in the pancreas — a discovery that could not have been made by examining the pancreas in mice, because the genes are not expressed there.

"This is a tantalizing link," says senior author Seung Kim, MD, PhD, professor of developmental biology. "It appears that genes whose expression changes from childhood to adulthood may be disproportionately associated with an increased risk for diabetes." Understanding the age-related changes in gene expression could lead to new diabetes treatments.

Postdoctoral scholar Efsun Arda, PhD, is the lead author of the study, published in the May issue of *Cell Metabolism*.

How much alcohol?

A FOAMING BEER MUG. A half-full wine glass. A shot glass of 40-proof liquor. • These are the visual aids used to teach U.S. teenagers about a "standard drink," each of them representing 14 grams of alcohol. In Austria, however, a standard drink contains 20 grams. In Iceland and the United Kingdom, 8 grams.

Inconsistency among countries in the definitions of a standard drink and of what constitutes low-risk drinking makes it difficult to conduct global research on alcohol use and addiction, say Stanford Medicine researchers. Throw in differences in measurement and terminology — alcohol is not exactly served by the gram — and you have a recipe for confusion among people trying to drink responsibly.

"There's a substantial chance for misunderstanding," says Keith Humphreys, PhD, professor of psychiatry and behavioral sciences and senior author of a study that surveyed the definitions of "standard drink" and low-risk drinking in 37 countries. "It is not possible that every country is correct; maybe they are all wrong." Psychiatric medicine resident Agnes Kalinowski, MD, PhD, is the lead author of the study, which was published in the July issue of *Addiction*.



'BE TRUE' NEEDS REDO

THERE'S NO evidence that promoting abstinence and fidelity changes sexual behavior, according to a Stanford analysis of U.S.-funded HIV-prevention programs around the world.

Since 2004, the President's Emergency Plan for AIDS Relief has allocated \$1.4 billion to abstinence and "be faithful" programs. The researchers found no statistically significant differences between PEPFAR and non-PEPFAR countries in the number of annual sexual partners per person, age of first intercourse or rate of teen pregnancy.

"Changing sexual behavior is not an easy thing," says senior author Eran Bendavid, MD, assistant professor of medicine. "When individuals make decisions about sex, they are not typically thinking about the billboard they may have seen." He points out that the abstinence-fidelity programs divert funds from evidence-based methods of reducing HIV risk that could save lives.

Nathan Lo, an MD/PhD student, is the lead author of the study, which appeared in the May issue of *Health Affairs*.

Not again
IN THE YEAR
and a half after
childbirth, women
generally want to
prevent a subse-
quent pregnancy.
But many women
in the developing
world lack access
to family-planning
services.

A new, low-cost
tool designed to
insert an intrauterine
device shortly after
childbirth could
change that.

Paul Blumen-
thal, MD, professor
of obstetrics and
gynecology at
Stanford Medicine,
collaborated with
colleagues at Popu-
lation Services
International to
invent the \$1 de-
vice, a long tube of
silicone and plastic
preloaded with an
IUD. They tested
the device in 80
postpartum women
in India, who said
placement of
the IUD caused
them little or no
additional pain
compared with the
birth of their child.
Blumenthal is the
senior author of
the study, pub-
lished in March in
*Global Health Sci-
ence and Practice*.

The technique
can detect as
few as one
or two tumor
DNA sequenc-
es among
400,000
nontumor DNA
fragments.



Cancer sleuth

WHILE CANCER PATIENTS are undergoing treatment, it's often necessary to biopsy their tumors repeatedly to detect mutations. Now, a group of Stanford researchers has refined a DNA sequencing technique that could allow oncologists to replace those invasive biopsies with a simple blood test.

The new approach helps weed out errors introduced during amplification, when snippets of tumor DNA captured from the blood are duplicated many times in preparation for sequencing. The researchers tagged the original DNA molecules with "bar codes" so they could distinguish duplication errors from true mutations. They paired that with a computational approach that flags recurrent errors at common locations for further analysis.

"By tagging DNA molecules at the top of the food chain, we can keep track of which molecules have been faithfully reproduced during the sequencing process and which have accumulated errors that were not present in a patient's tumor or bloodstream," says Ash Alizadeh, MD, PhD, assistant professor of oncology. Alizadeh shares senior authorship of the study, published in the May issue of *Nature Biotechnology*, with assistant professor of radiation oncology Maximilian Diehn, MD, PhD. Instructor Aaron Newman, PhD, and former postdoctoral scholars Alexander Lovejoy, PhD, and Daniel Klass, PhD, share lead authorship.

Once mutations have been identified, the technique can detect as few as one or two tumor DNA sequences among 400,000 nontumor DNA fragments. "Now we can detect even more sensitively the presence of specific mutations in the cancer DNA that could help drive treatment choices or detect the presence of residual cancer," says Diehn.

Worth the paper

A DECADE AGO, Grant Lipman, MD, was treating endurance athletes around the world. Their most common complaint? Not running 25 or 50 miles a day. Not extreme cold or extreme heat. It was blisters.

"What I kept hearing was, 'Doc-tor, I'd be doing so well, if only for my feet,'" says Lipman, clinical associate professor of emergency medicine.

So Lipman and colleagues tested inexpensive surgical paper tape, available at drug stores, on 128 runners in a 155-mile, six-stage ultra-marathon. They taped especially blister-prone areas on one of each athlete's feet and checked them for blisters after the race. The tape was highly protective: 98 of the ultra-marathoners developed no blisters in the taped areas. In contrast, 81 had blisters arise in untaped areas. Lipman is the lead author, and University of Washington sports medicine physician Brian Krabak, MD, is the senior author of the study, published online in April in the *Clinical Journal of Sport Medicine*.

WELL

NOW

WHAT HUMANS NEED TO FLOURISH

Plug “wellness” into a search engine and you’ll get 405 million hits — and a lot of advice. Everyone, from genuine experts to click-bait writers, has an opinion about what’s good for us. • We are told to strengthen our willpower, but indulge ourselves; exercise, but not too much; go vegetarian, but eat more meat; develop our social network, but indulge in more “me time”; have great sex, but not too much; safeguard our financial health, but spend our money on travel that leaves memories; keep our minds active, but empty our minds and meditate; volunteer; forgive; and be grateful.

“There’s been a lot of ‘expert speak’ on the concept of what it means to be well,” says associate professor of psychology and of medicine Catherine Heaney, PhD, who is leading a team at Stanford that has been working to define and measure wellness. “What there has been less of,” Heaney says, “is going to ordinary people and trying to get a sense of what being well means to them.”

BY JENNIE DUSHECK

ILLUSTRATION BY CHRISTOPHER SILAS NEAL



People long for a sense of well-being. For thousands of years, everyone — from philosophers such as Aristotle, Epictetus and Buddha to the smooth-talking snake-oil salesmen — have tugged at the problem of what makes for a good life.

Researchers at UC-Berkeley's Greater Good Science Center, for example, report six major underpinnings of happiness, one component of wellness: compassion, friendship, gratitude, forgiveness, exercise and mindfulness. Private foundations, including the Charles Koch Foundation, have taken an interest in funding well-being research. Even governments have gotten into the act. In 2008, a commission of economists assembled by Nicolas Sarkozy, the president of France, called for the development of broader measures of national well-being. Two years later, the United Kingdom did the same.

But what does it mean to be well? If we want to promote wellness for everyone, we have to, first, be able to say exactly what it is and, second, devise rigorous ways of measuring whether it is increasing or decreasing. Once we can measure it, we can begin to discover which factors promote it or diminish it. In this way, an ambitious Stanford project aims to tackle anew an age-old question.

THE PATH TO WELLNESS

In 2014, the Stanford Prevention Research Center launched the WELL program — its ultimate goal, to improve the health and wellness of whole populations. WELL, the Wellness Living Laboratory, emphasizes research on overall health rather than the absence of disease. Funded by an unrestricted \$10 million gift from the Amway Nutrilite Health Institute Wellness Fund, WELL proposes to identify what factors help people maintain health and wellness and to develop techniques to help people to change their lifestyles.

The center's WELL for Life program is both an observational study and an interventional study. WELL will observe more than 30,000 people over many years and also test behavioral modification and other interventions to help people make health improvements such as quitting smoking, eating better or exercising more. The center's health promotion arm, the Health Improvement Program, will enable the techniques to reach the wider population.

"This is an effort to change the world of medicine and health," says John Ioannidis, MD, DSc, professor of medicine and of health research and policy, who directs the center. "It may sound very ambitious, but I see this as a way to refocus the key priorities of biomedical research.

THINKING BIG

THE STANFORD PREVENTION RESEARCH CENTER

How's this for a goal: Increase human wellness around the world. Doable? It's a tall order, but the group taking on this challenge, the Stanford Prevention Research Center, has a history of success helping large groups of people overcome large problems. And now it's the home of the Wellness Living Laboratory project, which aims to build the evidence base of wellness and test ways to support it globally.

The center, founded in the 1970s, has its roots in a massive effort to reduce risk factors for cardiovascular disease. The founder, John Farquhar, MD, now professor emeritus of medicine and of health research and policy, led the landmark study that assessed the use of media campaigns to reduce heart disease risk in two California towns, Monterey and Salinas. [They were successful.]

The center's research now integrates many disciplines, including behavioral science, epidemiology and health education. Its current leader, John Ioannidis, MD, DSc, focuses on evaluating the validity of scientific studies and finding ways to optimize research practices. Ioannidis is the C. F. Rehnberg Professor in Disease Prevention and a professor of medicine and of health research and policy.

Among the center's pioneering efforts:

- Establishing the role of exercise, nutrition and cholesterol levels in heart disease
- Testing the effectiveness of nicotine replacement in treating nicotine addiction
- Examining the influence of social and cultural factors on health
- Analyzing methods for preventing eating disorders and obesity in adolescents

Today, the center's investigators continue to focus on finding ways to solve problems affecting large populations and to test potential solutions. Their studies include projects on motivating healthy food choices, preventing sexual assault, ending nicotine addiction, increasing physical activity and reducing such chronic diseases as heart disease, breast cancer, osteoporosis and dementia. The center also runs an evidence-based health promotion program for Stanford staff and faculty that provides expertise to outside organizations.

So, boosting wellness worldwide? It just might be feasible.

“The vast majority of biomedical research has focused on treating diseases,” he says. “A much smaller part has focused on maintaining health and maybe some prevention efforts. But there’s very, very little research that has tried to look at the big picture — what makes people happy, resilient, creative, fully exploring their potential and living not only healthy, but more-than-healthy lives.”

Among the things the WELL team wants to know: Is wellness the same for everyone, or do factors like gender or age influence how we perceive it? For example, among young adults, wellness might revolve around finances, career and athleticism. But as we age, social connectedness and resilience to stress may become more important drivers of our sense of how well we feel.

“We want to determine not only what makes people feel that they have a higher level of wellness, but also interventions that would help it,” says Ioannidis. “So we want to ask not only what is the profile of someone who feels good about their life, but how can we make that profile better?”

“And how can we intervene with simple means — things that we do in everyday life — not with drugs or devices or complex procedures in the hospital?”

“We know that a person’s ability to move more, to sit less and to eat healthfully are influenced by their environment. This includes social relationships, neighborhoods and public policy,” says Abby King, PhD, professor of medicine and of health research and policy, who studies what’s needed for healthy behavior change.

“It’s about helping people make connections between their own pursuit of well-being and their health,” explains Heaney. Maybe for some people, making a better life for their children is more motivating than reducing their risk of a heart attack in the distant future, she says. Once a doctor knows what motivates patients, it may be possible to harness that in the service of patients’ well-being and physical health.

During the first five years, the 30,000 participants — 10,000 each in China, Taiwan and the United States — will supply mountains of personal health information, ranging from general health and lifestyle information to genetic and other biological markers, says Sandra Winter, PhD, director of WELL. And it’s likely WELL will expand to other countries in the future.

Each of the thousands of participants will periodically answer scores of questions such as, “During the last two weeks, did your diet, physical activity and sleep habits influence your well-being?” or “How confident are you that you can bounce back quickly after hard times?”

LISTENING WELL

How do you ask people meaningful questions about a concept as fuzzy as wellness? To create an accurate vocabulary of wellness, trained interviewers sat down with more than 100 people from Santa Clara County and listened to their stories. Demographically representative of this diverse area, the 100 included men and women, young and old, and a variety of ethnic groups. Similar efforts took place in China and Taiwan.

Tia Rich, PhD, WELL senior research assistant, interviewed half of the Santa Clara County participants. She asked them to talk about a time of peak wellness, a time of low wellness and, finally, their current state. In each case, she also asked them to describe all aspects of their life that they wanted to share regarding each level of wellness.

And then Rich listened. The conversations lasted anywhere from 30 minutes to two hours. “The process of listening to 50 people share their life stories was extremely meaningful. It was really an honor to be trusted in that way,” she says.

THE DOMAINS OF WELLNESS

After transcribing the Santa Clara County interviews and sorting the responses almost line by line into categories, Heaney’s team identified 10 domains of wellness that people most commonly mentioned:

- Social connectedness
- Lifestyle behaviors
- Stress and resilience
- Emotional health
- Physical health
- Meaning and purpose
- Sense of self
- Finances
- Spirituality or religiosity
- Exploration and creativity

For these interviewees, having a social network was the single largest driver of wellness. Being integrated into a social network, having opportunities to receive support and companionship, feeling loved and feeling a sense of belonging, and also having others in your social network doing well is what most enhances wellness, said the interviewees. As one put it, “If my family is doing well, I will be doing well.”

But having a social network can be as much a burden as a comfort. “When people in your social networks are not doing well or when they act in ways that are socially undermining,” says Heaney, “that detracts from our sense of well-being.”

It’s important to manage our social connections so they contribute more than they detract. “It’s like the old saying,”

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

STRIVE, THRIVE AND TAKE FIVE

The science of well-being

AMERICAN INDIANS AND STANFORD RESEARCHERS
COME TOGETHER TO PREVENT DIABETES

in the circle

By Kathy Zonana

PHOTOGRAPHY BY GREGG SEGAL





ADRIAN KENDRICK
Peer mentor

Adrian Kendrick was struggling with irritable bowel syndrome. His mother, a public health nurse, had recommended several remedies, but Kendrick wasn't getting better. His mother made one last suggestion: a healing ceremony.

Kendrick is an enrolled member of the Oglala Sioux tribe, and grew up on and around the Pine Ridge reservation in South Dakota. But he was also an AT&T executive in the Bay Area, one of thousands of local American Indians straddling two worlds. He was game for his mother to set up a healing ceremony on the Navajo reservation where she was working, but he also kept it "super secret," he says. "You don't just do this."

A Navajo healer performed a night-long ceremony — "sundown to sunup" — and Kendrick came away "feeling totally revitalized and healed," he says. "My irritable bowel just suddenly went away.

"So where does it work?" he asks, gesturing to his head, and then his heart. "I don't know where it works, but it works."

Kendrick is one of 15 members of the American Indian Community Action Board, which is working with Stanford and San José State University researchers to prevent diabetes in American Indians and Alaska Natives, who are twice as likely to develop the disease as non-Hispanic whites. It's a rare collaboration. It was initiated by the American Indian community, which can have reason to be wary of medical studies. It is a research partnership with urban American Indians, an invisible majority of the indigenous population, and one with understudied and underfunded health-care needs. And after almost six years of hard work — building trust, seeking funding, surmounting challenges — it is as close to success, in the form of full enrollment in a randomized controlled

trial, as any project that aims to examine the root causes of diabetes in American Indians has ever been.

The study tests whether an enhanced diabetes prevention program that incorporates elements of traditional native culture, such as talking circles and storytelling, will be more effective than the standard program offered to American Indians in San Jose for many years. The enhancements aim to address the historical trauma that urban American Indians have experienced as a result of loss — of land, of family, of culture — trauma that, researchers say, can accumulate over generations and may be at the root of unhealthy lifestyle behaviors.

“American Indians have one of the highest diabetes rates in the entire world,” says Lisa Goldman Rosas, PhD, consulting assistant professor at the Stanford Prevention Research Center and assistant scientist at the Palo Alto Medical Foundation Research Institute. “The stakes are high, and I think the group really sees that. Every time we encounter a challenge, we all feel a responsibility — we’re the only ones who have gotten funded to do this.”

Sixteen people a year. In the mid-2000s, health educators Jan Vasquez and Ramin Naderi, who worked at a community health center in San Jose, had funding from the Indian Health Service to offer its group-based diabetes program to 16 people a year. The IHS had adapted the program from the landmark Diabetes Prevention Program trial, which had shown that losing 7 percent of body weight and increasing physical activity to 150 minutes per week was effective in warding off Type 2 diabetes among high-risk adults. It had a 22.5 percent success rate nationwide, but Vasquez, who has Apache and Comanche heritage, wasn’t satisfied. She was worried that the gains might be temporary, and thought perhaps the program could be strengthened.

So Vasquez and Naderi started presenting data about their participants at conferences nationwide, in the hope they would find an academic partner to conduct further research. At a conference in 2010, they bumped into Rhonda McClinton-Brown, a former colleague who now runs the Office of Community Engagement within the Center for Population Health Sciences at Stanford Medicine. Part of that office’s charge is to pair faculty with community groups so they can jointly conduct research.

McClinton-Brown’s matchmaker’s instinct pointed her to Randall Stafford, MD, PhD, professor of medicine at the Stanford Prevention Research Center, and Goldman Rosas, who were already comparing different approaches to diabetes prevention among Latino immigrants.

“It was a very nice pairing up of Lisa and me with the community,” says Stafford. But by no means did the researchers take it for granted that they would be able to establish a strong research partnership with local American Indians.

“It strikes me as a population you better know a lot about because there have been so many injustices,” Goldman Rosas says. A particularly cautionary tale: In 2003, the Havasupai Indians banished Arizona State University researchers from their reservation. At the tribe’s request, the researchers had conducted a genetic study on diabetes, which has sky-high rates among the Havasupai. And, under a broadly worded consent form, they had also used the Havasupai’s DNA samples to study such taboo topics as schizophrenia, inbreeding and migration — to the tribe’s surprise and distress. There was a lawsuit, and a six-figure settlement, and a pledge by the university to “remedy the wrong that was done.”

That was the story the new partners did not want to tell.

“I’ve always been reluctant to pair up with universities or colleges,” says Al Cross, a retired social worker of Hidatsa and Mandan descent who was the first person to join the project’s community action board, or CAB. “Somehow it seems that we get appropriated.” This study, though, addressed something he thought was important: historical trauma. “That was the big entrée for me to get involved,” he says.

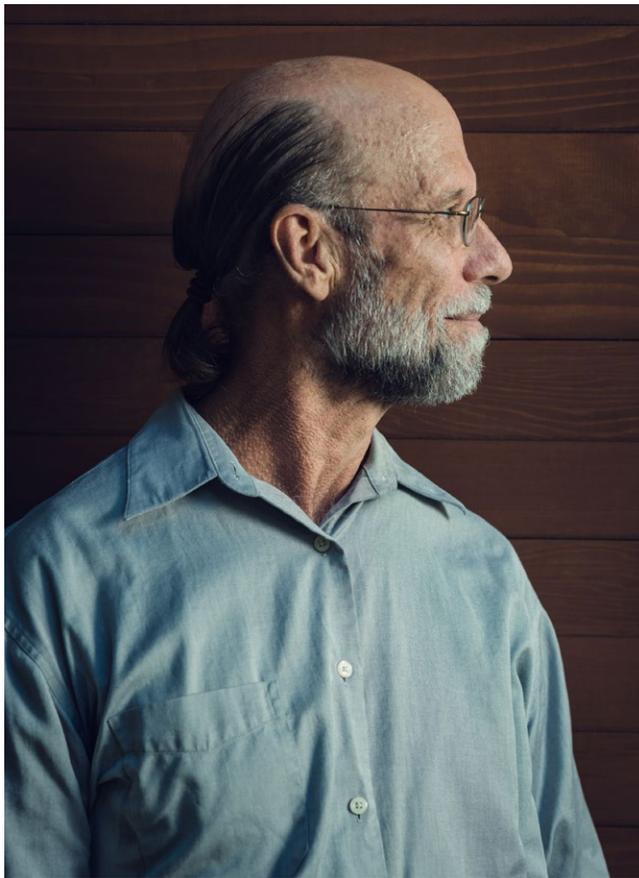
It took a few years to establish trust between the CAB and the researchers. “We entered into this long period of getting to know each other,” says Stafford. “Part of that for Lisa and me in particular was getting to know more about the community, learning more about the situation of urban American Indians, and educating ourselves about the important historical features of why people came to urban areas on the West Coast — it wasn’t all so benign as people just moving to the cities.”

Both partners had expertise to contribute and new knowledge to gain, which helped create a sense of equity, Vasquez says. “They knew nothing about the American Indian population, and we knew nothing about research.”

‘they knew NOTHING ABOUT THE AMERICAN INDIAN POPULATION, AND WE KNEW NOTHING ABOUT RESEARCH.’

PAUL AND ORENA FLORES
Digital-storytelling coordinator and treatment-group leader





In 1940, only 8 percent of American Indians lived in cities. By the end of the decade, federal agencies had begun to provide job assistance to those who were willing to relocate from reservations to certain designated cities in the West and Midwest. It was the latest chapter in the long and contradictory history of federal Indian policy, which has seesawed between segregating American Indians onto reservations and encouraging them to assimilate.

It had devastating effects. Those who relocated saw their family and community ties fray. Those who stayed saw their chances of maintaining robust tribal nations dwindle.

“When the Indians came to the city, the government was hoping they would lose their Indianness,” says Cross, who relocated to San Jose in 1960, at the age of 25. “It was just the opposite. Indians became really acutely aware of their own identity.” It was a new kind of identity, though — one forged by small numbers of people from different tribes, coping with isolation. “There were not enough to make an enclave,” Cross says. “There were not enough to command any kind of attention in the city. So the name ‘Indian’ became more general. Culture and identity were the main victims.”

Today, at least 70 percent of American Indians in the United States live in urban areas. San Jose, one of the major

relocation destinations, is home to about 50,000, representing more than 100 different tribes. Many are now second- and third-generation urban residents who have limited or no connection to tribal lands.

“What Indians who grew up in the city don’t understand is the importance of that land,” says Cross, who grew up on the Fort Berthold reservation in North Dakota. “There’s an identity attached to it.”

As the research team learned more about the cumulative impact of historical trauma across generations, they began to hypothesize that a diabetes prevention program that addressed its effects might be more effective than one that didn’t.

“People’s current-day behaviors and their problems aren’t just something they can overcome with willpower,” Stafford says. “People are living with the problems that their grandparents, great-grandparents and so forth have been subjected to.”

“We all have family, friends and children we are worried about, especially in terms of diabetes,” says Vasquez, who was motivated by the project to obtain a master’s degree in public health with an American Indian specialization, and now serves as the project’s research director. “Historical trauma is affecting everything you do. The social support system is broken down. Your family has changed. Your whole life is filtered through these things: lack of identity, never fitting in, never feeling like you belong anywhere — because you really don’t.”

Given this fragmented sense of identity, the researchers and the CAB knew they had to proceed thoughtfully in developing the study’s cultural enhancements. They decided to use an inclusive, pan-tribal approach. “There are those who say you should only learn your ways, and then there are those who are saying, learn something, otherwise you’re just fulfilling what the United States government wanted to do in the beginning anyway, which was to eradicate the native people here,” says CAB member Paul Flores, alluding to a history of armed conflict, often over land, that dates to the colonial era. “When we don’t practice our culture, we ourselves are completing that job that the government started.”

In this type of equitable research collaboration, there’s a continuum of typical community involvement, says Goldman Rosas, ranging from conducting outreach and raising awareness about a study to actually participating in the study. “This falls off that spectrum,” she says. Because the study was initiated by the community — which is rare — it has a special dynamic, Goldman Rosas says. “It is community-driven and community-run.”

The researchers and the CAB worked in tandem to develop and pilot-test enhancements to the diabetes prevention program. It wasn’t that the standard IHS program, in which a

THIS PAGE: LENNY GONZALEZ

lifestyle coach used behavioral strategies in 16 weekly group sessions to promote moderate calorie restriction and physical activity, was ineffective. For instance, Kendrick, the former AT&T executive, had completed it successfully in 2013, losing 20 pounds and reversing prediabetes. But with attention to historical trauma, maybe it could be improved.

The standard program — which serves as the control for the randomized controlled trial now underway — is lightly tailored to American Indians, “just in terms of the branding of it, suggestions about physical activity emphasizing, let’s say, dance, over playing tennis,” Stafford says. “We began to think about, well, what are the types of enhancements that people would value and might make the experience deeper and more transformational for people?”

The researchers and the CAB came up with three: talking

circles, a traditional method of group communication and problem solving; digital storytelling, a modern adaptation of oral tradition in which participants reflect on their lives and their health; and a photography project in which participants take pictures in response to questions about health, relationships, challenges and purpose. Participants are also given opportunities to participate in cultural celebrations that emphasize health and well-being. The intervention staff guides participants to the enhancements that seem most likely to help them grapple with their challenges, reinforce their cultural identity and enhance their social support.

“The idea is to identify health as something that is valued by the American Indian community, not just Western medicine,” Stafford says. Participants might begin to see that “exercise isn’t something that’s a prescription that the doctor

‘our people DON’T JUST DEFINE PHYSICALITY AS HEALTH. MEDICINE IS NOT SOMETHING OUT OF THE CABINET.’



RANDALL STAFFORD (OPPOSITE),
LISA GOLDMAN ROSAS AND JAN VASQUEZ
Members of the research team

is giving, but is doing something with movement that our ancestors did,” he says. “Or dietary changes really aren’t so much about extracting this or restricting that, but also looking back at how did our ancestors approach diet?”

“Our people don’t just define physicality as health,” says Paul Flores, a computer technology instructor at a local elementary school. “Medicine is not something out of the cabinet. Medicine could be a song; it could be a prayer; it could be food. So we had to keep that in context.”

McClinton-Brown says this project embodies the “pure sense” of a community-researcher partnership, the kind her office teaches about but doesn’t always get to see put into practice. The CAB, she says, is fully engaged in all aspects of the research. Several members contributed to the writing of the academic papers, and there are plans to write about the study for community publications in Indian Country. “I’ve never actually seen that before,” she says.

“I get the sense people come to the meeting because of something much bigger than the diabetes study,” Goldman Rosas says. This is especially true when a project hits the kind of roadblocks this one has. “The challenges are more severe than on any project I’d ever been on,” she says.

For starters, the researchers were unable to obtain funding from the National Institutes of Health because of the lack of data connecting historical trauma to unhealthy

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

CAN YOU REPEAT THAT?

It was a doctor's worst nightmare. Throughout the late '80s and '90s, clinicians had prescribed hormone therapy to millions of menopausal women to help with hot flashes and other unpleasant side effects. The treatment was also believed to lower a woman's risk of heart attack or stroke. It seemed like a win-win. But in 2002 a new study based on the Women's Health Initiative delivered some jaw-dropping results.

The study, which was steered by a national committee headed by professor of medicine Marcia Stefanick, PhD, of the Stanford Prevention Research Center, showed that women taking a combination therapy using both estrogen and progestin (the synthetic form of the hormone progesterone) actually had an *increased* risk of heart attack and stroke within the first five years. They also had a significantly increased risk of breast cancer.

In other words, doctors who thought they were helping their patients were doing the exact opposite.

"I found myself apologizing to my patients," recalls Adam Cifu, MD, a professor of medicine and general internist at the University of Chicago Medicine. "To this day I have patients who, when I recommend a prescription, say, 'This isn't like that estrogen therapy you gave me 20 years ago that you then told me to stop taking, is it?'"

The experience caused Cifu to begin to question the evidence upon which medical practice is based, and wonder how many other times established medical protocols have been proven not just invalid, but also harmful.

THE CRISIS IN RESEARCH RELIABILITY

BY KRISTA CONGER

ILLUSTRATION BY MARK SMITH



IN 2005, JOHN IOANNIDIS, MD, DSc, PUBLISHED A PAPER in *PLOS Medicine* provocatively titled “Why Most Published Research Findings Are False.” In it Ioannidis, who came to Stanford in 2010 as director of the Stanford Prevention Research Center, asserted that small study sizes, research bias, competition among scientists and financial conflicts of interest render the outcome of over half of scientific studies suspect.

Over the subsequent decade, rumbles of concern from researchers, clinicians and pharmaceutical companies about the reproducibility of published research findings have grown into a drumbeat of alarm that’s reached the popular press and even infiltrated late-night television. As comedian John Oliver quipped recently during a *Last Week Tonight* segment on scientific inaccuracy, “There’s no Nobel Prize

Findings that appear statistically significant? We should be rewarding quality research that will make an impact on real people’s lives — both those who are sick and those who wish to remain healthy.”

HOW TO REMAIN HEALTHY, and how to treat those who aren’t, is the crux of medical research. In 2015, the Stanford Prevention Research Center launched the Wellness Living Laboratory to determine the lifestyle and environmental factors that contribute to a person’s ability to live a long, healthy life. But as the hormone therapy experience shows, it’s often far from clear how to accomplish these goals because it can be hard to know which studies to trust.

In August 2015, Cifu and a colleague, Vinayak Prasad, MD, an assistant professor at the University of Oregon’s Health and Sciences University, published the results of a

WE SHOULD BE REWARDING QUALITY

for fact-checking” already-published research. And pressure from stakeholders is mounting. Earlier this year, for example, the pharmaceutical giant Merck suggested that universities be required to return licensing fees paid to them by drug companies if the original experiments can’t be replicated.

An economic study published in 2015 in *PLOS Biology* suggests that, if Ioannidis’ estimates are correct, taxpayers, who foot the bill for government grants for scientific research, are pouring billions of dollars down the drain. Every year.

These numbers have attracted the attention of major research funding agencies such as the National Institutes of Health and the editors of high-profile journals such as *Science* and *Nature*. In the past year, these organizations have launched efforts to ensure the accuracy of published research and to modify an incentive system that places greater value on splashy results than behind-the-scenes grunt work by multiple researchers who take the time to verify previous findings and the care to design methodologically robust further studies — steps that are often necessary to home in on scientific truth.

The overall aim is to issue a course correction to the U.S. medical research behemoth by bringing back into focus its core mission: How to benefit those who need it most.

“I think that, somewhere along the line, we began to miss the big picture,” muses Ioannidis. “What have we been rewarding in science? Quantity of publications?

review they and their colleagues conducted of research published over 10 years in one of the most highly regarded medical publications, the *New England Journal of Medicine*. They identified 146 cases of what they termed “medical reversal,” in which previously accepted medical practices — including stenting for stable coronary artery disease, arthroscopic surgery for osteoarthritis of the knee and vertebroplasty for osteoporotic fracture — were proven to be, well, wrong.

The problems can have deep roots. As Ioannidis’ research suggests, scientific errors can occur in the laboratory during basic and preclinical research, as well as in clinical trials. In 2012, the former head of global cancer research at Amgen Inc. tried something new: Rather than spending resources to build directly on published research, he first sought to confirm it. He chose 53 well-known cancer studies published in high-profile journals and tried to duplicate their findings. He and his team were unsuccessful 47 out of 53 times.

So how is it possible that the conclusions of seemingly reputable scientific studies fail to substantiate and even often appear to contradict one another? Ioannidis points to an episode from his past as one example of how things can go awry.

As a young assistant professor, he found himself scratching his head at a puzzling result. He was attempting to develop a mathematical model correlating the amount of virus in the blood of a person infected with HIV and that person’s expected life span. Logic, and science, dictate that the higher the

number of viral particles in the blood, the closer to death that patient would be. But Ioannidis' equation wasn't working.

"At some point, my calculations estimated that someone with an extremely high viral load would live 800 years," he says. When he double-checked, Ioannidis found that in one equation a positive sign had mistakenly been converted to a negative sign — a slip-up we've all probably made at some point. "Once I corrected the error, the result was much more reasonable, predicting that the person would likely live less than one year," he says. But that experience changed his career.

"I began to wonder what would have happened if the error was such that the result, although still wrong, was not so implausible," he says. "There are many reasons why we might get results that are incorrect, but not easily recognizable at first as wrong. Particularly if these results fit our own expectations and biases."

"It seemed to me after reading a lot of research papers that it was not at all uncommon to encounter major weaknesses in study design, analysis and conclusion," he says. "This is the core of scientific investigation, but it's not easy. You need a lot of training and experience, and even then you can still get things wrong if you're not very careful."

Errors in study design, if not detected, then creep into clinical recommendations as physicians succumb to the all-too-human desire to help people, Cifu says. "Doctors want to have something to offer that they think will help their patients. But problems can occur when physicians put their trust in data that are not terribly robust. This is easy to do when there is a physiologic rationale for the potential treatment."

For example, the initial study suggesting that hormone therapy might reduce the risk of heart attack or stroke was observational. Clinicians tracked the health outcomes

RESEARCH THAT WILL MAKE AN IMPACT ON REAL PEOPLE'S LIVES.

Ioannidis found himself increasingly devoting his time to studying when, how and why mistakes are made in a variety of biomedical fields. And in doing so he found some glaring problems.

FOUR STEPS TO BETTER RESEARCH

SCIENTISTS AND FUNDING AGENCIES around the world are putting their heads together to identify factors that can influence the accuracy of research findings. Among them:

- **How readily scientists share the data they generate.** Not sharing prevents others from trying to reproduce your findings and can result in the unnecessary (and costly) duplication of research efforts.
- **Whether they fully describe how they conducted their research.** A thorough description is necessary to ensure that others can try to replicate published findings.
- **What method is used to analyze the data.** Scientists sometimes succumb to "shopping" for a statistical method of analysis that makes their findings appear more significant.
- **How career accolades and grant funding are awarded in the researcher's field.** Name-dropping high-profile journals in one's CV often carries more reputational weight than studies in lesser journals that report negative results or attempts to replicate others' work.

of women who chose whether to take hormone pills and found that those who did had lower rates of heart attack and stroke than those who decided to forgo the treatment. (In contrast, the Women's Health Initiative randomly assigned women to receive either hormone therapy or a placebo, in a study format known as a randomized controlled trial.)

Although the observational study wasn't rock-solid evidence — randomized controlled trials are considered to be superior — the lure of hormone therapy was hard to resist. Doctors were inclined to accept the findings of the less-robust observational study rather than demanding more-solid evidence of the treatment's efficacy because the reasons why it should work seemed so sensible.

"There was good biochemical and biophysical rationale for why this therapy would work," says Cifu. "The problem is, it didn't. In retrospect, the women who took estrogen were younger, thinner and had better cholesterol levels than those who didn't take it. So it was probably not the hormone therapy that benefited them, but everything else."

CLEARLY, HELPING BOTH PHYSICIANS and researchers understand how to design and evaluate published studies is an important component of increasing research accuracy. In 2014, Ioannidis helped launch the Meta-Research Innovation Center at Stanford, or METRICS. Co-directed by

C O N T I N U E S O N P A G E 5 3

LEAVING FRAILTY BEHIND

She is an author of extraordinary success. Laura Hillenbrand's *Seabiscuit* and *Unbroken* are literary phenomenons: Together, they have sold more than 13 million copies, and both have been made into blockbuster motion pictures. *Seabiscuit*, published in 2001,

tells the story of a racehorse that captured America's heart during the Great Depression. *Unbroken*, published in 2010, is the biography of World War II hero Louis Zamperini, who survived a bomber crash into the Pacific and more than 2½ years as a prisoner of war in Japan. Hillenbrand wrote the books while besieged by chronic fatigue syndrome, or ME/CFS, which has at times ravaged her like a tidal wave. Stricken in 1987, she has endured vertigo and exhaustion so severe that for many years she was incapacitated and housebound.

Recently, Hillenbrand has made a lot of changes in her medical treatments and in her life. There's optimism in her voice and a sense of wonderment at new beginnings. A big one is a move across the country to be with her boyfriend in Oregon, where she finds solace in afternoon car rides with views of resplendent Mount Hood.

For this special issue of *Stanford Medicine* on well-being, we were curious: What does the word "well" mean to someone who has been unwell for so long? Executive editor Paul Costello spoke with Hillenbrand about her illness, her newfound strengths and how she is leaving frailty behind.

COSTELLO: Does the term "being well" register for you?

HILLENBRAND: I don't really think about that as an aspiration, exactly. I think about if I could do this thing, if I could ride a bike for miles, or if I could climb to the top of the Empire State Building. What I think about is a life in which I don't have to monitor my body. A life in which I'm not constrained in terms of what I want to do and not paying a huge price for what I do. I'm doing much better now than I've done in years, and I've started riding horses. That's a great joy to me because it was something I did when I was a healthy person and I was younger.

COSTELLO: Is horseback riding therapeutic for you?

HILLENBRAND: Riding is very therapeutic. It's also therapeutic just as a physical accomplishment. It's a sport. For decades I didn't do sports. I maybe could walk around the block. Now I put on my hel-

met and my boots, and I just feel like I'm more of a normal person. I love that. It's a marvelous feeling to wed yourself to an animal of such strength.

COSTELLO: It sounds like your life has taken a shift.

HILLENBRAND: Everything has come together to give me a little bit of push. I started to test the boundaries and found out, "Well, I could do this. I could do that." Each one of those things that I did would make me feel like, "Maybe I can try the next thing." It's an extremely slow process, and sometimes I overstep and slip backwards. But I keep trying. Once I got out here to Oregon, I got on a bike, which was another thing I was really into when I was healthy, and now I'm starting to ride a bike. Not very far. Not very well. But I'm doing it.

COSTELLO: You moved from Washington, D.C., to Oregon. Did you have to prepare yourself?

HILLENBRAND: It took years to get ready to do this. To put you in the perspective of where I was, I had not left Washington, D.C., since 1990 because of vertigo, which has been a problem for me for most of the time I've had CFS. It's not a common kind of vertigo: It has been absolutely constant. It feels like the floor is pitching up and down. It looks like the room is moving around me. My desk is moving. Everything looks and feels like it's moving. It's hell.

I began to try to inure myself by getting in a car and riding for five minutes. It would be awful and I would feel terrible. I was so dizzy for an hour afterward, but I just wanted to see: If I keep doing this, can I teach my brain how to tolerate it? I'd go a little longer and a little longer. And over two years, I went from being just miserably dizzy after five minutes to being able to go two hours.

Once I hit two hours, I started thinking maybe I could come across the country. My boyfriend was living in Oregon. I wanted to be with him. I wanted to start a new life. D.C. was not the right place to be for someone with CFS who was very intolerant of heat. I also

wanted a simpler world around me because complicated things are difficult with the cognitive problems from CFS.

I was in love and I wanted to be with the man I was in love with. We got an RV and we took a monthlong trip crossing the country and it was a miracle for me. It was the most wondrous thing.

COSTELLO: What did you discover on the trip?

HILLENBRAND: Every single thing was beautiful. Every drop of rain, every stretch of highway, every blade of grass was beautiful because I was not in a bed, I was not in a house. People kept saying, "Well, you're going to have to be bored in the Midwest because it's not pretty." I thought it was gorgeous. I was gasping at the grasslands of Kansas. And I thought Illinois was resplendent. And then we went to the Badlands and I'd never seen a canyon before. I just shrieked when I saw it.



It was a surprise. My boyfriend didn't tell me we were going. He said, "Don't look at the map. I don't want you to know where we are." We just pulled up and the land drops away and there are canyons everywhere. I can't describe how overwhelmed I was by the beauty.

We went to the Black Hills and we went to Spearfish Canyon. We went out to the West Coast. I put my hand in the Pacific Ocean. [laughs] We started at the Atlantic Ocean in Delaware. I got in the water in the Pacific. What I experienced was an overwhelming sense of gratitude because I had been set free. I was not well. I am not well.

I am always dealing with symptoms, but I was free enough to have that experience, to see America.

COSTELLO: Love has really changed your life.

HILLENBRAND: It's the biggest thing that got me to take this leap. It was very, very, very risky for me to do this. I could have died on this trip. When I push too far ... at one point, when I tried to take a trip in 1991, I went into shock and very nearly died.

I could have landed in bed for another 10 years. It was so risky, but I just believed that I could do it. I believed in the person I was with. I thought, I have to try. I cannot live my whole life in a room. I can't do it. I won't do it. I'm willing to risk everything to escape.

COSTELLO: Can you describe how you experience the illness?

HILLENBRAND: The typical experience of it is akin to being bound in plastic so that you can't move your arms and legs, you can't speak and be heard. You are suffocating. It closes off the world to you in a most profound way so that all that is left of you is the thoughts in your mind, because you just aren't capable of doing anything, of interacting with the world at all. There was a period of time where I didn't leave the house for two years. I was too weak to do it. That is the physical experience of it. You become a purely intellectual thing because you are no longer a physical creature at all.

The parameters of my strength are nothing like that of a normal person. There's a red line I cannot cross, because to cross it means to plunge into a "crash," a devastating state of exhaustion in which I can't stand, sit up, or sometimes even speak.

In terms of what that has given me, I feel like independent of what the cause of suffering is, there is this place that suffering takes you that is common to people suffering from all different kinds of things, serious diseases or terrible grief or all of the things that fell us in our lives.

In writing *Unbroken*, which is about servicemen at war and prisoners of war and people in horrific states of suffering, I felt like I was able to climb into their bodies and minds maybe better than I would have been if I had just been a regular healthy person.

I felt like I knew what Louis Zamperini felt when he was being held prisoner on Kwajalein Island and having medical experiments done on him by the Japanese. Not that I am comparing my disease to the experience of a prisoner of war. That's a different and horrible thing that's inflicted upon you by others. But the quality of the suffering ... when he and I would discuss it, he knew I knew something of what he felt. He told me that enabled him to delve more deeply into it with me than he had with other people. He felt like if he told me this story, I would write it down right.

At the end he told me that what I wrote was so true to his experience that he kept having to put the book down and look out the window and tell himself, "I'm here. I'm here. I'm here. I'm not there anymore."

WEB EXTRA

Hear the conversation at
<http://stan.md/29mzj39>

standing up to sexual assault

RESEARCHERS SEEK
TO TRANSFORM A GENERATION
IN KENYA

“What makes you a girl?”

The question comes out with a flamboyant roll of the “r,” and the young Kenyan teacher with pink-highlighted hair captures the attention of chattering school-age girls. Bashful, some hide their faces and giggle. Others shoot their hands up to answer. “Breasts,” says one little girl earnestly. “Buttocks!” shouts another. The teacher calls on a third student, who primly states, “I was going to say hips, but it’s almost the same thing as buttocks.”

These fourth- and fifth-graders in Nairobi, Kenya, are just the latest in a cohort of students learning how to ward off sexual assault in their impoverished communities. The self-defense

BY LAURA HEATON

PHOTOGRAPHY

BY NICHOLE SOBECKI

TRAINERS SHOW FOURTH- AND FIFTH-GRADERS
HOW TO DEFEND THEMSELVES.





'Some women came to my rescue and

training is the focus of a collaboration between Stanford researchers and three nongovernmental organizations to carry out the largest and most rigorous randomized trial ever conducted of an empowerment and self-defense program to prevent sexual assault. The challenge for the trainers and the researchers is vast: Surveys by national organizations reveal that as many as 46 percent of Kenyan women experience sex-

So we just lived like that. No punishment. Nothing.”

More than 20 years later and with daughters of her own, Elizabeth survived another rape. She was working as a housekeeper in the home of an older man, who tricked her into one of the bedrooms by saying he would leave her payment there when she finished cleaning. When she went into the room, he slammed the door and pinned her on the bed. “I was so furi-



ual assault as children. A parallel training for their male peers simultaneously seeks to halt a striking pattern: 52 percent of perpetrators are the boyfriends of the girls they rape. A sexual violence prevention group based in Nairobi estimates that only 10 percent of attacks are carried out by strangers.

Elizabeth was 9 years old when she was raped the first time. Two cousins, a boy and a girl, had moved in with Elizabeth's family when their father died. One day, Elizabeth left the house with the 13-year-old boy to find firewood. “This cousin of mine grabbed me and pushed me down. Then he raped me,” she says, staring straight ahead. “I didn't share with anyone,” says Elizabeth, who is now a trainer in the self-defense program the Stanford team is studying. “I was feeling it was just normal for any girl, any woman.” He attacked her again a month later while Elizabeth's mother was out of the house, and this time the boy's sister caught him. “When my mother heard, she just took the boy to our grandma. She just removed him from this house to another house, but nothing else happened. She left it at that.

ous. But I felt like, ‘How can I tell people about this? I'm a woman with children. How can I be talking about this rape?’” Although she tried to suppress the trauma, the buried emotions came tumbling out one night when a stranger tried to attack her while she was showering at what she calls the “shanty bathroom,” a public shower that residents use for a fee. “This time I screamed, and I was shaking everywhere,” Elizabeth says. “Some women came to my rescue and asked me, ‘What is the problem? Why are you shaking so much and this man has not even raped you yet?’ That's when I opened up and told them it's because this has happened to me before. It was common in our community, so those women felt like it's just normal.”

Nairobi, the largest and most cosmopolitan city in East Africa, has in many ways epitomized the narrative of a continent on the rise, with its tech startups and influx of international companies. But the city also has a gaping divide between rich and poor. Ramshackle slum neighborhoods teem with hundreds of thousands of people struggling to make a daily wage. They get by with little government effort to drain

asked me, “Why are you shaking so much and this man has not even raped you yet?”



STANFORD RESEARCHERS CLEA SARNQUIST AND MICHAEL BAIOCCHI (FAR LEFT, BACKGROUND) WORK WITH KENYAN RESEARCHERS AND DATA COLLECTORS TO REFINE THEIR LATEST SURVEY. ABOVE, A DATA COLLECTOR ADMINISTERS THE QUESTIONNAIRE TO A FEW OF THE 4,000 GIRLS WHO WILL PARTICIPATE.

sewage, collect garbage or combat crime. Asked about root causes of the sexual violence epidemic in her community, Elizabeth points to the police, whom she says can easily be paid off to side with the perpetrators.

So the little girls in their lavender-striped school dresses — and the mothers and grandmothers who raise them — cope with severe rates of sexual violence seemingly without recourse.

But that’s precisely the impression that the group No

Means No Worldwide is working to combat. In Kenya, girls may face deep patriarchy and a murky justice system, but with their voices — and sometimes a well-landed elbow jab — they’re powerful beyond their size and age.

No Means No’s six-week empowerment and self-defense program seeks to quash the idea that girls should be obedient and soft-spoken, even when facing a potential attacker. Dynamic trainers — like Elizabeth — teach and model a curriculum that preaches self-worth, starting with feeling confident in their changing bodies. “Just raising the spirit of the girls has enabled them to be able to overcome assault, to feel that something can be done about rape,” says Esther Nyambura, another self-defense trainer, who has worked with No

'As the boys mature they'll know how

Means No for five years. The students practice screaming, calling out the behavior by name ("That guy in the green shirt just touched my buttocks!"), lying or acting crazy, learning that their first line of defense is to get away.

They're also taught tactics to use when the attacker is someone they know, like their boyfriend, teacher or uncle. "We tell them that the assailant wants them to keep a secret,"

going to pay your school fees, who's going to pay your rent?"

The expectation that girls don't have the right to fight back, protest or even speak up about an assault combines in devastating ways with the entitlement boys are taught they have to girls' bodies. Nyambura says that when male activists in her organization have asked boys why they assault women, "some of them did not know that they're doing anything



Nyambura says. "By letting the assailant know that someone else knows about this, it can really stop the assault."

Many of the trainers grew up or still live in the slums where they now lead workshops. "I come from Korogocho, and I know the challenges of Korogocho," Nyambura says, referring to a neighborhood that borders the country's largest landfill.

In her previous job as a preschool teacher, Nyambura was startled to hear the experiences her young students recounted without inhibition during morning circle time. Those impressions and the work she does now with No Means No Worldwide have led her to conclude that the high rate of sexual violence stems in part from the way girls are socialized. She says girls are taught, "You have to be nice to everyone, even strangers, even if you're being assaulted. We've had cases where we say, 'Who did you tell?' And the last people that the girls tell are their parents. Almost 90 percent don't tell their parents, because their parents will be like, 'Shh! Shut up. No one should know this.' If your dad is jailed, who's

wrong. They say things like, 'What's the big deal? I'm having fun.' Most girls are not raped at gunpoint or with a knife — no. They're coerced, threatened, groomed toward behaving in a certain manner. It's really about the social norm, which is why we're targeting kids at a young age. As the boys mature they'll know how to respect women and the girls in their life and even intervene if they see someone being assaulted."

Ever since No Means No Worldwide began its Kenya trainings in 2010, working alongside local partner organization Ujamaa ("togetherness like family" in Swahili), the team has collected ample anecdotal evidence from testimonies and surveys that suggest a powerful impact.

Lee Paiva, the San Francisco-based founder of No Means Now Worldwide, says she had been working on an earlier iteration of the training when the question of effectiveness suddenly loomed large. She was in the midst of fundraising and had gotten used to citing the number of participants who

to respect women and the girls in their life and even intervene if they see someone being assaulted.'



FOR BOTH GIRLS AND BOYS, THE STUDY FOCUSES ON EMPOWERMENT. THE GIRLS' CURRICULUM EMPHASIZES SELF-WORTH AND KNOWING HOW TO WARD OFF AN ASSAULT. BOYS ARE ENCOURAGED TO THINK ABOUT WHAT IT MEANS TO BE A MAN AND HOW TO CONFRONT VIOLENCE IN THEIR LIVES.

had gone through the training. "This little still voice inside of me said, 'What did you teach them?' I just really wondered about that. What did those kids actually get? What is that money really going to do? And in that moment I knew — I'm not doing this anymore until I absolutely know what that child got out of this."

Paiva's husband, Jake Sinclair, MD, a Bay Area physician and the founder of Ujamaa, approached Stanford faculty members — Yvonne Maldonado, MD, professor of pediatrics and of health research and policy; Neville Golden, PhD, professor of pediatrics; and David Cornfield, MD, professor of pediatrics — about analyzing the data and building upon it to tease out the tangible effects of the program. They launched the Stanford Gender-Based Violence Prevention Collaborative, which is now spearheading the most rigorous and expansive study ever conducted of a behavior-based sexual assault prevention program. The two-year assessment is funded by UKAID as part of the British government's What

More than half of the girls who had used the skills to fend off sexual harassment or rape.

Works to Prevent Violence Against Women and Girls Programme, a multi-country, multi-intervention set of studies.

The Stanford prevention collaborative has already conducted several pilot evaluations of the program and come away with striking results. A study published in 2014 in *Pediatrics* found that more than half of the 1,978 high school-aged girls who had completed the self-defense course had used the skills to fend off sexual harassment or rape. Further, researchers found that the rate of rape dropped during the time the girls were participating in the training: When the study began, about one in five of the girls reported being forced to have sex during the previous year. By the end of the study period, the rate had fallen by more than a third.

The survey also revealed a dramatic difference in the likelihood a girl would report an attack. In the “standard of care” group — girls who didn’t receive self-defense training — about half of those who had been abused told someone about the incident. But among the girls in the training, 75 percent said they spoke up, generally to a friend or relative.

This past January, Stanford Gender-Based Violence Prevention Collaborative members Clea Sarnquist, DrPH, the 2014 study’s lead author and a senior research scholar in pediatrics, and Michael Baiocchi, PhD, traveled back to Kenya to launch the most ambitious evaluation of the program yet. Baiocchi, an assistant professor of medicine at the Stanford Prevention Research Center, is its principal investigator.

A statistician, Baiocchi specializes in causal inference — analyzing “real-world, messy data where you’re still trying to prove the cause-and-effect relationship,” he says. He and the research team have designed a closed-cohort study that, unlike previous evaluations, will track changes in a fixed group of about 4,000 girls. (Earlier studies homed in on specific classrooms but didn’t track who was interviewed over time.) In this larger, more rigorous study, behavior trends can be traced and analyzed, leading to better understanding of how girls are adapting to the trainings and their social situations.

“You can put together numbers from data collected observationally, but people can doubt the links you’re drawing,” says Baiocchi. “By doing an actual randomization, following people through time and doing really careful measurements, your conclusions are much more solid.”

Donors are eager to see this level of exactitude, to know the kind of impact they can expect from the projects they pay for, Baiocchi says. As the development and humanitarian

fields mature, it’s no longer seen as responsible to simply give things away, because untested interventions are both financially unwise and prone to spark unintended consequences in the communities that the projects aim to help. “So this is the highest level of rigor, the equivalent of what it would take to get through the FDA,” Baiocchi says.

In the summer heat this past January, a veteran team of Kenyan researchers and data collectors gathered with Baiocchi and Sarnquist in a Nairobi hotel before fanning out across the city to start collecting the baseline data. Banquet tables were dotted with coffee cups and mint wrappers — fuel for several days of intensive discussions to refine the survey and prepare for data collection in the schools.

Over the following months, when the researchers arrive at the schools with the questionnaires, they would have just under two hours — a school administrators’ rule — to gather the rambunctious 11- and 12-year-olds, have them select colored beads from a hat to randomly determine who would participate, and then have them sit quietly and answer 14 pages of questions. The children would also need to sign an assent form to acknowledge that their involvement is voluntary. Adding to the feat is the reality that many of the students have low levels of literacy, despite being in school.

While debating the plan, the Kenyan researchers raised concerns arising from their work on previous surveys: Some parents might be wary about having their daughter stay after school to answer questions, or they may expect to be compensated for participating. Better to collect cellphone numbers not only for the child’s own family members but neighbors as well; phones get stolen or lost, and people move.

“The attrition rate could be around 25 percent, according to some studies already done,” says Mary Amuyunzu-Nyamongo, PhD, founder and executive director of the African Institute for Health and Development, which is partnering with Stanford to lead the field research. “We may lose some of the children [to follow-up] because they move between slums, between informal settlements and rural areas.”

Logistics aside, the content of the questionnaire is sobering, if entirely relevant for capturing the range of hardships these children face day to day. “In the last four weeks, how many times did you go to sleep without dinner because of lack of food at home?” “In the past 12 months how many times did two or more men or boys force you to have sex with

had completed the self-defense course

them at the same time against your will?” Choose between never, once, two to three times and four or more times.

Even among the data collectors, some of the questions — read aloud during the discussion session — hang in the air. “If 25 percent of Kenyans have been abused, that means that 25 percent of the people sitting around this table...,” Amuyunzu-Nyamongo’s voice trails off. She notes the importance of offering support services even to the researchers. “There’s one who came up and said, ‘I wish I had known this before, because I’ve gone through an experience like this.’”

Watching these various teams at work — the data collectors huddled with groups of students in rumpled uniforms, all heads bent over the survey; the Stanford researchers quietly observing from kid-sized wooden benches as their project, months in the design phase, unfolds in the real world; the trainers whose enthusiasm and confidence dares girls to shout, “Hands off my body!” with conviction — it’s apparent that dedication to the broader mission runs deep.

“I’ve seen grannies be able to fight back against rape just by having an awareness to speak up about what’s happening to them,” says Nyambura, the trainer. “They need to believe that they’re worth defending and something can be done. Women have done this before and prevailed.”

Stanford statistician Baiocchi agrees that the shift from lack of agency to a sense of control may be the most powerful element of the trainings. “One of our beliefs is that part of the reason that rape is occurring is because the girls don’t feel like they can change what happens to them,” he says. “We’re monitoring how those perceptions change, because we want to see whether the girls who we help with self-efficacy are the people who have the biggest change when it comes to rape.”

For Lee Paiva, No Means No Worldwide’s founder, the work is profoundly personal. “There are so many different ways of being a survivor,” she says. “My survivorship has allowed me to, in many ways, experience what I experienced and get up and be a voice. Because not everybody can.”

When she was 16 years old, Paiva was sexually assaulted by an acquaintance while sleeping in the living room in a house full of people. “I remember thinking I didn’t want to wake anybody up! I didn’t want to trouble them!” She started taking self-defense classes because she wanted to learn to fight back. But she came away with a new confidence not just grounded in the physical skills but from believing her

instincts. “I just needed to know that it’s OK to do what I want to do in that situation, which is scream, yell, call out to people, really fight him, push him off of me.”

Paiva’s own evolution informs a tenet of the No Means No trainings: “We’re starting at a baseline with understanding that just because the culture might say it’s OK, just because it has been happening for so long... You know how it feels when it happens to you, and you want it to stop. Period.”

Teaching physical tactics to schoolchildren has met some criticism from those who claim that fighting back may make girls more vulnerable during an assault or even aggressive in other contexts. The Stanford researchers say, however, that when tested — mostly among college-age American and Canadian women — those theories have proven unfounded. The research team believes that knowing how to fight back, even if the victim doesn’t have to, is empowering. “In our previous surveys, most girls didn’t get to the physical skills. Most used verbal skills under attack situations,” Sarnquist says. “But we believe that having those physical skills to back them up probably does make girls much more assertive and strong on the verbal skills.” Ultimately, many of the key questions in these debates are empirically testable, and that is what the Stanford team plans to do.

Talking about rape, asking, “What could you do if you face a drunken assailant?” of a classroom of 11- and 12-year-olds, could seem harsh. But it’s not too early, research shows. “The goal is to get to them before, while they’re still at this 7 percent annual incidence rate, not at this 18 to 25 percent annual rate,” says Sarnquist. “The hope is that you give them this training, you give them lifelong skills, so that as they’re entering the highest-risk ages — 12, 13, 14 years old — they already have these skills in hand.”

Down the hallway from the girls, the still-high-pitched voices of their male peers ring out, “The REST of my life can be the BEST of my life only if I make it!” The boys recently started a new curriculum, Source of Strength, that pairs with the girls’ training. (Stanford’s research team has set aside some funding to run an initial assessment of the boys’ program.) “What we do is help boys face the violence in their lives squarely,” says No Means No founder Paiva. “Boys tell our trainers: ‘How do I live my life to avoid getting hurt by somebody bigger, older or in authority?’ Our goal is to help

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

CASH FLOW

**WHEN ASSISTANCE PAYMENTS ARE LESS FREQUENT,
PEOPLE MAKE WORSE FOOD CHOICES**

It's a conundrum faced around the world: Why do some government-sponsored cash assistance programs contribute to unhealthy behaviors? A series of studies by Stanford Medicine

epidemiologist Sanjay Basu, MD, PhD, has revealed a simple answer: Payments made to recipients are often ill-timed. By demonstrating the big impact of small changes to payment systems, Basu is helping governments at home and abroad to improve the health of their low-income citizens — changing the broader discourse around nutrition assistance programs in the process.

Basu began to explore the issue after a 2013 international meeting on chronic disease prevention, where he met representatives from several middle-income countries with an alarming rise in high blood pressure and diabetes. Among those countries was Peru, which became one of Basu's major project sites. He and former postdoctoral scholar Justin White, PhD, started to examine the effects of cash payment frequency on the purchase of "temptation goods" — including alcohol, tobacco and sweets — that are typically associated with chronic diseases like diabetes, hypertension and high blood pressure. Basu and White, now an assistant professor at UC-San Francisco, paid particularly close attention to these purchases by low-income Peruvians who live in rural areas and eke out an existence by farming the steep hillsides.

"We're very interested in exploring this issue in countries like Peru and India, because they're especially well-positioned to take full advantage of prevention programs," says Basu, an assistant professor of medicine at the Stanford Prevention Research Center. "They're middle-income nations in a state of so-called epidemiologic transition from infectious to chronic diseases. Yet many chronic conditions haven't fully ramped up in these areas, so prevention measures can be really effective."

Basu and his team analyzed a recent change in the payment schedule of Peru's cash assistance program: The government moved from twice-monthly to once-monthly payments, without changing the overall payment amount. Under the new schedule, the team observed a striking increase in the purchase of alcohol and sweets in particular — nearly 70 percent in

BY STEPHANIE BRUZZESE

ILLUSTRATION BY JULIETTE BORDA

some cases. Their results were published in January in the *Journal of Health Economics*.

“We suspect two behavioral issues may be to blame for this increase,” Basu says. “One, there’s the ‘payday’ effect, where people tend to make larger discretionary purchases around receipt of a regular income stream. And two, going without temptation goods for a longer period of time may lead people to binge once they finally do receive a payment. As they say, never shop on an empty stomach.”

Based on Basu’s results, the Peruvian government is revising its program’s payment schedule to every two weeks — and may even increase the timing to weekly, should the initial results prove positive. Basu is also in conversation with Brazil about adapting the program for the country’s low-income communities.

“This approach is very translatable,” notes Basu, who has now incorporated lessons learned from the Peruvian study into a new program for San Francisco’s low-income neighborhoods — hoping to learn whether more frequent voucher distribution helps to mitigate the purchase of temptation goods in these communities. Starting in the city’s Tenderloin, South of Market, Bayview and Outer Mission districts, participants will receive \$20 in food vouchers per month, with recipients randomly split into two groups: those who receive a \$5 voucher at the beginning of each week, and those who collect a \$20 voucher once a month. All participants will provide Basu with detailed dietary information.

A pilot study of 250 adults from the Tenderloin and South of Market districts, which Basu conducted with UCSF associate professor Hilary Seligman, MD, has already shown positive effects. “Some of the folks in our pilot had chronic conditions that are really hard to control,” Basu says. “We see that these conditions profoundly worsen when people face ‘food insecurity’ — another term for hunger — from inappropriate resources to purchase foods.”

In addition to increased payment frequency, Basu has identified other factors that likely influence outcomes in these types of programs. “The success of patients who receive vouchers in

a program like this is often related to other factors in their lives, such as when they have to pay the rent, or receive their work paychecks,” he says. “In other similar programs we’ve studied, we’ve discovered that in many locations like the Bay Area, rent prices vary widely, but voucher programs and other nutrition assistance programs are not adjusted for the cost of living, which profoundly affects what families are able to afford.”

Basu points out that adjusting for these factors could improve nutrition in ways that reduce longer-term costs of caring for diseases like diabetes, which has made federal agencies, like the Centers for Medicare and Medicaid Services,

more open to subsidizing these programs. He has also begun working with the U.S. Department of Agriculture to develop another pilot for its Supplemental Nutrition Assistance Program, testing out alternative ways to distribute SNAP’s food stamps.

“This approach has the potential to change the national discourse around food stamp programs,” Basu says. “The National Academy of Medicine has identified a large research gap in translating the results of nutrition studies and poverty studies to workable programs that benefit communities.”

Basu plans to continue to dig into the various political, social, fiscal and other considerations that contribute to optimal health in low-income communities. “For example, the food stamp program is considering an increase in the amount of assistance it provides to low-income residents of high-food-cost areas, so those residents can use the extra assistance for transportation to stores with less expensive food,” he says.

“There’s certainly no one-size-fits all strategy when you’re dealing with the public health aspects of chronic disease,” says Basu. “We’re taking a precision health approach based not on genetic codes, but on ZIP codes — where very different people from very different parts of the world receive ‘treatment,’ in the form of tailored assistance programs, that is specific to their circumstances. If we get to the point where we can customize to the neighborhood or even to the person, that’s very policy amenable.” **SM**

— Contact Stephanie Bruzzese at stephbr@stanford.edu



THE END GAME

AIMING TO
EXTINGUISH TOBACCO'S HARMS FOR GOOD

Americans' love affair with the cigarette hit a peak in the early 1960s. With major marketing efforts and few regulations, it was fashionable to light up everywhere — in restaurants, movie theaters, airplanes, even hospitals. Back then, half of all American men and a third of women were smokers, lured by advertising featuring movie starlets, elite athletes, revered astronauts, rugged cowboys and even Santa Claus with cigarettes in hand.

But the smoke started to clear in 1964 with the first of 30 reports by the U.S. Surgeon General on the dangers of tobacco and the addictive nature of nicotine. The following decades saw sweeping government bans on smoking in restaurants, bars and workplaces; higher tobacco taxes; and the biggest hit against tobacco companies: a 1999 federal racketeering charge that resulted in billions of dollars in penalties, strict limits on tobacco advertising and an anti-tobacco media campaign. These steps led to a significant decline in smoking prevalence and reductions in deaths from lung cancer, heart disease and other smoking-related illnesses. • Yet tobacco still holds many Americans in its grip, with deadly effects. More than 40 million adults light up every day, and over 500,000 people die each year of diseases caused by smoking. And while cigarette use is declining among children and adolescents, exposure of young people's brains to nicotine is climbing for the first time in decades. A recent report from the federal Centers for Disease Control

BY RUTHANN RICHTER

ILLUSTRATION BY JEFFREY DECOSTER



and Prevention documented that use of electronic cigarettes among youth has skyrocketed in the past four years, with prevalence climbing from 1.6 percent to 16 percent among high-school students.

“Millions of kids are being introduced to nicotine every year, a new generation hooked on a highly addictive chemical,” U.S. Secretary of Health and Human Services Sylvia Burwell said recently while announcing a new federal ban on e-cigarette sales to youth.

These disturbing trends have inspired a new generation of scientists, including several at the Stanford Prevention Research Center, to turn to innovative technologies, including social media and telemedicine, and new policy approaches to end the use of what some call the world’s deadliest consumer product. They are reaching out to particularly vulnerable groups, such as young people, in an effort to stop tobacco consumption, which accounts for \$170 billion a year in direct health-care spending, according to a 2015 study in the *American Journal of Preventive Medicine*.

“There is still no bigger killer, and this is a totally unnecessary health burden,” says Michelle Mello, MD, PhD, a Stanford professor of law and of health research and policy who has been promoting anti-smoking policies. “We have made enormous progress in reducing tobacco’s use, but it’s time for the end game.”

THE SEDUCTION OF TOBACCO

Nicotine, the addictive substance in tobacco products, can enslave users; some smokers say nicotine addiction is harder to kick than heroin or cocaine addiction in part because the drug remains so pervasively available. When nicotine is inhaled, it goes directly to the brain within 10 seconds, where it binds to receptors that stimulate the release of the neurotransmitter dopamine, which signals pleasure. But the feeling is transient, and the brain adapts so that more and more of the drug is needed to maintain normal brain function. In the absence of the drug, users go through a withdrawal process that can make them irritable, anxious and depressed and cause disturbances in concentration and sleep as well as weight gain.

For years, behavioral scientists and pharmacologists have been trying to develop better ways to help smokers quit. The

traditional method involves cognitive behavioral therapy, in which smokers are coached on ways to distract themselves from intense tobacco cravings, such as going for a walk or visiting a supportive friend. That is usually combined with nicotine replacement drugs, such as over-the-counter patches, gums and lozenges or prescription inhalers and nasal sprays, which help reduce cravings. Some drugs, such as the antidepressant bupropion (Zyban) and the stop-smoking drug varenicline (Chantix), also help greatly. Yet even with medication and counseling, only about 30 percent of smokers are able to successfully quit smoking over the long term.

Clinical psychologist Judith Prochaska, PhD, associate professor of medicine at the Stanford Prevention Research Center, says advances in behavioral approaches are much needed, both to improve success rates and to reach more people. Further, she says if scientists can find more effective methods for helping smokers quit, these principles can be applied to many other behavioral issues, such as overeating or alcohol addiction.

“Tobacco is a fantastic model for better understanding how to optimize health outcomes via effective behavior change,” says Prochaska, who is the president-elect of the Society for Research on Nicotine and Tobacco, the leading professional society in the field.

She and her team are exploring new ways to tackle tobacco addiction, capitalizing on technologies such as social media tools, computer-assisted interventions and telemedicine. She says these technology-based treatments are more personalized and less costly, and can reach large numbers of smokers over vast distances — particularly young people, who are especially hard to engage.

In a recent trial with 160 smokers, Prochaska and her colleagues combined standard interventions with a virtual, peer-to-peer support group using Twitter. In the study, called Tweet2Quit, half of the participants were randomized to private support groups of 20 individuals. These individuals received twice-daily, automated prompt questions to keep them engaged, such as, “How are you rewarding yourself for quitting?” and “How are you organizing your life to avoid tobacco smoke?” All participants received a nicotine patch and were referred to the National Cancer Institute’s smokefree.gov website for information on quitting.

The results were impressive, with 40 percent of those in a Tweet2Quit support group free from smoking for more than two months, compared with 20 percent of those exposed to

‘THERE IS STILL NO BIGGER KILLER, AND THIS IS A TOTALLY UNNECESSARY HEALTH BURDEN.’

traditional methods. The study, supported by the National Institutes of Health, was published in February in the journal *Tobacco Control*.

Prochaska and her colleague Connie Pechmann, PhD, a professor of marketing at UC-Irvine, were able to “listen in” on the lively private Twitter chats. “I wasn’t surprised when I saw the results because I could see people were really working at it,” Pechmann says. “They were really attached to one another, were committed to quitting and felt an obligation to quit — that they would let the group down if they didn’t. It was like a sports team. They wanted the group to win.”

Those in the private Twitter groups developed online friendships. “They knew they could text each other any time of the day or night if they felt a craving and needed help fighting it off,” Prochaska says. “We saw group members sharing openly that they slipped and had a cigarette and their fellow group members responding, ‘Don’t give up — we are there for you.’ This concept of a peer-to-peer support group where we encourage online engagement is novel, and the findings are highly encouraging. It has been powerful observing our participants supporting each other with breaking free from their addiction to nicotine.”

With a new, \$2.5 million NIH grant, the researchers are expanding the study to more than 1,000 people who will each be matched with a “buddy” who can cheer them on. The researchers will follow the participants for six months to see whether they are able to stop smoking.

Prochaska and her colleagues also are using online tools to reach out to a particularly vulnerable group: unemployed smokers. In a recent study published in *JAMA Internal Medicine*, the researchers found that smokers have a much harder time finding work, and when they do get a job, they are paid \$5 less per hour on average than nonsmokers. It is well-documented that employees who smoke cost employers more than nonsmoking employees, due to higher health costs, greater absenteeism and working while sick.

With funding from the California Tobacco-Related Disease Research Program, the team is recruiting smokers at local unemployment centers to test a first-of-its kind online program focused on job seekers who smoke. The study is unusual in that it meets smokers where they are — both physically and psychologically. Participants don’t have to travel to a distant site for counseling, and they receive guidance based on their readiness and drive to quit. The trial, which also uses mobile texting, will help participants identify the barriers to change and strategies for overcoming those obstacles.

The researchers will examine, over a six-month follow-up period, whether the participants stop smoking, find jobs, and

experience improved health and financial well-being.

“If it works, it could be an argument for clustering other health-related programs in the same location,” as many people at these unemployment centers have limited access to health care, says Cati Brown-Johnson, PhD, a postdoctoral scholar at the Stanford Prevention Research Center collaborating on the project.

REACHING OUT TO ALASKA

When it comes to smoking and health, probably one of the most at-risk — and understudied — groups in the country is people of Alaska Native heritage.

Nicole Jeffery, a clinical research coordinator at the Stanford Prevention Research Center, knows this all too well. Part Yup’ik, Jeffery grew up in Barrow, Alaska, and is among the few of her high school classmates to attend college; she graduated from Stanford in 2009. Tragically, about 10 percent of her high school classmates are already dead, she says, victims of alcoholism, drug abuse and suicide.

She and her colleagues are recruiting participants for a novel telemedicine project — a long-distance counseling program — that they hope will combat some of the health problems that have plagued Alaska Native people and serve as a model for how to change health behaviors, including smoking, among underserved groups. Prochaska is the principal investigator for the NIH-funded project, which focuses on smoking and other risk factors for heart disease.

“If this can be shown to be effective, that’s a new tool available to community members in the villages,” Jeffery says. “That is huge.”

Jeffery lost her grandmother, a longtime smoker, to lung cancer. She says Alaska Native people suffer from disproportionately high rates of heart disease, cancer and chronic health problems in major part because of lifestyle behaviors: 42 percent smoke, and many are sedentary and have given up healthy, native diets for processed Western foods that are high in calories and sodium and low on nutrition. They also feel abandoned by a health-care system with few doctors to treat the most basic ailments and with specialty care that is a costly plane ride away.

“I often think about the people at home — of going there for Christmas and hearing people in church tell me, ‘They don’t know what’s wrong with me, and they don’t care.’ This is the community I love and the people I know, and it hurts when you see them not get the care they deserve,” says Jef-

fery, who is starting medical school this fall at the University of Washington with the goal of becoming among the first native physicians to practice in Alaska.

Through the telemedicine trial, she counsels individuals in remote villages via video hook-up from her Palo Alto-based office. During the weekly, 45-minute sessions, she and her colleagues encourage study participants to adopt better diets, exercise more and reduce smoking. She acknowledges there are challenges to doing research in rural Alaska, including weather disruptions, dropped calls due to poor internet connections, and heavily burdened community health workers. It also takes time to build trust and to demonstrate that the research is not on the community, but rather, with and for the community.

“Rural Alaska does have unique barriers. So I think it needs a unique solution,” Jeffery says, smiling. “I think our team has rolled with the challenges. But what we are doing is so needed. And people are so grateful.”

The researchers, based at Stanford and in Anchorage, have recruited more than 80 individuals with a goal of enrolling 300 participants, all daily smokers and of Alaska Native heritage. Participants do not have to commit to stop smoking when they join, though the counselors encourage them in that direction.

“People have different motivations for quitting smoking,” Jeffery said. “People will tell me, ‘I want to be here for my kids. I don’t want to have heart problems.’ Others just aren’t ready yet.”

A GENERATION ON THE LINE

At age 16, Prit Pandya is an anti-smoking crusader of a different sort. A junior at Milpitas High School in California, he has been spending his weekends visiting local outlets that sell tobacco and helping document their sales strategies, logging what he finds on his iPad. He’s part of a team of Santa Clara County interns on a project with Stanford to collect data on tobacco marketing, with an eye to influencing state and local tobacco policy.

“I want to create more awareness in teens,” says Pandya, who’s a member of his school’s tobacco prevention club. “I want them to make better judgments — to see how small judgments you make may harm you in the future. One cigarette right now might make you happy, but you don’t know how it is damaging to your lungs in the future.”

Reaching teens is crucial, experts say, as 88 percent of adult smokers got hooked before the age of 18.

“The best way to keep a 50-year-old from smoking is to keep a 15-year-old from smoking,” says Robert Jackler, MD, professor and chair of otolaryngology — head and neck sur-

gery, who has done extensive studies on tobacco advertising.

Teens are particularly susceptible to nicotine, as the brain’s frontal lobe — the area involved in reward, planning, attention and motivation — is still developing. When it is exposed to the dopamine surge of the drug, it readily adapts and learns to value this reward over other pleasurable activities, Prochaska says. This sets up the teen for a lifetime of addiction. Yet teens tend to see themselves as invulnerable, immune to the lure of the drug, says developmental psychologist Bonnie Halpern-Felsher, PhD, a professor of pediatrics and adolescent medicine at Stanford who studies teen and young adult attitudes about tobacco, alcohol and other health risks.

“When you ask adolescents, ‘Can you become addicted?’ they will say yes,” Halpern-Felsher says. “When you ask them, ‘Can you quit tomorrow?’ they say yes. They don’t understand that you don’t have control over the product.”

That has made teens a favorite target of the tobacco industry, whose products are ubiquitous and readily accessible to youth, even in states like California that have waged long anti-smoking campaigns, says Lisa Henriksen, PhD, a senior research scientist at the Stanford Prevention Research Center.

“Everybody complains that there are so many fast-food restaurants, but in California there are 28 tobacco retailers for every McDonald’s,” she says. “These retailers are literally omnipresent.”

That is key because teens who frequent retail outlets with widespread tobacco advertising, such as convenience stores and small markets, are significantly more likely to start smoking than those who are less exposed to this advertising, she found in a 2010 study, published in the journal *Pediatrics*.

“You can walk up to pay for soda or a snack on the way home from school and when you go up to a cash register, you are confronted with a very large display of cigarettes and tobacco products. They are placed in every store so they are maximally visible,” she says.

She and her colleagues have been documenting the latest trends in tobacco marketing, sometimes enlisting the help of students, like Pandya, to visit tobacco sellers and report back on what they observe. The biggest trend is the surging popularity of so-called electronic nicotine delivery systems, often displayed on the front counter in convenience stores, liquor stores and other retail outlets. These are battery-powered devices in the shape of a conventional cigarette or palm-sized box that can be filled with “e-liquids” containing various levels of nicotine. The user presses a button that ignites a coil inside the device to heat the liquid and create a puff of vapor that is inhaled. These products, available in vape shops as well as general retail stores, are sold in thousands of different flavors, including apple pie,

chocolate and caramel frappe, making them appealing to youth.

In the past four years, the number of high-school students using these electronic devices has skyrocketed while cigarette smoking among these youth has declined from 15.8 percent to 9.3 percent, according to a recent report from the CDC.

“Cigarette smoking is passé. What’s new is vaping and marijuana. Kids think it’s less dangerous than smoking,” Pandya says, based on what he’s observed among his peers. The safety of the relatively new — and until recently unregulated — electronic nicotine products remains highly controversial, as there are no long-term studies to document their risks.

In two recently published studies, Halpern-Felsher and her colleagues showed that youth harbor misperceptions about e-cigarettes. E-cigarettes lack the lung-damaging tar and the carbon monoxide of combustible cigarettes and most deliver nicotine more slowly to the brain. But Jackler and other experts say they contain enough of the drug to form an addictive habit. Moreover, studies show that American teens who start with e-cigarettes are more likely than nonusers to begin smoking conventional cigarettes, Halpern-Felsher says.

She says young people get very little information about the health risks of e-cigarettes from schools, parents, health educators, health-care providers and others. For that reason, she is teaching youth about the dangers of these nicotine offerings through a new online tool kit she plans to distribute to school districts across the state and hopes to make a national model. She says using “scare tactics” with kids — simply telling them a product is unsafe or that they’re likely to develop lung cancer years down the road — isn’t very effective.

What is effective is stirring outrage among teens about how they are being manipulated and lied to, as the tobacco industry did in the early days when it claimed cigarette smoking was perfectly safe. That is the model established by the Truth Campaign, created in 1999 by the nonprofit American Legacy Foundation to provide honest information to young people about the behavior of the tobacco industry.

“I tell kids that industry leaders have been dishonest before. Can you trust them? And I point out that over 500,000 people die every year from smoking. So the industry needs replacement smokers,” Halpern-Felsher says. “I had one middle-schooler tell me, ‘I’m mad. I don’t want to be a replacement smoker.’”

Henriksen also hopes that documenting tobacco marketing practices will help inform widespread policy changes that will discourage tobacco use in teens. These would include a ban on

menthol and other flavored tobacco products, limits on who can sell tobacco, restrictions on tobacco displays and tobacco-free policies on college campuses, among other changes.

Some of these efforts already have paid off: In May, California Gov. Jerry Brown signed legislation to raise the legal age for buying tobacco from 18 to 21, making California the second state in the nation, after Hawaii, to raise its age limit. New

legislation also expanded tobacco-free laws to cover school property at all times, regulated e-cigarettes like traditional tobacco products and increased licensing fees for tobacco distribution and sale.

Tobacco-control forces in California also announced recently they have enough signatures for a fall ballot initiative that would increase the state’s tobacco tax by \$2 a pack, the first increase since 1988. Raising the price of cigarettes is a proven strategy for discouraging young people from buying tobacco products, as youth are particularly sensitive to price, Jackler says.

There have been steps at the federal level as well, with the Food and Drug Administration enacting sweeping new rules that include a ban on sales of electronic nicotine products to anyone under age 18. The new regulations, which go into effect in August, also require e-cigarette makers to apply to the FDA to sell their products and to provide details on the ingredients and how the products were made.

Prochaska says the state’s new tobacco initiatives are certain to help California reduce its smoking rates, just as regulations against lighting up on airplanes, in restaurants and in hospitals did in the ’80s and ’90s. Recently, she and Henriksen received funding from California’s Tobacco-Related Disease Research Program to study the impact of closing the loopholes in the state’s 1994 smoke-free workplace laws to include owner-operated businesses with no employees; hotel lobbies, meeting and banquet rooms; warehouse facilities; employee break rooms; and workplaces with five or fewer employees — one of the new laws just signed by Gov. Brown.

She says restrictions on public smoking make it less socially acceptable and have contributed to significant declines in tobacco use and in smoking-related diseases and death. Today, 19 percent of men and 15 percent of women nationwide are regular smokers, far less than the heyday of the early 1960s.

“Although it has been an uphill battle against a behemoth of an industry, with widespread influence and financial means,” Prochaska says, “I am optimistic about the future.” **SM**

— Contact Ruthann Richter at richter1@stanford.edu

‘I HAD
ONE MIDDLE-
SCHOOLER
TELL ME,
‘I’M MAD.
I DON’T WANT
TO BE A
REPLACEMENT
SMOKER.’”

ULTERIOR

MOTIVATION

THE POWER OF SERENDIPITOUSLY HEALTHY HABITS

In the late 1990s, The Culinary Institute of America got a call from managers at a national chain restaurant who wanted help making some menu items healthier. A team of the institute's chefs devised new versions of the recipes. The results were delicious. The restaurant leaders wanted customers to know.

"They were proud of what they were doing and wanted to put a 'healthy' icon next to those dishes on the menu," recalls Greg Drescher, now the institute's vice president of strategic initiatives and industry leadership. "We strongly advised against that; we said, 'Change the recipes, put the new items on the menu, but don't say anything about health.' They said, 'No, we want to help our customers find those healthy items.'" What unfolded next was an accidental experiment in human behavior.

The icon wasn't ready when the recipes were, so the new dishes were put on the menu without it. Customers loved them. Eventually, the menus were reprinted to incorporate the icon. Now the customers could see which items were healthiest.

"Almost all those dishes tanked," Drescher says. "From the consumer perspective it was like saying, 'Thank you for pointing out the dishes I should avoid.'" His story illustrates a health paradox: Although many of us believe we should eat better and exercise more, we may resist so-called healthy choices. Or we may try to make them, feel like we're failing and give up.

The paradox is a big obstacle to solving the national obesity epidemic. To get around it, two Stanford nutrition scientists are shifting their focus away from asking people to diet or exercise for health reasons. Instead, they're running scientific studies that tap our existing motivations to change, such as the pleasure we get in trying a tasty new food or the sense of purposefulness we derive from joining a large social or cultural movement.

BY ERIN DIGITALE

ILLUSTRATION BY CHRISTOPHER SILAS NEAL

“When people make a big change in their diets, it’s often because of an ‘aha’ moment, almost a religious experience,” says nutrition scientist Christopher Gardner, PhD, professor of medicine at the Stanford Prevention Research Center. “People may say, ‘I want to be a good citizen of the planet,’ or ‘I’m contributing to a broken social food system and I want to be part of the solution.’ They *need* an ‘aha’ moment connected to something much bigger than them.”

“So we’re asking, ‘Does a health-behavior-change intervention need to look, smell, feel, sound and taste like health education?’” says childhood obesity expert Thomas Robinson, MD, professor of pediatrics and of medicine at the School of Medicine. “Or can you intervene to improve health for reasons that are totally unrelated?”

The evidence that Robinson and Gardner are gathering suggests they can succeed with an approach they sometimes call “stealth health.”

Stealth-health research isn’t about sneaking carrots into the spaghetti sauce. “It is not deceptive; we’re not keeping anything from participants in our studies,” Robinson says. “Instead, we’re thinking about what is most motivating to them and having them pursue those goals, with better health tagging along as a side effect.”

PART OF THE MOVEMENT

Robinson has spent decades studying traditional obesity-prevention and weight-management programs for children and families. But his curiosity about motivation goes back further, to a curiosity he noticed as a Stanford undergraduate in the early 1980s.

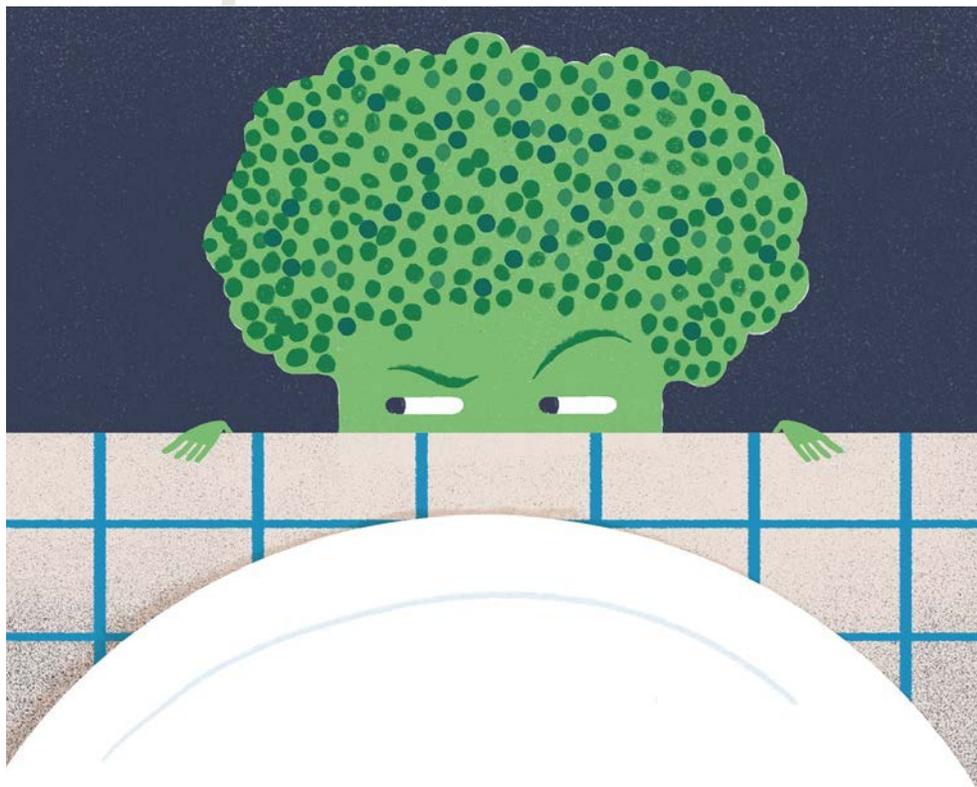
“Students would demonstrate and march against South African apartheid, but I didn’t see them going to East Palo Alto to teach kids to read,” says Robinson, who is the Irving Schulman, MD, Endowed Professor in Child Health. Why was discrimination halfway around the world more motivating than struggling kids next door?

“If you are trying to change the world by marching to end apartheid, or tackling a problem like climate change, even if you don’t succeed in the short term — and generally you don’t — you succeed in being part of the movement,” Robinson

says. “But if you tutor a kid and it doesn’t work out so well, you are really setting yourself up for a failure experience.”

He believes the traditional approach to weight loss is similar. “If you don’t lose weight, it’s a very immediate failure experience, right in your face. It affects your confidence that you can make changes.” Robinson and Gardner want to circumvent this sense of failure.

Robinson’s first foray into the science of using motiva-



tion to set kids up for success targeted the TV. In a series of studies, the televisions of participating families were outfitted with an electronic device to track children’s screen time. Kids in his studies focused on all the things they could do instead of watching TV, participated in cooperative and competitive activities to reduce their screen time, and received social recognition at school and praise from their parents for cutting back their TV viewing. The activities worked: In studies lasting up to two years, children reduced their sedentary behavior, ate fewer calories and gained less weight than children in a control group.

Next, Robinson and his team designed after-school dance programs for girls at risk for obesity, focusing the curriculum on fun and cultural pride. African-American girls learned historical African dances, as well as contemporary hip-hop and step dancing, while girls of Mexican ancestry learned ballet folklorico, a form of traditional Mexican dance.

The girls got excited about learning new choreography, wearing colorful costumes and performing at community

events. Their families — in impoverished neighborhoods where it's hard to get a decent turnout at back-to-school night — showed great enthusiasm, too. “On a rainy Friday night in the middle of Oakland, we would average three family members in the audience for each girl performing,” Robinson says. “That would include parents, the older brother who could have been out with his friends, the grandma in a wheelchair from diabetes. It was really remarkable.” Compared with a health-education program given to a control group, the dance classes had larger positive effects on girls' cholesterol, insulin levels and depressive symptoms, and showed some signs of slowing obesity. In the study of African-American girls, after two years, the prediabetes rate was only about one-third of that observed in girls receiving the control treatment of health education.

These successes led Robinson to think more about what motivates school-age kids. His interventions are influenced by the work of Albert Bandura, PhD, a Stanford professor emeritus of psychology who recently received the National Medal of Science for his career studying human motivation.

“Kids love learning new things, they're very social, they love being experts, they like being able to exert independence and develop their own identities,” Robinson says. And kids' motivations can infect their families. “Parents' lives are really crazy, but if your children have something they want to do and they pull you in, it pops up on your priority list.”

Recently, Robinson and his colleagues tested the impact of environmental sustainability programs on behavior change with Girl Scouts in the Bay Area. Children have the greatest stake in preserving the environment for the future and are often excited to help with sustainability efforts, Robinson says. And some behaviors, like walking and biking instead of driving, or eating less meat, fast food and highly processed and packaged foods, are beneficial for both the environment and for health. A recent study testing a five-session curriculum for Scouts and their families, published in *Nature Energy* in July, showed that girls increased their own conservation behaviors and got their parents to save fossil-fuel energy around the house by making changes such as turning off power strips at night, adjusting the temperature of the refrigerator and washing clothes in cold water. But when it came to eating less meat or walking to school, it was harder for kids to move their families' dial. Although the girls changed their eating and transportation behaviors, the effects were not as large and did not extend to their parents.

The mixed results highlight a pitfall of the “stealth health” approach: Behavior changes aiming to achieve a goal other than health improvement — say, environmental protection

— may not produce large enough effects to show a measurable impact on an individual's health. The good news is that health improvement programs at any scale — from improving an individual's diet to funding construction of new sidewalks to passing a soda tax — can be strengthened by planning with motivation in mind, Robinson says.

Robinson is now folding his motivational techniques into traditional studies of health-behavior change, too. A treatment program he's testing for overweight Latino kids teaches them to exercise more, reduce their screen time, and eat smaller portion sizes. But instead of talking only about health benefits, the trial's messages are designed to resonate with participants' shared experiences as Latinos, such as enjoying traditional foods, critically evaluating the way the media represents their culture and receiving social support from their community. Kids in the study play on sports teams that emphasize fun over winning and don't make them feel out of place for being overweight. And parents and coaches learn to use praise, constructive criticism and rewards to help motivate their children to stick with the recommended diet and activity changes. These studies are ongoing.

ROW, ROW, ROW YOUR... VEGETABLES?

Stanford varsity rower Meredith Fischer didn't expect a single college class to upend what she ate. Her dietary habits were entwined with her identity: A childhood nickname, Meef, which began as her little brother's attempt to say “Meredith,” stuck because it rhymed with *beef*, which she loved. Once, in high school, she'd had a whole slab of baby back ribs in a single sitting, right before her team rowed a national-championship final. They won.

Then, in the winter of 2015, during her junior year, she took Robinson and Gardner's Food and Society class.

“I was the biggest carnivore in the world before I took that class,” Fischer says. “I never, ever would have considered being vegetarian.”

Fischer didn't realize that Robinson and Gardner designed the class with students' motivations in mind. “We want them to explore their deeper values,” Robinson says, noting college students are developmentally ready to evaluate their beliefs. Food and Society students lead class sessions for one another to consider difficult questions: Are agricultural subsidies and food assistance programs appropriately designed, given that they may influence which crops are grown or which foods people purchase? Should you buy organic? How do your cultural values impact what you eat? What are the ethical and

labor implications of eating fast food?

“We live in a world in which there’s a lot of uncertainty, so we ask students, ‘How are you going to behave in that context in a way that you feel good about?’” Robinson says. “We want them to struggle with making decisions when they don’t have professors giving them all the answers.”

Fischer did. She was worried about California’s extreme drought, and after a class discussion of the carbon emitted and water used in livestock production, she wondered out loud to

amounts of higher-quality, grass-fed beef. A third student was troubled by the business practices of fast-food franchises and had stopped eating fast food. So it went around the room.

“It was my epiphany, seeing that no one topic resonated with everyone,” Gardner says. After 20 years of trying to get research participants to eat better for health reasons, he was thoroughly convinced that he should try to get people to eat better for their own reasons. Today, Gardner and Robinson are testing the Food and Society class in a community-college

**THE HEALTH BENEFITS OF FISCHER’S NEW DIET
HAVE BECOME A REASON TO STICK WITH IT. ‘BUT HEALTH ALONE
WOULDN’T HAVE BEEN AN INCENTIVE FOR ME TO START.’**

a friend if she could eat vegetarian for a week. Her friend said, “There’s no way, Meef. I’d literally give you until dinnertime.”

The dare was impossible to resist. “It was hard at first; I was really hungry,” Fischer says. “But I also like to challenge myself. I wanted to prove people wrong.”

Once she figured out what she should eat instead of meat, her new diet got easier. Her coach — initially alarmed by her sudden vegetarianism — calmed down after Fischer got advice from a nutritionist in Stanford’s athletics department. Her performance on the water didn’t suffer. To her surprise, Fischer realized she wanted to stay vegetarian.

In the year since she first took her vegetarian dare, Fischer has learned that meat consumption is associated with greater risks for cancer and heart disease. The health benefits of her new diet have become a reason to stick with it. “But health alone wouldn’t have been an incentive for me to start,” she says.

Fischer’s experience in the class isn’t an isolated example; Robinson and Gardner published a 2010 study of the first cohort of their Food and Society students that showed significant improvements in students’ diets when compared with the diets of students taking other nutrition-related classes: more vegetable and less high-fat dairy consumption, as well as some signs that students reduced their intake of sweets and high-fat meats.

“It was a big surprise,” Gardner says. “We never talked to the students about health.” At the end of the term, he had asked students which topics left the biggest impression on them, thinking maybe the course materials could be winnowed down. An assignment about animal agriculture had caused one student to stop eating meat. A second student, raised on a ranch, said he knew food animals could be raised ethically, but that the class discussion on agricultural contributions to global warming had prompted him to eat smaller

setting to see if the format will succeed beyond Stanford.

This raises a larger question: If framing healthy behaviors around people’s own motivations is so effective, why hadn’t it been tried sooner? Robinson thinks it may be because scientists have been reluctant to look at their own motivations. “One limit in public health is that we want people to do things for the ‘right’ reasons,” he says. “But we know that’s not how people behave.”

ACCOUNTING FOR TASTE

Today, Gardner is working with The Culinary Institute of America’s Drescher on a new stealth-health target: food cooked by the pros.

“We have some great data that show that more than 50 percent of Americans’ food budgets is spent on items designed by chefs,” Gardner says. That includes grocery-store items such as frozen dinners and deli-counter dishes, as well as restaurant food. Often, it isn’t as healthy as it could be.

“It’s regular or unleaded: Here’s a piece of steak or half a chicken, or over here are our vegetarian items,” Drescher says. This pattern leaves customers feeling forced to choose between healthy and tasty, and, as his anecdote about the failed menu icon illustrates, diners know which they’d rather have. So Drescher wants to scratch out the dividing line altogether. Healthy food should be “unapologetically delicious,” he says. Behind the scenes, he’s working to convince chefs that unapologetically delicious foods can simultaneously be nutritious, environmentally friendly and profitable.

In 2012, Drescher launched the Menu of Change initiative

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

In his tidy Clark Center office, bioengineer Paul Yock, MD, opens a file cabinet and pulls out a large plastic envelope. Inside is a long, narrow blue tube with a tiny metal tip. Unearthed recently in a collaborator's closet, it is one of the original ultrasound catheters Yock designed in the late 1980s to peer into patients' blood vessels. It is also among his proudest inventions.

“That let us see directly what was going on inside a patient's coronary artery,” he says. It also gave the first information about why the stents surgeons use to hold blood vessels open were causing blood clots. Unbeknownst to the physicians, the stents weren't expanding all the way and were blocking blood flow. With the assistance of Yock's device, cardiologists could verify that stents were fully expanded, resulting in many fewer blood clots. Yock has created other devices that went on to much wider use, but none transformed the patient experience in quite the way of that innocuous-looking blue tube.

To Yock, it's a perfect example of the way a medical technology can dramatically improve patient care. It's also an example of how technology can increase the cost of health care. Initially, each disposable ultrasound catheter cost more than \$1,000 — though at the time, the cost was largely irrelevant to the doctors or patients because it was covered entirely by insurers.

“Most health economists would say that new technology has actually been the biggest driver of the increase in health-care costs,” says Yock, director of the Stanford Byers Center for Biodesign, which trains young medical-technology entrepreneurs.

“In the past we've had a very odd market system in health-care technology where a government and private payers were uncoupled from the consumers — the patients and the physicians. Basically, any new invention that actually improved health

AT WHAT COST?

TEACHING INVENTORS
TO MAKE HEALTH CARE BETTER
AND CHEAPER

BY AMY ADAMS

P H O T O G R A P H Y B Y G R E G G S E G A L

Sam

USING EXISTING
INTRAVASCULAR DEVICES
AS MODELS, BIODESIGN
FELLOWS DEVELOP A
PROTOTYPE OF A UROLOGICAL
DEVICE TO TREAT
UNDERACTIVE BLADDER
IN WOMEN.



Bear da
2. sphin
3. bladder

GIORGIA
HALO

‘ONE OF MY FRIENDS WRITES A NEEDS STATEMENT

would get paid for,” Yock says. That unconstrained spending has improved health care, but at a price.

Now that system is changing, and Stanford’s training program for device designers needs to change with it. After 15 years of teaching the art of patient-focused medical-technology innovation — resulting in the formation of 41 companies that have developed devices to treat more than 500,000 patients — Yock and his colleagues are expanding Stanford Biodesign’s focus to include medical cost innovation: developing devices that help patients at a cost that provides maximum clinical value.

“There is nothing that says we can’t invent technologies that deliver important health benefits without driving up costs excessively,” says Yock, a professor of bioengineering and of medicine, and the Martha Meier Weiland Professor.

He stresses that medical cost innovation isn’t a shift to lower-quality innovations. Complications, longer hospital stays and readmissions — all things patients would rather avoid — also add to costs. Innovative devices to reduce those outcomes would lower the cost of hospital stays and get patients back to their lives more quickly.

The challenge is to revise the training model to include reasonable cost as a goal for innovations.

ITERATION, ITERATION, ITERATION

YOCK IS A SELF-DESCRIBED gizmologist whose inventions have helped more than 20 million people, by his estimate. In person, he bursts with youthful enthusiasm for inventing, and for the way his inventions can help people. He admits to drawers full of invention ideas — some he has acted on; most not worth the effort, he realizes in retrospect. Despite Yock’s gray, relatively sparse hair, it is easy to imagine him as a young cardiovascular trainee, as he says, “cuddling up” to legendary cardiologists and entrepreneurs Thomas Fogarty, MD, and John Simpson, MD, PhD, who mentored him through early innovations.

In starting the program that became Stanford Biodesign, Yock wanted to recreate elements of the environment that had

helped him be successful as an inventor. “I hoped to replicate the mentoring I had gotten but on a more systemic scale,” he says.

The result is a program that creates small teams of individuals from around the world and from many different backgrounds, including clinicians, basic scientists, engineers and business professionals. Teams of three to four members each work for a year to identify unmet needs and develop a device prototype to address one of those needs. In addition to learning background information in the clinical area of focus for that year, students get training in some less obvious subjects, like how to brainstorm effectively or resolve conflicts in groups. At the end of the year, some teams go on to form companies to further develop and market their devices.

One factor that got the program off the ground was being housed in the interdisciplinary Clark Center, situated between the schools of engineering and medicine. “It’s the perfect location for exposing fellows to those two worlds that they need to understand to be successful,” Yock says. Being in proximity to Silicon Valley, with its concentration of experts in medical-technology innovation, was also essential.

The first year, the program had four fellows who learned an early version of what has become the Stanford Biodesign method. With some iterations and updates, that method is now documented in the seminal book on the topic, *Biodesign: The Process of Innovating Medical Technologies*. It was written by Stanford Biodesign leaders, and has spread through international biodesign outposts in four other countries.

The Stanford Biodesign process goes something like this: First, a team of fellows will follow surgeons and clinicians in a given specialty and identify all the apparent needs — places where doctors routinely hit snags or where patients express discomfort. This list of hundreds of needs can range from the narrow, like designing a less painful way of carrying out a routine procedure, to the broad, like changing the way heart failure is managed worldwide.

This step of starting by assessing what’s needed is an unusual one. More typically, says Yock, inventors start with a technology and then find a problem to which they can apply it — an approach that’s more prone to result in devices that flop in the market or fail to help patients, he says.

With hundreds of documented medical needs in hand, a

FOR EVERYTHING. HE HAD NEEDS STATEMENTS FOR A CONDO HE WANTED TO BUY.*



biodesign team then uses a series of carefully designed filters to find the best one to tackle.

Which needs represent the biggest barriers to quality health care? Which solutions are likely to be accepted by providers? There go half the needs. Which needs can realistically be addressed by a team with their skill sets? Which needs are not yet being addressed by competitors in the marketplace? Goodbye to another set of potential problems to solve.

Once all the potential needs are weighed against the criteria, one will likely bubble up as the best combination of a genuine need that meets the team's constraints. Decision made.

"The process is very freeing," says Holly Rockweiler, who finished the one-year fellowship program in 2015. Rather than agonizing over what medical need to address, teams follow the protocol and the right need chooses them. Before the Biodesign fellowship, Rockweiler had worked on a number of medical technologies. "That experience wasn't all I had

BIODESIGN FELLOWS JONATHAN SCHWARTZ, MD, ELISE DEVRIES AND ANDREW GANTON USE A CORONARY BALLOON AND PARTS FABRICATED IN A 3-D PRINTER TO TEST THE PROTOTYPE OF THEIR UROLOGICAL DEVICE (TOP AND RIGHT). YOCK (BOTTOM LEFT) ENCOURAGES TEAMS TO ASSESS WHAT A GIVEN CLINICAL SPECIALTY NEEDS, THEN FIGURE OUT WHICH ONE TO ADDRESS.

hoped for when I became a biomedical engineering major," she says. It was missing the patient.

She is now CEO and co-founder of Madorra, which is developing a product to treat vaginal atrophy in breast cancer survivors that her team began prototyping as Stanford Biodesign Innovation fellows.

The process works so well, says Rockweiler, that her classmates have adapted it for other decisions. "One of my friends writes a needs statement for everything," she says. "He had needs statements for a condo he wanted to buy."

BOTTOM LEFT: TIMOTHY ARCHIBALD

WHEN INNOVATORS LOOK AT MEDICAL NEEDS TO BY LOOKING FOR PLACES

TAKING COST INTO ACCOUNT

IN ITS 15-YEAR UPDATE, Stanford Biodesign isn't changing its process, which has proven successful time and again. Instead, it's moving cost evaluation up front, and teaching fellows about health-care economics.

This shift is both practical and personal. Personal because, though they are proud of improvements they've made to patient care, Yock and the other leaders of Stanford Biodesign recognize that collectively, new medical technologies are contributing to the cost crisis in health care. Practical because in order to fight those cost increases, insurance companies are exploring new reimbursement policies, in some cases limiting the ability of hospitals or clinics to get reimbursed for expensive devices. These changes hurt the prospects of a new device that was designed without an understanding of today's health-care economics.

In the past, most U.S. insurers would pay for nearly any procedure or device that had been approved by the Food and Drug Administration. Today, insurance companies are more likely to put a total price on the cost of an episode of care, such as inserting a stent — including all doctors' expenses, devices, time in the hospital and rehab. With this pricing, hospitals are less likely to purchase and use a pricey device, since they can't bump up reimbursement to cover it.

In this environment, when innovators look at medical needs to address, they are best served by looking for places where current treatments escalate medical costs. Are there ways of shortening hospital stays, moving care from a hospital to the clinic, or even allowing patients to receive care at home rather than in a medical facility? Those are factors showing that innovative devices could help patients and lower overall costs, and therefore be successful.

That last point is critical. Regardless of how desperately needed or creatively designed, no device will ever help a patient unless entrepreneurs are able to secure money from investors to develop the technology and bring the device to market.

"The reality is that the only way for improvements in health care to get to patients is to build a sustainable business around it," says Todd Brinton, MD, associate professor of medicine. Brinton was a biodesign fellow himself and now runs the fellowship's educational programs. "If you can't get investors around an idea, it will never reach patients. In order to be successful you have to be able to tell investors how they will be rewarded."

Mohit Kaushal, a venture capitalist with Aberdare Ventures and a former biodesign student, now helps teach fellows about health-care economics and the ins and outs of how to lure venture capitalists like himself to fund their ideas.

"In the old days you could get an increase in price for small health improvements," Kaushal says. "Today, what you hear from VCs is that devices are much harder. It's a whole new distribution system."

Thomas Krummel, MD, co-director of Stanford Biodesign, takes a practical view of this shift. He speaks in the short, staccato sentences of someone with a no-nonsense attitude.

"There's a sort of pragmatism to this that fits my view of the world," says Krummel, a pediatric surgeon. "Insurance companies aren't going away. So how do we understand how we fit into this ecosystem? If you understand that, then you can bring technology to patients rather than having a daydream."

As an example of this new worldview, he points to Precise Surgical, founded by biodesign fellows from the class of 2012. While in the program, the team noticed that infections following surgery dramatically increased the cost of treating patients. Reduce infections and health-care costs would go down. Those former fellows are developing a device that protects the edges of the incision site during abdominal surgery to reduce exposure to infections.

"You can do math around reducing infection rates," Krummel says. "That's a good startup. They have a simple technology with a clear path to understanding the value."

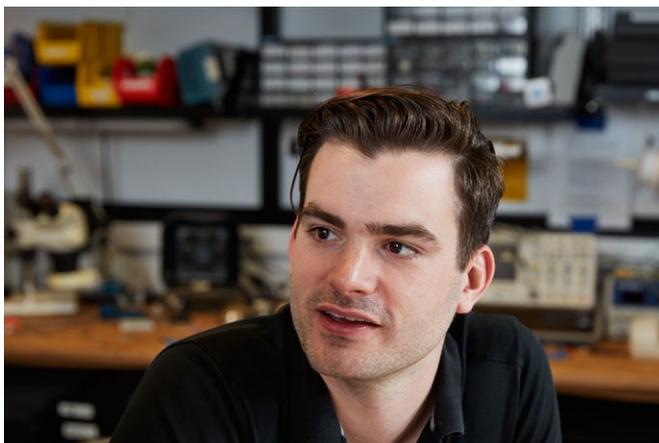
GOING GLOBAL

Stanford Biodesign has developed relationships with fellowship programs in Ireland, India, Singapore and, recently, Japan. In each case, the overall process and patient focus remain the same, but the details are adapted to each country's needs.

"The key thing is to bring the team approach to another country but use nationals as the local experts," Yock says.

Those experts better understand how health care is delivered and paid for in that country, how purchases are made, local patent processes, and any barriers relating to animal or clinical trials that could slow some kinds of inventions.

ADDRESS, THEY ARE BEST SERVED WHERE CURRENT TREATMENTS ESCALATE MEDICAL COSTS.



Those differences in infrastructure can significantly alter which kinds of technologies are successful, particularly with the Indian program, which operates in an environment far removed from resource-rich Silicon Valley.

Until this year, the India Biodesign program sent fellows to Stanford to learn the process before going back to their home country to apply it. They are now trained entirely in India by program graduates.

Harsh Sheth, MD, who was an India Biodesign fellow at Stanford last year, says one big challenge to working in India is access to manufacturing and distribution networks, though years of returning biodesign fellows are starting to change that by expanding the networks and establishing connections for the newer fellows.

“The landscape and environment for medical technologies is improving slowly,” he says. He and fellowship team members Shashi Ranjan, PhD, and Debayan Saha are developing a very low-cost device that fits inside the nose to filter

BIODESIGN FELLOWS VÉRONIQUE PEIFFER, PHD, AND JUSTIN HUELMAN EXPERIMENT WITH WAYS TO VISUALIZE PERSPIRATION, SO THEY CAN TEST THEIR APPROACH TO TREATING PATIENTS WITH PALMAR HYPERHIDROSIS (EXCESSIVELY SWEATY HANDS). AFTER BEING PAINTED WITH IODINE, THE SWEATY PARTS OF PEIFFER'S HAND REACT WITH THE STARCH IN STANDARD COPY PAPER.

out excessive air pollution, which can cause health problems ranging from asthma or coughing to heart disease.

“In India, the criteria we used were different, but the process was the same,” says Ranjan. For example, they look for needs they can address with devices sold directly to consumers so they won't be thwarted by the patchy clinical distribution network and the absence of widespread insurance coverage in India.

Yock says that when the Indian fellows were in the U.S. program, they were an inspiration to other fellows because of what they could achieve with little cost. “They make do with

C O N T I N U E S O N P A G E 5 6

inflammation implication

how
our
aging
immune
system
goes
haywire

Danger stalks the body from without and within. For most of human evolution, the biggest killers have been foreign invaders — not other humans, but the microbial pathogens that mosquitoes inject into us (malaria, dengue, yellow fever) as well as countless other variously transmitted bacterial and viral pests.

But the gears have shifted. Medical and public-health advances have so vastly reduced the death toll from microbes that today's leading killers spring from within. People are living long enough to acquire debilitating bug-free disorders such as heart disease, strokes, cancer, osteoarthritis, Type 2 diabetes and neurodegenerative syndromes such as Alzheimer's.

A common element in all of these appears to be inflammation — not the intense, temporary, ad

hoc (or, as immunologists say, acute) variety that's actually helpful when you run a fever while you're fighting off an infection, but another kind that's stealthy, steady and pernicious, like a leaky faucet. It doesn't seem like a big deal until the water bill comes.

With advancing age, there's an escalating tendency for our immune system to go haywire. It becomes less capable of protecting us against infections and cancer or responding to vaccinations but, paradoxically, increasingly prone to wallowing in a state of vague, non-specific irritation that's called chronic low-grade inflammation.

Along with this progression — which immunologists have dubbed “inflammaging” — comes a growing vulnerability to disease.

If we knew why and how inflammaging occurs, we might be able to find ways to forestall or override it. For example, researchers at Stanford and elsewhere are gaining deeper insights into the inflammatory underpinnings of the world's No. 1 killer, cardiovascular disease, leading to studies testing new treatments. Two huge national trials are now exploring whether anti-inflammatory medications used by patients with autoimmune diseases can prevent heart attacks and strokes.

Similar insights and ideas for treatments are emerging for other diseases of aging, too.

BY BRUCE GOLDMAN

ILLUSTRATION BY
MARK SMITH



THE TWO ARMS OF THE IMMUNE SYSTEM

Many scientists theorize that a big factor in inflammaging, and the susceptibility to many diseases that comes with it, is that one of the immune system's two arms — the “adaptive” immune system — is increasingly tied behind its back, leaving the other arm — the “innate” immune system — to pick up the slack.

We don't hear that much about the innate immune system, which is present even in such evolutionary ancient organisms as sponges. We moderns couldn't live without it, either. This arm of the immune system is fast and powerful, but hasty and somewhat indiscriminate.

We've perhaps heard more about the immune system's slower to respond, but far more targeted, other arm: the adaptive immune system, which evolution has installed in us vertebrates to provide highly selective protection against infections and cancer while sparing healthy tissues. The adaptive immune system consists mainly of cells called lymphocytes.

Stated loosely, any given lymphocyte is narrowly focused on a particular biochemical shape or, in science-ese, “antigen.” Recognizing this specific antigen on a tumor cell or pathogen or in a vaccine, the lymphocyte proceeds to undergo round upon vigorous round of rapid-fire replication. But that lymphocyte will proliferate only in response to the antigen to whose shape it's attuned.

“A healthy young adult's body harbors billions of lymphocytes that, in the aggregate, can recognize 100 million different antigens,” says Jorg Goronzy, MD, professor of medicine, whose career has focused on the aging immune system. “But typically only a handful of those billions of lymphocytes are geared to respond to any given antigen.” When a pathogen appears on the scene, this handful has to turn into an army, meaning lymphocytes have to divide like crazy. It takes them days or weeks to fire up to full fighting strength.

“If you had to wait that long to be able to take on a pathogen, you'd be dead,” Goronzy says.

But you don't. The innate immune system's various constituent cell types all feature, both internally and on their surfaces, families of “pattern recognition” receptors that sense broad, generic signs of infection and injury: for instance, material smacking of bacterial cell walls, or DNA bearing tell-tale microbial sequences. These abundant,

one-size-fits-all fighter cells can quickly sense the presence of a virus or bacterium and, without bothering to distinguish among the millions of varieties of each or needing to proliferate, respond swiftly, fiercely and wantonly, often inflicting collateral damage on healthy tissue.

That can spell trouble.

SLOWLY SIMMERING

It's not just a single invisible hand steadily turning up the inflammatory dial as the years go by, but many.

Like our closets, our bodies accumulate junk as we age. Garbage that can't be metabolized piles up within aging cells or gets sloughed off alongside them. One job of innate immune cells known as macrophages (derived from the Greek words for “big” and “eater”) is to ingest and metabolize all that garbage, preventing dead and dying cells from throwing off inflammation-promoting substances. But macrophages' garbage-gobbling gumption declines with age.

Meanwhile, chronic viral infections we accumulate — cytomegalovirus, Epstein-Barr virus, herpesviruses — are constantly challenging the immune system to a fight. Bacteria, trillions of which happily inhabit our intestines (where they usually do us much more good than harm) poke through our older, and therefore leakier, gut linings into the circulation, angering our innate immune system, which doesn't know them and doesn't like them. The body becomes an increasingly pro-inflammatory environment.

As we get older, our adaptive immune system gradually goes to seed. We end up with not enough different kinds of lymphocytes, and too many of some of the kinds that we do have. Every battle against a microbial foe or incipient tumor

leaves behind milling masses of surplus immune warrior cells with time on their hands. That can foster autoimmune disease. A team led by Cornelia Weyand, MD, professor of medicine and chief of that department's division of immunology and rheumatology, has identified a kind of lymphocyte whose job it is to keep other lymphocytes in check. This regulatory lymphocyte acts as a sort of military policeman that quiets down the adaptive immune system after it has been, however justifiably, in a state of battle readiness. With time, this class of regulatory lymphocytes begins to fail, leaving us with continuous, simmering inflammation. Weyand's group has tied deficits in these cells' capacity to do their policing to the likelihood and se-

IT'S NOT
JUST A SINGLE
INVISIBLE
HAND STEADILY
TURNING
UP THE
INFLAMMATORY
DIAL AS
THE YEARS
GO BY,
BUT MANY.

WHAT CAN WE DO?

While researchers sort out the factors that lead low-grade chronic inflammation to increase as we age, there may be steps we can take on our own to slow it down.

For example, it may pay to watch your waistline. A potbelly in some respects resembles a huge gland capable of secreting inflammation-producing proteins into the circulation. That's because fat cells are notoriously capable of releasing hormones and other chemicals like IL-6 and TNF-alpha, which drive potentially aggressive immune cells called macrophages wild. And belly fat is loaded with shocking numbers of macrophages. Plus, the pattern-recognition receptors that are the primary initiators of the inflammatory response can, during particularly inflammatory times,

sprout on fat cells, too. The chronic low-grade inflammation and macrophage infiltration typifying belly fat have been linked to both Type 2 diabetes and cardiovascular disease.

Vaccinations are another smart bet. "We think vaccination is one of the best interventions we have to prevent immune aging," says Cornelia Weyand, MD, professor and chief of immunology and rheumatology at Stanford. "Every time we have an infection, we pay a price. The more we can keep the immune system from being called into action, the better we can preserve it."

Finally, your grandma was right about dietary fiber — which essentially translates

to "complex carbohydrates we can't digest but our gut-dwelling microbes can." Justin Sonnenburg, PhD, associate professor of microbiology and immunology, has found evidence that a lack of fiber in the diet may be, among other things, forcing our gut-resident microbes to subsist by scavenging sugar molecules from the long strings of them composing the mucus layer that lines our gut. The consequent thinning of the intestinal barrier, he thinks, may provide a portal allowing gut microbes to break out into the bloodstream, helping to induce a simmering inflammatory environment.

"Good fences make good neighbors," he says.

verity of strongly age-related autoimmune diseases such as giant-cell arteritis, a condition affecting one in 500 older people but never seen in people under age 50. The team is now analyzing blood from patients with cardiovascular disease to see if similar regulatory lymphocyte deficits play a major part in that far more common condition, as well. (Preliminary evidence suggests this may be the case, Weyand says.)

Meanwhile, as we age, it's harder for the adaptive immune system to respond to novel pathogens. Our remaining lymphocytes — having encountered life's continuing barrage of troubles — are increasingly dedicated to recognizing and responding to specific "remembered" antigens they've previously encountered, and less flexible in their aggregate ability to recognize and respond to novel antigens that characterize new tumor cells or pathogens. Also, lymphocytes in this jaded, battle-hardened state are more prone to spontaneously secrete inflammatory factors than when in their "naïve" state.

In short, there are many ways for people's immune systems to go astray with age.

A CASE IN POINT

Between a quarter and a third of all deaths in the United States are traceable to impaired flow of oxygen-rich blood to the heart (coronary heart disease) or the brain (stroke). The underlying process, atherosclerosis — the gradual buildup of plaques in our arteries — was once thought to be the simple

result of eating too much fat, which was believed to coat the insides of our arteries and congeal into plaques that thicken over time, impeding circulation.

"But you don't just gradually have circulatory shrinkage until you finally gasp for breath," says Weyand. "Heart attacks and strokes occur all of a sudden. Why?"

Fatty substances are indeed a prime constituent of an arterial plaque, but there's more than fat deposition going on there. For one thing, plaques are stuffed with a variety of dead or near-dead smooth-muscle and endothelial cells associated with blood-vessel walls.

Those plaques also contain lots of immune cells — chiefly macrophages, those "big eaters" that devour invading bacteria, debris and dead cells left behind after injury or infection.

Mature macrophages generally assume one of two personae. The gentler ones, called M2 macrophages, nibble dead cells and extracellular detritus, releasing healing factors that encourage new cell growth and stimulate blood flow, and otherwise overseeing tissue repair.

"Our body turns over more than 100 billion cells per day, every day," says Nicholas Leeper, MD, associate professor of vascular surgery and of cardiovascular medicine. "Those cells all need to be cleared before they undergo a kind of death in which they release inflammatory material." All hail the M2 macrophages.

C O N T I N U E S O N P A G E 5 6

FEATURE

Well now

CONTINUED FROM PAGE 9

she laughs, "When you're a parent you can never be happier than your least-happy child." So, ultimately, we need to find ways to support those we love while remaining somewhat stoic about their problems, so our own well-being doesn't decline, too.

The second major domain was lifestyle behaviors such as eating well and getting plenty of sleep and exercise. People looked back on times when they were engaging in healthy behaviors as times of great well-being, says Heaney.

As one interviewee reported, "I'd been outside all summer long just doing labor. I mean, sometimes you dig ditches, and sometimes you're pruning Mrs. McGillicuddy's pansies, whatever it is, you're outside all day long, which really nourishes the animal, I'm here to say. And I remember my mother, for some reason we were driving along, and I said, 'I'm at the peak of my physical health.'"

WELLNESS AND RESILIENCE

The team also found that stress and resilience to stress were important factors in wellness. Major changes, such as a divorce or moving from another country, were especially likely to induce stress. But participants also spoke with pleasure about how well they had coped during a difficult time.

One interviewee said, "Even the worst of times, even the most difficult of times, there's always been light and strength, and that is because I have a very rich inner life. And in the end, I have hope."

Some people can adapt to the most dire of circumstances. In her book *The Pursuit of Happiness*, Carol Graham, PhD, an economist and a senior fellow at the Brookings Institution who studies happiness and well-being, reports that even though poor people around the world are less happy than the wealthy, some of the poorest often report high well-being.

Even those with serious illness may report a sense of well-being. "I was surprised by the extent to which people did not talk about illness," Heaney says. People who had cancer might not even mention it in the context of their well-being. "Having an illness or not having illness was not what was important. What was more important was the experi-

ence of it and the extent to which a person felt like they were managing or coping.

"People would actually say, 'Yeah, you know, a time of particularly high well-being for me was when I was diagnosed with heart disease,'" says Heaney. "And you're like, 'What?'" But they would then go on to say, "Yeah, because I learned how resilient I am. I learned how strong I am. I have come out of that a better person and I learned what matters to me."

The last five domains, which came up less often, included having a sense of meaning and purpose, which could encompass accomplishments or, alternatively, a sense of why we are here; a sense of self (a measure of confidence and self-esteem); financial comfort; spirituality; and, finally, exploring (or pioneering) and creativity.

BUILDING THE QUESTIONNAIRE

Using the 10 domains, Heaney and her team wrote 72 questions designed to probe people's experiences of wellness. The questionnaire is already online for a small test group of WELL participants, and ultimately it will be available for all 10,000 U.S. participants.

Participants are asked, for example:

During the last two weeks, how often did you feel...

...that you were very capable?

...that you were interested in your daily activities?

To get at resilience, Heaney and her team included questions such as:

How confident are you that you can...

...bounce back quickly after hard times?

...adapt to change?

...deal with whatever comes your way?

...see the humorous side of problems?

The 72 questions have been translated for use in the China and Taiwan arms of the WELL study, field tested to make sure they have the same meaning in all three sites and modified to adjust for cultural or language differences. Additional modules may be added in each country to address determinants of wellness that are specific to that culture.

While the questions themselves might vary a little from site to site, it remains to be seen how different the answers will be.

More broadly, each of the three WELL for Life sites will look a bit different, says Winter. "In the Bay Area, we've really been focusing on an online registry. In China, we are using a more traditional study approach in which peo-

ple are going to come in in person, and we'll gather physiological data such as BMI, height, weight, grip strength, plus blood samples and a battery of survey questions. And just as in Santa Clara, we'll be following these people over time." Meanwhile, the Taiwan arm of the study will add a biobank of tissue samples collected from all 10,000 participants.

Ioannidis says these tissues may reveal biological markers for wellness. "Just as we can monitor diabetes by looking at blood sugar levels," he says, "is there some wellness biomarker that can tell us something about how one feels about one's life? Are there biomarkers that indicate levels of wellness and that change as people's levels of wellness increase or decrease?"

"Of course, this is exploratory," he says. "I cannot promise that we will have hundreds of biomarkers explaining everything about wellness, but it's possible that some of them will be of interest." That would be a huge step forward.

How confident are you that you can...

...overcome obstacles?

...stay focused under pressure?

...think of yourself as a strong and resilient person?

...manage any unpleasant feelings that you might have?

...not get disheartened by setbacks?

In a few years, the WELL project team may be able to help us answer questions like these with "very confident." **SM**

— Contact Jennie Dusheck at dusheck@stanford.edu

FEATURE

In the circle

CONTINUED FROM PAGE 15

lifestyle behaviors. Moreover, they were troubled by comments on their grant application to NIH's National Institute on Minority Health and Health Disparities: In questioning assimilation of urban American Indians, one reviewer used the derogatory term "half-breeds." (The study eventually secured a grant from the Patient-Centered Outcomes Research Institute.)

Then Vasquez — the fulcrum of the project — was let go from the community health center at which she worked, without explanation. Goldman Rosas says she has since learned this is "really common" in organizations that serve American Indians.

"When I freaked out about it and called the scientific advisers and the CAB, everyone was just like, stay the course; this is par for the course," she says. Vasquez alighted at the San José State University Research Foundation, and the researchers were able to modify the PCORI grant accordingly. "I couldn't do this project without Jan," Goldman Rosas says.

Small issues keep popping up: What is an appropriate data-retention period that allows the researchers to complete their work but doesn't create mistrust in the community? Where should the question about race and ethnicity appear on the questionnaire? (Not at the beginning, said the CAB. It's too traumatizing.) "I'm used to that question for Latinos being complicated, but not traumatizing," Goldman Rosas says.

"A lot of the things that go on in working in American Indian communities are really out of this trauma we're talking about," Vasquez says. "That's why I think we're so unique and amazing. When we talk to people all around the country, they ask, how did you get this far? How are you still together? How are you accomplishing so much?"

In fact, "there have never been challenges with the CAB," Goldman Rosas says. When the board was without a place to meet during Vasquez's job transition, they convened at a restaurant. "They were kind of unfazed by the whole thing, which gave me hope," Goldman Rosas says. She characterizes their reaction as, "A terrible thing has happened, well, see you next week."

"Which really says a lot about the community and what they go through," Vasquez says. "It's like, 'You haven't seen trauma.'"

It's one thing when Kendrick tells you that many of his classmates back on his South Dakota reservation have died of complications from diabetes. He's 71. It's another when Orena Flores, who spent her childhood on the Fort Yuma reservation in Winterhaven, California, says the same. She's 32. "They've already passed on. A lot of them have," she says. "There's so many who are unhealthy, overweight and just sick. I want that to stop."

Orena Flores teaches the enhanced classes for the study participants, the classes infused with elements of native culture. In addition to providing a standard diabetes prevention curriculum, she leads talking circles for the groups of five to 10 participants. The talking circles are

informed by her Fort Yuma Quechan, Maricopa and Mojave heritage, and she explains how they may differ from those of other tribes. That resonates with some; for others, it's their first time in a talking circle.

"A lot of them say, 'I want to come and learn my culture.' And that's where I start," says Orena Flores, who is active in a traveling native dance troupe and is married to Paul Flores. "I think I've helped the people who identify as Native American but they're not really sure what tribe. I say, 'That's OK. A lot of people are like that. It's from history and things that happened. It's not your fault. So let's find something that fits you.'"

Initially, she says, many participants are focused on losing weight, stat. "We're not focusing on just weight," Orena Flores tells them. "We're focusing on making a gradual change in life."

When making that gradual change gets discouraging, peer mentors like Kendrick are there to support participants. "I know where you're going to be when you hit, let's say, week eight or nine, when you start talking about eliminating or defusing negative thoughts," he says. "Will people backslide? Absolutely. Will people lose their way? Sure. But they'll fall back on how they connected to their heritage and find some inner strength."

Once a week, at the end of class, Paul Flores comes in to help participants create multimedia digital stories. "I tell them our history has a rich culture of storytelling. And we want to keep our traditions alive, but we've put a modern twist on it, which is why we call it digital storytelling. When you tell a story, you gain power over that story. So if your story is going to be one of redemption, or overcoming an obstacle, the more you tell a story, the more power you're going to have over that incident in your life."

By the end of the 16 weeks, the tenor of the group has shifted. "Once they get motivated, they start motivating each other," Orena Flores says. "When the classes are ending, they're all a group together that has formed a bond, and I love seeing that. As long as that seed is planted and they're able to go out and spread it, it's wonderful."

"This whole idea of transformation is about getting each individual to step up, to be motivated around their own health and the health of the community, maybe in a way that's greater than what we would expect within the control group," Stafford says.

Although it's a little hard to speculate about future research before results are in hand, Stafford sees some "logical next steps" for the partnership. One might be to develop a program for managing diabetes. "There is truly a value in working upstream and trying to prevent the disease," he says, "but you're not going to always be successful, and there's a population out there that needs help."

Inspired by conversations with Al Cross, McClinton-Brown envisions research on the health and economic impacts of relocation over generations. "The CAB has the capacity to seek and get additional funding," she says. "Lisa is in it for the long haul. Randy is very invested. The trust is there."

Several CAB members, including Orena and Paul Flores, have a broader vision in mind. "If the community participates in this, and we do well, then not only will we have healthier native people, but we will be on the next step to building the ultimate goal," Paul Flores explains. "We want to establish a community center." There, he'd like to equip American Indian kids — "because I love the kids; that's our future" — with computer skills such as graphic design, web design and animation. Orena Flores pictures a vibrant gathering place that offers native dance classes and powwows with healthy foods. "It can't just be diabetes prevention; we've got to offer more," she says. "We are a very good, powerful group, and we will get it done." **SM**

— Contact Kathy Zonana at kathy@stanford.edu

FEATURE

Can you repeat that?

CONTINUED FROM PAGE 19

Ioannidis and associate dean of clinical and translational research Steven Goodman, MD, PhD, the center is the first in the country to devote itself to making the practice of research more accurate and efficient across many scientific fields.

One of their aims is to educate scientists on how best to design preclinical and clinical studies, and how to choose appropriate statistical methods to analyze the resulting data.

"A big problem in much published research is the use of suboptimal methods," says Ioannidis. "Over the years, the quantitative component of biomedical research, as well as research in general, has become more prominent. There are now very few

disciplines in which researchers can do high-quality, influential work without also incorporating high-quality quantitative analysis.”

Collaboration among researchers and statisticians or computer scientists skilled in handling large amounts of data is one way to ensure that a study’s findings are robust and accurate. Another is to increase transparency and to encourage researchers to cross-check one another’s results. The journals *Science*, *Science Translational Medicine* and *Nature*, as well as major funding organizations including the National Institutes of Health, have launched efforts to promote data sharing and open access to scientific articles. The journals have agreed to eliminate the word limit on sections of an article devoted to describing in detail how the research was conducted, to encourage authors to provide more raw data to others in their field and to ask editors to partner with statisticians when necessary to assess how the study was analyzed.

The NIH’s newly created Rigor and Reproducibility website includes a training module for researchers that emphasizes enhanced transparency and good study design. In addition, several NIH institutes have deployed a checklist that reminds grant reviewers to review the key components of proposed research, including any plans for randomization and data analysis. They are also considering assigning reviewers to assess whether the proposed research is built on a strong foundation of previously verified studies.

“Sometimes some sloppiness creeps in,” said NIH director Francis Collins, MD, PhD, at a 2015 conference in Washington, DC. Collins cited the hypercompetitiveness of many scientific fields and the scarcity of available research funding as potential reasons for poor experimental design. “Maybe the right controls were not quite done, or you had a control but it wasn’t the perfect one. Or you didn’t repeat the experiment two or three times to be sure you always got the same result. And maybe you just sort of glossed that over when you finally submitted your paper, either because there was a space constraint, or because you were tired of writing that section, or, sorry to say, in some instances people don’t really want to give away a few of their lab secrets.”

In early 2014, Collins and the NIH’s principal deputy director, Lawrence Tabak, DDS, PhD, described the organization’s plans to

enhance the accuracy of scientific research in an article in *Nature*.

“We need to renew our attention and our commitment that we’re about doing science that’s rigorous, that’s going to hold up, that we’re looking for truth,” says Collins.

That commitment, however, will require upending the culture of how science is conducted and rewarded in this country. For decades, career capital has been amassed in the form of prompt, frequent publication of one’s results in preferably high-profile scientific journals. Numerous prestigious papers are parlayed into increases in grant funding and academic promotions. But the process doesn’t include incentives for collaboration or for verifying others’ work. It also discourages the publication of negative results.

Former National Cancer Institute director Harold Varmus, MD, has suggested changes to the summary of a researcher’s achievements that is required as part of a grant application. Rather than listing major publications, Varmus proposes instead that researchers include a narrative that describes five major accomplishments. This structure, which is used by the Howard Hughes Medical Institute, would give grant reviewers a more holistic view of a researcher’s career.

So how will we know if, or when, these efforts will succeed? Ioannidis is confident that the tide is shifting but thinks it will take time to see meaningful change.

“Until the early ‘90s, there was not even an effort to look at the biomedical literature in terms of the totality of the evidence,” he says. Nowadays, “we’re seeing action on nearly all possible fronts, from scientific journals to funding agencies to professional organizations.”

Earlier this year, Ioannidis published an analysis of a random sample of 441 studies published in biomedical journals between 2000 and 2014 to ascertain how many followed any of the practices recently suggested to increase research transparency and accuracy. He found that none shared all the raw data, only one shared the full protocol and many did not report on funding and conflicts of interest.

But there are some promising signs.

“There are focused areas where in the last few years data sharing has improved,” says Ioannidis. “For example, more genetic data is being deposited in the National Center for Biotechnology Information’s database

of genotypes and phenotypes, which relates gene variants to disease states. There’s also a clear push to share more data for clinical trials and to make protocols routinely available to others.”

Gradual shifts are to be expected when recalibrating an entire culture, however.

“It’s an evolution,” Ioannidis says. “Science is a process of accumulating evidence. By scrutinizing that evidence carefully, we can begin to develop a gradient of truth. If we can make biomedical research more efficient, and more reliable, we can improve the health outcomes of real people.” **SM**

— Contact Krista Conger at kristac@stanford.edu

Q & A

Leaving frailty behind

CONTINUED FROM PAGE 21

COSTELLO: Are there any scenes from either of your books that you return to when you are facing a challenge that seems insurmountable?

HILLENBRAND: Stanley Pillsbury was the top turret gunner on Louis’ B-24 bomber. There is a very harrowing experience that these men went through when fighting off Zeros [Japanese fighter planes] after bombing Nauru Island.

A Zero was coming at Stanley Pillsbury and he had been shot in the leg with a cannon. His leg was horribly mangled. He was terrified. He was a very quiet and recessive kind of man. He did not have a swaggering kind of personality that you think of in a war hero, but he had this moment where he’s in agony with his leg dangling down and the plane has been hit 600 times by cannon fire and bullet fire. It’s likely to crash.

Somewhere inside himself Stanley found this wondrous strength and he pivoted in his motorized chair and he took aim. He could see the Japanese pilot flying toward him, and he thought, “I have to kill this man.” But he had to do it to save all the men aboard his plane. He fired and he shot down the Zero and he saved everybody on the plane.

That is something I go back to a lot because Stanley had no idea that he had that kind of strength in him, that he could do that. None of us knows what we would really be in these circumstances of extremity. Stanley found out that day. I like to remember that

when I feel frightened. When I feel too small for my circumstances, I remember Stanley.

COSTELLO: Your books are beloved. You've reached epic fame. How has that outside success impacted you?

HILLENBRAND: Having been able to write the books was lifesaving for me. It gave me an ability to connect with the world. It gave me an escape from my body. It enabled me to create things that had importance.

These are not books that the world will turn upon forever. These are stories from history, but they are very inspiring stories, and they do bring joy and relief and peace to people when they read them. That means a great deal to me.

I had lost the ability to connect with the world in any way at all. Even just talking on the phone I couldn't do much of the time. I was able, though, to write these books and tell these stories, and reach out to people I would never meet all over the world and create something. It validated my life.

It changed the way I thought of myself, also. Most patients will tell you that it's terribly humiliating to have this particular disease, because it isn't taken seriously. You are treated with terrible contempt, sometimes by your own family. You lose that respect that you normally receive in conversing with the world because people are really spilling contempt on you all the time.

It gets to you after a while. You start to feel like nothing because you're told that all the time. That you're lazy, and that you're useless. These are words that I heard a lot. When I wrote those books, I proved I wasn't lazy and I wasn't useless.

COSTELLO: Were you proving something to yourself?

HILLENBRAND: I was proving what I was. It was really, really hard to write a book with this disease. It's never easy to write a book, but to do it with vertigo and to do it with exhaustion it took every bit of me. I would do it again because of the self-respect I got out of it.

COSTELLO: Are you angry at the medical community over the disease being so misunderstood?

HILLENBRAND: I felt very, very angry for a long time about it, angry with specific doctors who were particularly appalling in their behavior toward me. I was angry over the damage

that caused, physically and emotionally.

I don't feel contempt for the medical community. Different doctors are different people. I got my diagnosis from a wonderful guy, the head of infectious diseases at Johns Hopkins, who was the first person who was willing to say, "You have a serious disease, and the other people who have dismissed you are simply wrong. I don't know what's wrong with you, but I believe that you're very ill." That took humility for him to say. I am so grateful for it. I walked out of there happy even though he said, "I can't treat you. I don't know what to do for you." But simply telling me, "I respect you, and I have a limit to my understanding of disease," was a beautiful thing.

My physician in Washington, D.C., would exhaust himself trying to help me, and he would stay with me for hours. He would make house calls because I couldn't come to him. He was wonderful to me.

I don't blanket the whole medical community for what some people did back then, and I am treated with much more respect now.

COSTELLO: What gives your life meaning?

HILLENBRAND: I want my life to touch the lives of others in a positive way if I can possibly do that. I want to give as much of myself and whatever gifts I have to other people to make the world better if I can. I write with the goal of serving my subjects in terms of telling their stories and trying to illuminate the world a little bit with what those stories have to offer about living and about history. Those are the things that motivate me every day. A weirdly beautiful gift the disease has given me is to appreciate everything in this world, even the things that you simply take for granted if you're well. **SM**

This interview was condensed and edited by Paul Costello

FEATURE

Standing up to sexual assault

CONTINUED FROM PAGE 29

boys get through these formative years without adopting the entitled attitudes and behaviors, the negative gender norms storming their lives at this age and the 'violence as power' paradigm."

Most sexual violence prevention curricula for boys are designed for college-age men or perhaps high school students, says Sarnquist, the Stanford researcher. Focusing on primary-

school boys is "unusual and innovative." The new training is less about bystander intervention and more about empowering boys by emphasizing their agency. "The most important point is that it plays on their strengths. So it's this positive spin on what it means to be a man, to become a man, and tries to install pride in masculinity." She says that the No Means No team views this approach "almost like a vaccine."

That emphasis on empowerment is the heart of the work with both the boys and the girls, and it's the feature of the program that most animates the Stanford researchers. By learning at an early age to protest abusive behaviors, a generation can grow up to expect and enforce new norms. Sexual violence won't be wholly stopped by this intervention, Sarnquist and Baiocchi acknowledge. But a dramatic shift is possible and, as early research suggests, already underway. "What a win that is for the community," says Baiocchi. "Because the change is being powered from within, these girls and boys are changing what's considered OK." **SM**

— Contact Laura Heaton at medmag@stanford.edu

FEATURE

Ulterior motivation

CONTINUED FROM PAGE 41

with scientists at Harvard's T.H. Chan School of Public Health, one of several collaborations they've conducted to bring meals supported by nutrition science to commercial kitchens. And last year, Gardner and Drescher expanded the effort with the Menu of Change University Research Collaborative, led by Stanford and the culinary institute, which is asking scientists, chefs and administrators on 37 college and university campuses to advance healthy, delicious, plant-based menus in their cafeterias and to prompt more food research. They're collecting data on how effectively chefs make changes such as reducing meat served and decreasing food waste, and are working to expand the effort to food served in other settings, such as at large workplaces (Google is getting involved) and hospitals. The larger goal is to test how to improve what people eat in these places, while simultaneously helping college students feel like healthy eating is the norm.

Menu of Change includes two important pieces of advice that relate to motivation: "Lead with menu messaging around flavor" and "Celebrate cultural diversity and discov-

ery.” Menus should tell the right stories about healthy items; it’s not a matter of disguising what’s in a dish, but rather of talking about it in a way that will appeal primarily to customers’ taste instead of scolding them into doing what’s good for them. “A great majority of Americans are way more open to culinary adventure than they once were,” Drescher says. Chefs can take advantage by presenting their creations as mini-vacations to interesting locales.

One healthy-cooking technique the collaborators are studying, dubbed “the flip,” changes what’s at the center of the plate. It seeks a middle ground between huge, carnivore-sating portions of meat and none at all. “We can say, ‘But it’s not vegetarian! This salad has steak in it; it’s global cuisine; we’re going for flavor profile,’” Gardner says. Behind the scenes, the health justification for the change is grounded by epidemiological data linking high consumption of red meat and processed meat with obesity, Type 2 diabetes, cardiovascular disease and some forms of cancer, as well as evidence that diets high in vegetables and fruits protect against several chronic diseases.

To help convince chefs that the “protein flip” would work, Drescher and his team collected data on what happened when they replaced some meat in hamburger patties with ground sautéed mushrooms. “We started to make prototypes and said, wow, this is really good,” Drescher says. He enlisted a food science team at the University of California-Davis to analyze whether the flavor stood up to traditional all-beef mixtures. The results, published in the *Journal of Food Science* in 2014, were convincing: Adding mushrooms boosts flavor with less sodium, less fat and fewer calories. It solves other problems, too.

“In volume food service, you can’t serve medium-rare hamburgers because of food-safety concerns, so the protein dries out,” Drescher says. “The mushroom hydrates it, plus you get this umami factor that’s not as present otherwise.” Umami is the savory “fifth taste” (in addition to sweet, salty, bitter and sour) that is abundant in foods like soy sauce and ripe tomatoes; it’s part of what makes a burger delicious. The data have already convinced some huge food-service companies to buy less meat. London-based Compass, which has a \$14 billion North American operation, reduced red meat purchases by 10 percent in the fall of 2015, the first year that it began following Menus of Change principles.

STEALTH-HEALTH YOURSELF

Today, motivation-focused health interventions are moving outside labs and restaurant kitchens. On the “stealth exercise” front, there’s GirlTrek, a nonprofit that encourages African-American women to form groups in their neighborhoods for daily walks. “This is not a fitness organization, this is a campaign for healing. ... We walk to heal our bodies, inspire our families and to reclaim the streets of our neighborhoods,” the organization’s mission statement reads in part. So far, 67,000 women and girls have pledged to walk regularly in their neighborhoods.

Robinson and Gardner have even snuck stealth-health elements into their own lives. Gardner leads a weekly volleyball game at the medical school that’s been going since 2001. Yes, it’s exercise, he says, but the players are mostly there to have fun. (The net they use was purchased with “employee morale” funds from the prevention research center.)

As for Robinson, after moving to San Francisco, he started taking public transportation and joined Stanford’s Commute Club, which gives financial incentives to employees who reduce their car trips to campus. He’s not quite sure what motivated him — maybe the money he saved, maybe the environmental benefits, maybe the fact that he really hated being stuck in his car. One thing’s for sure, though, Robinson says: “I don’t take the train for my health. But as a side effect, I noticed that after I stopped driving, my HDL went up by 10 points.” He attributes at least part of the rise in his “good cholesterol” to his daily walks to and from the train, which provide a stealthy bit of exercise he wouldn’t otherwise get. “That,” he says, “is pretty cool.” **SM**

— Contact Erin Digitale at digitale@stanford.edu

FEATURE

At what cost?

CONTINUED FROM PAGE 47

what they have in an amazing way,” he says. It is much harder to get products manufactured in a consistent way in India, venture capital is limited, clinical trials are hard to carry out and patents aren’t always respected — all of which change the way fellows think about how to get their innovative ideas to patients.

Yock hopes that exposing fellows to oth-

er ways of thinking about innovation will improve their own chances in global markets.

TECHNOLOGY MATTERS

Brinton says that in designing the fellowship program to meet today’s market, here and internationally, the goal isn’t just to help bright young people start companies. It’s to help patients.

“At Stanford we are training people to be leaders in their fields,” he says. “We train the physicians how to use technology that saves people’s lives, and now we are training them in how to develop new inventions with the same goal — to better care for patients.”

Brinton and Yock see medical-technology innovation as a discipline that has a natural home in a university setting. It’s a complex and interdisciplinary set of skills that needs the broad intellectual resources of a campus and medical system to develop fully.

Mastering those skills creates innovators who can go on to have large-scale impact on patient care. Krummel says that as a surgeon he can do quite a bit of good, one patient at a time. “Teaching is multiplicative. My students can develop a new technology that is used all over the world,” he says. “I could never personally do that much good on my own.

“That’s a great reason to get up in the morning and go to work. In the end, given that we are all consumers of health care, anything that can be better, safer, cheaper — there’s a public good there.” **SM**

— Contact Amy Adams at amyadams@stanford.edu

FEATURE

Inflammation implication

CONTINUED FROM PAGE 51

So-called M1 macrophages, on the other hand, are pugnacious, proactive and perhaps a bit paranoid. They blow the whistle on infectious pathogens or suspected tumor cells, recruiting other types of immune cells to the scene and squirting out pro-inflammatory signaling proteins that act both locally and systemically to ramp up the entire immune system to high-alert status. They also attack the pathogens or tumor cells directly.

Cardiovascular catastrophes — heart attacks and strokes — now appear to be tripped off by macrophages, the very immune cells charged with clearing plaques.

The buildup of dead cells and fatty-plaque components in atherosclerotic lesions should

normally be prevented by M2 macrophages' garbage-disposal service. But with age, their job performance falls off, while M1-types' activity ramps up. M1 macrophages' unremitting secretion of inflammatory substances can render plaques brittle, increasing the risk that a chunk will break off and form a clot that can trigger a heart attack or a stroke.

In a study published in *The Journal of Experimental Medicine* in February, Weyand found that the macrophages of coronary artery disease and stroke patients have a defect that turns them into not only M1s, but sugar-holic M1s to boot. They slurp up too much glucose from the blood, ratcheting their internal metabolic activity into overdrive. That, in turn, prods them into churning out buckets of a pro-inflammatory substance called IL-6, which brings still more angry immune cells to atherosclerotic lesions and perpetuates an inflammatory vicious circle.

In a series of experiments with potential therapeutic implications, Weyand and her colleagues showed that several different biochemical interventions could prevent macrophages' sugar-high-crazed inflammatory rampage in atherosclerotic lesions. The discovery could give rise to new ways of curing or preventing cardiovascular disease. Tests in mice indicate, for example, that it may be possible to design compounds that prevent defective macrophages from hyper-metabolizing glucose, or that moderate the inflammation-inducing effects of that hyper-metabolism.

Weyand's got nothing against macrophages, per se. "We can't live without them," she says.

Leeper likewise bears no grudge. "Macrophages set out with good intentions," he says. "We think they're trying to do the right thing with atherosclerotic plaque, but they choke on it instead."

In a study published in July in *Nature*, Leeper discovered an important reason dead cells pile up in atherosclerotic lesions to begin with: They sport a "don't eat me" signal, in the form of a cell-surface protein called CD47 that deters macrophages' voracious salvos. Irving Weissman, MD, professor of pathology and of developmental biology, and his colleagues have identified high levels of CD47 on cancer cells as a strategy that tumors use to evade immune attack.

Leeper's study found, serendipitously, that CD47 is overexpressed on the dying and dead cells in atherosclerotic plaques,

obstructing macrophages' efforts to clear those cells from the scene. When he and his associates blocked this protein with anti-CD47 antibodies, they were able to counter plaque buildup and vulnerability to rupture in several different mouse models of atherosclerosis. Many mice even experienced regression of their plaques.

His team also found that TNF-alpha, like IL-6 an important pro-inflammatory substance, promotes elevated CD47 expression in dying cells in atherosclerotic tissue. Rendered inedible, the cells die in place and secrete still more TNF-alpha-inducing substances. And so forth.

Leeper notes that people with autoimmune disorders characterized by abundant systemic inflammation, such as rheumatoid arthritis or lupus, are at elevated risk for premature cardiovascular disease. But patients taking anti-TNF drugs for rheumatoid arthritis or lupus have fewer heart attacks and strokes than would otherwise be expected for these patients.

It's already known that aspirin, a nonsteroidal anti-inflammatory drug, lowers cardiovascular risk, and that statin drugs — vaunted for cutting cholesterol production — also exert a pronounced anti-inflammatory effect. But the fact that each of these drugs works by multiple mechanisms makes it hard to prove that it is specifically their anti-inflammatory properties that are producing cardiovascular benefits. Two national trials are enrolling more than 25,000 patients at heightened risk of cardiovascular events to explore whether medications whose effects are known to work only through anti-inflammatory mechanisms can prevent heart attacks and strokes.

In addition, CD47-blocking antibodies are now being administered to cancer patients in early-stage clinical trials underway at Stanford and the University of Oxford. If those antibodies prove safe, they'll be strong candidates for repurposing to combat cardiovascular disease.

Low-grade chronic inflammation is implicated in not just cardiovascular conditions but cancer, Alzheimer's and Parkinson's, Type 2 diabetes and both rheumatoid arthritis and osteoarthritis — age-associated diseases all, with at least one affecting most people age 65 or older. That age — one the great majority of people born in industrialized countries can expect to reach — describes one

Executive Editor:

PAUL COSTELLO

Editor:

ROSANNE SPECTOR

Associate Editor:

KATHY ZONANA

Art/Design Direction:

DAVID ARMARIO DESIGN

Director of Print and Web Communication:

SUSAN IPAKTCHIAN

Writers:

AMY ADAMS

STEPHANIE BRUZZESE

MICHAEL CLAEYS

KRISTA CONGER

ERIN DIGITALE

JENNIE DUSHECK

BRUCE GOLDMAN

LAURA HEATON

RUTHANN RICHTER

SARA WYKES

Copy Editor:

MANDY ERICKSON

Circulation Manager:

ALISON PETERSON

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



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

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

in seven Americans now and will encompass about one in five in 2030, according to the U.S. Census Bureau. So many leaky faucets spell not only big bills to come, but an inflammaging-fueled flood headed our way. If researchers can find the factors underlying this flood, there's hope that the right washers and wrenches can stop the drip and help us all live to a healthy old age. **SM**

— Contact Bruce Goldman at goldmanb@stanford.edu

OPENED WITH CARE

**THE HAND-PAINTED BOXES SENT TO A STANFORD
PATHOLOGIST HOLD TUMOR SAMPLES — AND HOPE**

Eduardo Zambrano's office at Stanford Hospital is overflowing with small, colorful boxes, each of which once contained a tumor sample mounted on a glass slide or embedded in wax. The boxes, covered in suns, stars, flowers and other images of life and hope, were hand-painted in Latin America as a gesture of gratitude from families of sick children living there. "Behind each one of these boxes is a child with cancer, and to know we've been able to help them is very special to me," says Zambrano, MD, chief of pathology at Lucile Packard Children's Hospital Stanford. • In the past 12 years, Zambrano has received nearly 1,000 of these samples from pediatric oncologists in Latin America who treat desperately poor patients. An expert in pediatric solid tumors, he volunteers his time to examine the samples under the microscope and then issue a diagnosis.

The children's cancers are often advanced — typically because they lack an accurate diagnosis or appropriate treatment. Poverty adds other burdens: A patient who had been treated for advanced neuroblastoma returned to the medical center because rats had bitten his feet at home while he slept, Zambrano says.



Eduardo Zambrano reviews tumor samples from pediatric cancer patients in Latin America, which arrive in boxes hand-painted by family members or local artisans.



"Very often the diagnosis from the home country is either incomplete because they don't have the resources to perform the confirmatory tests, or it's wrong because they don't have the expertise in pediatric tumors," says Zambrano, a professor of pathology and of pediatrics at the School of Medicine. "It's frequent that I have to give them a significantly different diagnosis."

Though he has reviewed cases from Mexico, Bolivia, Guatemala, Brazil, Argentina and his native Ecuador, many of the samples come from Venezuela, where he has a long-standing collaboration with a pe-

diatric oncologist whom he texts or emails every day. She sends him photos of children in recovery, as well as notes of thanks. "You are a little angel who helps all of us," reads one in Spanish.

Zambrano has met some of his young patients and their families in Venezuela, though it's become too dangerous to travel there because of political and economic chaos, he says.

"It's a tragedy in Venezuela. For me, it's really an obligation to provide this service to them and a way to pay back for what I received in my childhood in South America" as a member of the "privileged minority," he says. While growing up, he says he witnessed deep inequalities — critically ill poor who were denied access to the hospital — that he hopes now to help address.

Because some of the cases he diagnoses are rare or advanced forms of cancer not often seen here, they also serve as valuable teaching tools.

"These cases have served me tremendously in teaching my residents and fellows," he says. In recent months, he has been working with colleagues both inside and outside of Stanford to obtain financial support for the service.

"I consider it very valuable, and it's something that really moves me," he says. "A lot of meaning would be lost if I couldn't do this work. And it's important to have meaning." — RUTHANN RICHTER

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

Change Service Requested

The beat goes on

AFTER RARE TRANSPLANT, WOMAN CAN HEAR HER HEART IN ANOTHER

Tammy Griffin had cystic fibrosis, a genetic disease that causes mucus to build up in the lungs and other organs. Her lung capacity had diminished so much that she was on oxygen full time. She needed new lungs, and because her damaged lungs had displaced her heart, a heart-lung transplant was her only option.

Linda Karr had right ventricular dysplasia, a genetic disease that causes a dangerously abnormal heart rhythm. She could hardly walk down a hallway without stopping to rest. She needed a heart transplant.

On Feb. 1, both women got the organs they needed. Griffin received a heart and lungs from a deceased donor. And Karr received Griffin's heart. It is only the eighth "domino transplant" of a heart-lung and a heart performed at Stanford, and the first one since 1994.

One surgical team removed the heart and lungs from the deceased donor, a second one implanted them in Griffin and a third team implanted her heart in Karr. Joseph Woo, MD, professor and chair of cardiothoracic surgery, oversaw and coordinated the three teams, as well as leading the second team.

Griffin's heart "was an innocent bystander pushed out of its normal position in the middle of the lungs as her right lung shrank and the left one expanded," says Woo, the Norman E. Shumway Professor in Cardiovascular Surgery. In other words, it could work just fine for someone else.



HEART-LUNG RECIPIENT TAMMY GRIFFIN DONATED HER FORMER HEART TO LINDA KARR.

"I didn't want my heart thrown away," says Griffin, "and I thought, I'll be able to meet the person who has my heart! How many people can say that?"

"We hope this story will raise awareness of how scarce organs are," says Woo. "People are waiting and dying on those transplant lists. We would like to see that change."

Karr's first question for her doctor after surgery was, "How is my heart donor doing?" Six weeks later, she found out, when she and Griffin met for the first time. "I feel as though a world of possibilities opens up now for my future — kind of a second chance in life," Karr told Griffin.

"Me, too. I feel the same way," Griffin responded.

Griffin had the opportunity to hear her old heart beating inside Karr's chest, and Karr promised Griffin she'd take good care of it. "Even though we were strangers before today," she said, "you'll always be part of me." — SARA WYKES

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