

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

Spring 2017

special report

SEX, GENDER AND MEDICINE

Of mice, men and women
Everyone's data matters

Identity

Caring for transgender kids

Surprise

Our brains are not the same

Barbra Streisand

On matters of the heart

Making strides

Academic medicine aims for parity

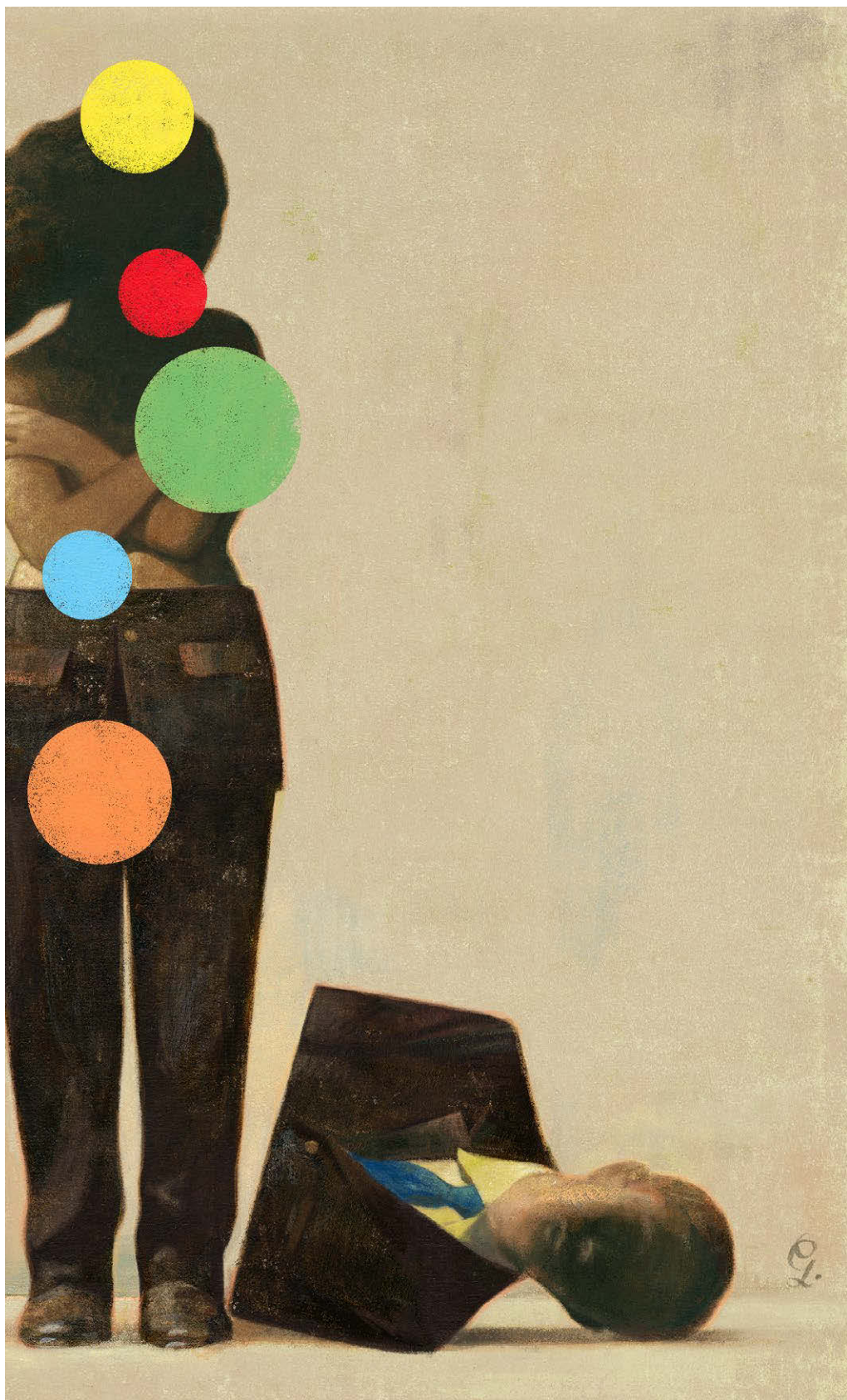
plus

Being frugal

Meet the scientist behind
the \$1 microscope

What ails health care

An excerpt from
An American Sickness



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

Spring 2017



THINK TYPING

A BRAIN-COMPUTER INTERFACE THAT'S FAST AND ACCURATE

One rainy day in October 2007, Dennis Degray was taking out the trash when he slipped, fell and landed on his chin. He severely injured his spinal cord, becoming paralyzed from the neck down. "I've got nothing going on below the collarbones," he says.

But above the collarbones, in the motor cortex of his brain, he now has two implanted electrode arrays, each the size of a baby aspirin. In a recent study, he and two other participants, who have severe limb weakness from amyotrophic lateral sclerosis, demonstrated the fastest, most accurate typing to date using only their brains to control an on-screen cursor.

"This study reports the highest speed and accuracy, by a factor of three, over what's been shown before," says Stanford professor of electrical engineering Krishna Shenoy, PhD, a senior author of the paper,

which was published online in February in *eLife*. "We're approaching the speed at which you can type text on your cellphone."

The study is part of the BrainGate collaboration among Stanford, Brown University, Massachusetts General Hospital, Case Western Reserve University and the Providence VA Medical Center, which aims to provide brain-computer interfaces that help people communicate and move despite neurological disease, neurological injury or limb loss.

Shenoy's lab pioneered the algorithm for the interface, which transmits signals from the brain to a computer via a cable, then translates them into point-and-click commands for an on-screen keyboard. With minimal training, the participants were able to visualize the arm, hand and finger movements necessary to type a letter and then watch as the cursor selected it on the screen.

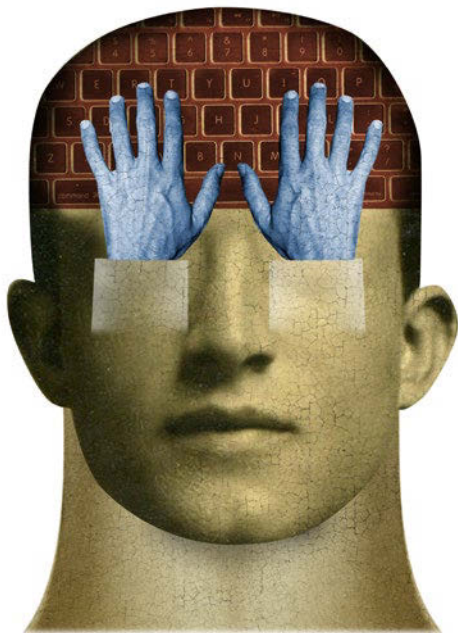
Degray was able to copy sentences and phrases — think "The quick brown fox jumped over the lazy dog" — at a rate of 7.8 words per minute. The other two participants' average rates were 6.3 and 2.7 words per minute. They did not use automatic word-completion software, which likely would have made their typing faster.

"Our study's success marks a major milestone on the road to improving quality of life for people with paralysis," says professor of neurosurgery Jaimie Henderson,

MD, a co-senior author of the study who implanted the devices in two of the three patients. The tiny silicon chips are just over one-sixth of an inch square, with 100 electrodes that penetrate the brain to about the thickness of a quarter and tap into the electrical activity of individual nerve cells in the brain region controlling movement, the motor cortex.

Shenoy says the day is coming, perhaps five years from now, when a wireless brain-computer interface can be fully implanted without cosmetic impact and used around the clock without caregiver assistance. "I don't see any insurmountable challenges," he says. "We know the steps we have to take to get there."

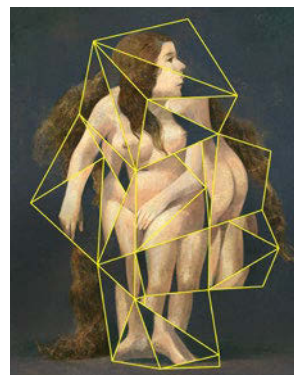
Meanwhile, those who have tested the latest typing interface are enthusiastic. "This is like one of the coolest video games I've ever gotten to play with," says Degray. "And I don't even have to put a quarter in it." — BRUCE GOLDMAN



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

SPECIAL REPORT

Sex, gender and medicine



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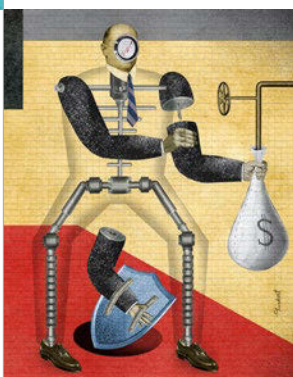
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It's a long-standing debate: Are individual differences the result of our genes or our environment? Nature or nurture? For psychologists seeking to understand why we behave as we do, and for scientists and physicians looking for the underlying causes of disease and illness, it's a vitally important question.

In recent years, both sides have capitulated to what seems like an obvious compromise: It's both. Our genes *and* our environment play leading roles in shaping who we are. But to Siddhartha Mukherjee, physician and author of *The Gene*, this compromise is “an armistice between fools.” The answer — nature or nurture — depends on the question.

Take sex and gender. The genes that govern gender identity are hierarchically organized, Mukherjee argues. At the top, nature acts alone. A variation in a single chromosome determines whether our sex is male or female.

Geneticist Nettie Stevens, a Stanford graduate, first came to this conclusion in 1905 based on her pioneering discovery that male mealworms produced sperm with either X or Y chromosomes, while females produced eggs with only X chromosomes. At the time, it was commonly believed that sex was determined by environmental factors, such as maternal nutrition. Stevens showed that sex was determined by nature, and nature alone.

Gender, on the other hand, is determined lower in Mukherjee's hierarchy. There, genes interact continually with the forces of history, society and culture, making gender and gender identity not an either/or, but a spectrum based on an infinite number of influences and interactions.

Consider that women consistently outlive men in developed countries — a robust finding spanning time, place, religion and political regime. Genes and environment each play an important role, but together they cannot explain the gap.

Looking at mortality data for 187 countries over the past five decades, Stanford Medicine's Mark Cullen found that women consistently exhibit a greater survival “resilience” to social and environmental adversity. This lends support to the “socio-biologic” explanation. Women live longer because they are hardwired to demonstrate social behaviors that promote survival, such as nesting and family protection. The female survival advantage is not the result of the simple addition of nature plus nurture, but rather of a complex interaction between the two.

Unraveling the complex interplay of cause and effect is at the heart of Stanford's precision health vision. To keep people healthy, we must first understand the basis of health and disease — to explore nature and nurture in a way that goes beyond the outdated dichotomy and incorporates sex and gender as essential factors influencing individual differences.

Keep reading to learn about some of the ways that we at Stanford Medicine are working to advance the scientific understanding of sex and gender — from nature to nurture and back again — to improve the health of all individuals.

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

The caffeinated fountain of youth

A RECENT STUDY by School of Medicine researchers implicates an inflammatory process found in older adults in cardiovascular disease, but the process is dampened among those who drink more caffeinated beverages.

"More than 90 percent of all non-communicable diseases of aging are associated with chronic inflammation," including cancers, dementias and cardiovascular disease, says lead author David Furman, PhD, consulting associate professor at the Stanford Institute for Immunity, Transplantation and Infection.

The study, published in February in *Nature Medicine*, showed that two clusters of genes whose activity is associated with the inflammatory protein IL-1-beta are more active in older people. Those with high activity in one or both clusters were more likely to have high blood pressure, increased activity of possibly damaging molecules called free radicals



and several breakdown products of nucleic acids that can be produced by free-radical action; a follow-up study revealed they were more likely to have stiff arteries.

Those with low cluster activity were eight times more likely to report having a family member who lived to age 90. They also tended to drink more caffeinated beverages. The researchers verified that their blood contained more caffeine and a number of its breakdown products, which, they showed in a lab experiment, prevented the inflammatory action of the nucleic-acid breakdown products.

Stanford scientists have developed nanostraws

600 times smaller than a human hair to sample the contents of cells. More at <http://stan.md/2qwGLRk>

Collaboration station

THE SCHOOL OF MEDICINE has launched a center to support collaborations between faculty and Silicon Valley technology companies to develop, test and implement new digital health tools.

The Center for Digital Health will serve as a clearing-house for faculty and companies that are interested in working together, enable faculty to research the efficacy of technological interventions efficiently, and provide training and education. Clinical associate professor of medicine Sumbul Desai, MD, is the center's executive director.

Old drugs, new tricks
RNA VIRUSES ARE A TRICKY BUNCH. Their replication process is error-prone, which means they mutate quickly — all the better to evade typical antiviral medications. Plus the “one drug, one bug” approach to developing antivirals is slow and costly, and there’s inevitably a new viral threat on the horizon.

So Shirin Einav, MD, Stanford assistant professor of infectious diseases and of microbiology and immunology, is trying a different approach, one that’s not susceptible to drug resistance: making host proteins less hospitable to viruses. She recently led a study showing that a combination of two cancer drugs inhibited both dengue and Ebola in mice. In a lab dish, the combination was also effective against West Nile and Zika viruses.

The drugs erlotinib and sunitinib

are used to treat various types of cancers. They also inhibit the activity of two enzymes that strengthen viruses’ bonds to host proteins, regulating their travel inside our cells.

The drug combination was effective in preventing fatal progression of dengue in 65 to 100 percent of mice, depending on the experiment, and in preventing the fatal progression of Ebola in half of them. Each drug was substantially less effective alone.

The study was published online in February in the *Journal of Clinical Investigation*.

TUSKEGEE’S LEGACY

IN THE INFAMOUS Tuskegee study, 399 African-American men with syphilis were passively monitored by medical researchers for 40 years, despite the availability of effective treatment for most of that time.

Disclosure of the study in 1972 correlates with an increase in medical mistrust and mortality among African-American men, according to a working paper for the National Bureau of Economic Research by Stanford assistant professor of medicine Marcella Alsan, MD, PhD, and University of Tennessee economist Marianne Wanamaker, PhD.

Life expectancy at age 45 for black men fell by 1.4 years after the study was revealed, accounting for 35 percent of the disparity between black and white men in 1980.

Alsan has now launched a pilot project to evaluate the willingness of black men to seek preventive medical screenings.

Pain gain

A COMMERCIALLY AVAILABLE DRUG APPROVED TO treat opioid-induced constipation may also block two of the most problematic side effects of opioids: a growing tolerance to them and a paradoxical increased sensitivity to pain. Patients with these side effects may require ever-larger doses, raising their risks of addiction and of respiratory failure.

School of Medicine researchers led by assistant professor of anesthesiology, perioperative and pain medicine and of neurosurgery Gregory Scherrer, PhD, PharmD, first demonstrated in mice that knocking out the opioid receptors in the pain neurons outside the brain and spinal cord — leaving those in the central nervous system intact — allowed the mice to receive long-lasting pain relief from morphine without the two detrimental side effects. They then administered the constipation drug methyl-naltrexone bromide, which blocks the opioid receptors in the mice’s peripheral pain neurons but not those in the central nervous system, with similarly successful results.

Scherrer is the senior author of the study, published in the February issue of *Nature Medicine*.



Tumor sentinels

IN ONE TYPE OF CANCER IMMUNOTHERAPY, A MEDICAL TEAM harvests a patient's own T cells from blood, genetically engineers them to boost their cancer-fighting properties, then releases them back into the patient's bloodstream. The technique shows promise, but researchers don't necessarily know how well, or even whether, it is working until months later.

A new Stanford-led study allows researchers, for the first time, to see where immunotherapy cells go in the human body: whether they have found a tumor, how many cells have arrived at the tumor and whether they are alive.

"This is the first demonstration in humans of actually noninvasively imaging the immune system in action," says Sanjiv "Sam" Gambhir, MD, PhD, professor and chair of radiology and senior author of the study, which was published in January in *Science Translational Medicine*.

In the culmination of a 10-year effort, the researchers engineered the T cells to better recognize the patient's cancer cells, then added a "reporter gene" that made a protein they could see with a positron emission tomography scan. The protein lit up on the scan, revealing how many T cells had reached the tumor. In one patient, the cells migrated both to a known tumor and an unknown one.

Patients can be repeatedly imaged to track T cell behavior over time, which will allow researchers to better understand and refine immunotherapy.

THE 1-CENT LAB

THE SURVIVAL RATE OF BREAST CANCER PATIENTS in low-income nations is 40 percent. In developed nations, it's twice that. Malaria, tuberculosis and HIV all tell similar stories. With better access to inexpensive diagnostics, those narratives could be changed.

Researchers at the School of Medicine have developed a cheap, reusable "lab on a chip" that is expected to cost as little as 1 cent per chip to produce.

The system has two parts: a silicone microfluidic chamber for housing cells and an electronic strip printed on flexible polyester using a regular inkjet printer and commercially available conductive nanoparticle ink. It separates cells based on their intrinsic electrical properties using a process called dielectrophoresis.

The technology could usher in a diagnostics revolution like that brought on by low-cost genome sequencing, says Ron Davis, PhD, professor of biochemistry and of genetics.

Davis is the senior author of a study describing the technology, published in February in *Proceedings of the National Academy of Sciences*.



3-D anatomy

GINA MILNER needed a new heart valve, and her doctors hoped to perform a minimally invasive procedure rather than open-heart surgery. But because Milner had had a heart defect repaired in childhood, her anatomy was complex. It was difficult to plan her surgery using standard imaging.

So Milner became the first patient at Lucile Packard Children's Hospital Stanford to benefit from software that turned her CT scans into a 3-D image. "We were able to tell that we would have enough space to work with," says clinical associate professor of cardiothoracic surgery Katsuhide Maeda, MD, who performed the less-invasive surgery. Virtual-reality technologies, he says, "have big advantages for our patients."

'We were able to tell that we would have enough space to work with.' Virtual-reality technologies 'have big advantages for our patients.'

of mice, and men

IT WAS 2012, AND SOME OF AMY BRAUN'S LAB MICE WEREN'T BEHAVING NORMALLY. THIS WAS VERY EXCITING. • Rather than scampering about investigating their surroundings and introducing themselves to other mice, whiskers quivering, they eschewed social interactions and ran in circles. Placed into a water tank, they appeared disoriented and confused. Unlike their peers, they swam hesitantly along the walls, unable to find and remember the location of a platform hidden underneath the surface. They were pale shadows of their mousey selves.

It was exactly what the researchers, who were studying brain development in autism and schizophrenia, had expected to see. But there was just one — major — hitch.

"We realized, when we looked more closely," says Braun, "that we were seeing this aberrant behavior only in male mice. The females behaved like our control animals. We thought, 'Well, this is sort of weird.' Later we realized that the weird thing was that we actually looked at the female animals at all."

At the time, many researchers focused their studies only on male lab animals, under the belief that the normal hormonal cycling of female animals would render them more biologically variable. They worried that this perceived variability would make it harder to achieve statistical significance in their studies. A 2010 study in *Nature* found bias toward the use of male animals in eight out of 10 research disciplines.

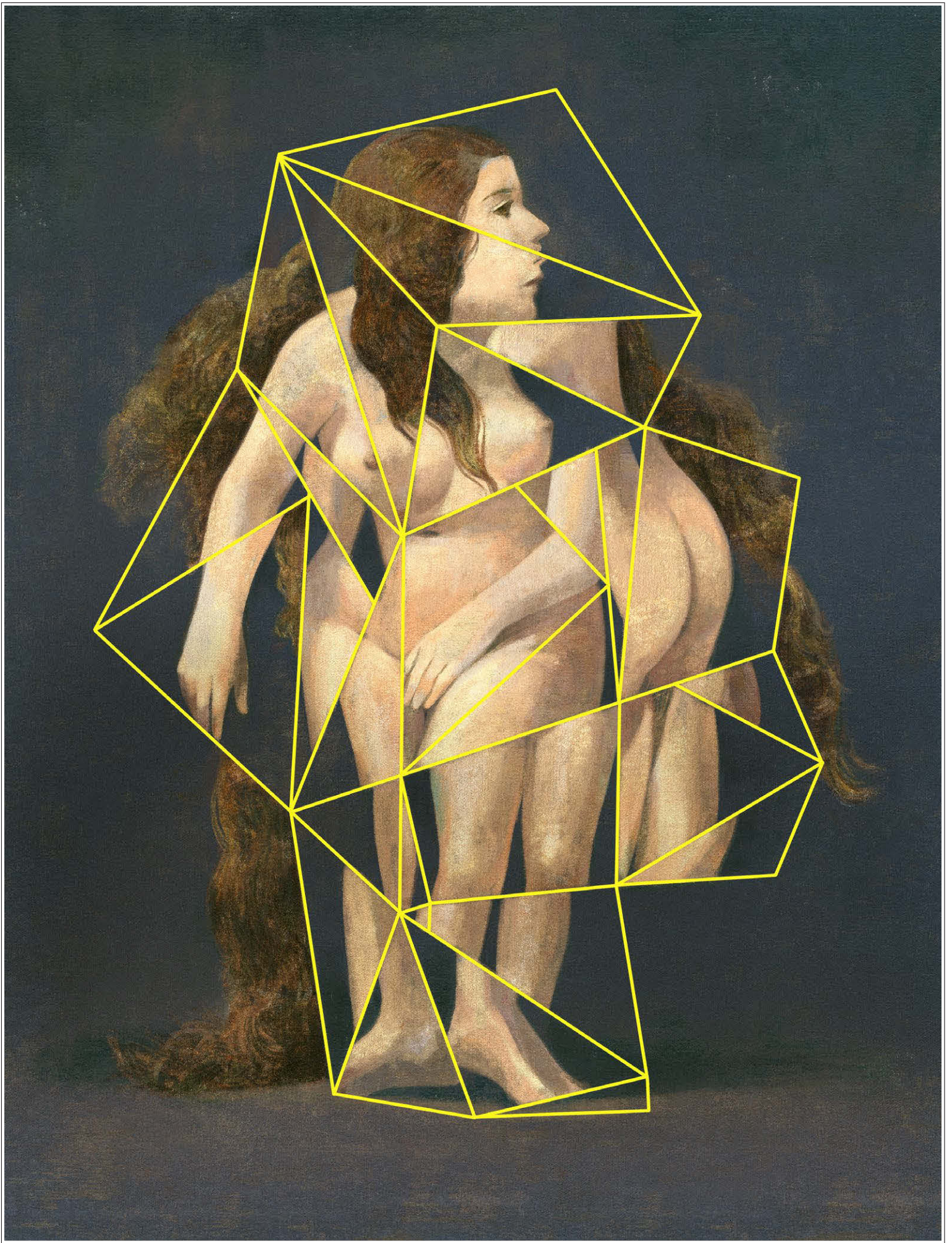
The problem was particularly egregious in Braun's field of neuroscience, in which studies of male animals outnumbered those of female animals nearly sixfold. Colleagues who saw Braun's data counseled a simple fix: Leave out the results on the

women

MAKING RESEARCH MORE INCLUSIVE

BY KRISTA CONGER

ILLUSTRATION BY GÉRARD DUBOIS



females. That didn't sit well with Braun, a graduate student in the laboratory of Theo Palmer, PhD, an associate professor of neurosurgery.

"I thought 'Wait, what? This is all biology. Let's instead figure out what is going on.'"

IT'S OBVIOUS THAT SEX is important in health, health care and medical research. Women are more likely to suffer from autoimmune diseases, have osteoporosis and be diagnosed with depression and anxiety; men are more likely to develop Parkinson's disease and cardiovascular disease early in life. Knowing predispositions like these can help physicians make a diagnosis or researchers develop new therapies. Yet medical research has usually left females out.

And an increasing body of research suggests that the influence of a person's biological sex on their health is just the tip of the iceberg. Hovering just beneath the surface is a mixture of behaviors, expectations, cultural norms and attitudes that together define a given individual's gender. Gender is inextricably linked to sex, but not defined by it. And it indisputably affects health.

For example, a 2016 study from a group of Canadian researchers suggested that successful recovery from acute coronary syndrome (a term describing a blockage of blood flow to the heart, as happens during a heart attack) was dependent not on whether the patient was male or female, but rather, on each person's gender characteristics: Patients with more

research studies, but it has no such requirement for gender. Yet.

"Both sex and gender influence human health and disease," says Janine Clayton, MD, the director of the National Institutes of Health's Office of Research on Women's Health. "It is increasingly clear that it is both an ethical and scientific imperative to conduct research and report on the results for both men and women."

There's just one tiny little problem, points out Stanford professor of medicine Marcia Stefanick, PhD.

"We don't know how to measure gender," says Stefanick, director of the Stanford Women and Sex Differences in Medicine, or WSDM (pronounced "wisdom"), Center. "Sex is generally assigned at birth, based on external genitalia, after which a broad range of biological, particularly reproductive, sex differences are assumed. Individuals are then, usually, forced into a binary model of gender — with distinct masculine and feminine categories — when the possibilities are much broader and more expansive."

Stefanick and Stanford's Londa Schiebinger, PhD, argue that gender is instead a point on a continuum with infinitesimal gradations. Together they are developing a way to measure gender in such a way that it can be accurately correlated to health outcomes. If successful, their approach could transform how medicine is practiced.

"Basically, we want to blast the standard attitudes about masculinity and femininity out of the water," says Schiebinger, who is the John L. Hinds Professor of History of Sci-

'WE WANT TO BLAST THE STANDARD ATTITUDES ABOUT MASCULINITY AND FEMININITY

traditionally feminine traits, such as responsibility for caregiving, were more likely than those with more traditionally masculine traits, such as being the primary income earner for their households, to suffer another coronary episode or die within the following year, regardless of their biological sex.

Governmental and funding agencies are taking note of this and other examples of gender and sex disparities. The World Health Organization urges the incorporation of gender into health care policy worldwide and, in 2010, the Canadian Institutes of Health Research established policies requiring health and medical researchers to include both sex and gender as critical variables in any planned studies or clinical trials, as did the European Commission in 2013. In 2016, the U.S. National Institutes of Health began requiring that grant proposals include information as to how sex will be incorporated as a biological variable in

ence and the former director of Stanford's Clayman Institute for Gender Research. "We want to get rid of the notion that you can assume there is a prepackaged set of characteristics that belong to men or to women. We want to develop a new instrument to measure gender that will allow us to better understand how gender and sex interact to impact health."

It would be difficult to argue that Braun's lab mice have a gender. Most researchers would agree that their behavior is governed primarily by biology, rather than by the societal expectations of their furry cage mates or their own mouse-conceived ideas of "self." But in people, sex and gender together make up a complex stew of biology and behavior that can be difficult to swallow for researchers, who want simple answers.

As Braun's experience shows, although it's much easier to



AMY BRAUN'S COLLEAGUES SUGGESTED OMITTING HER RESULTS ON FEMALE LAB MICE. INSTEAD, SHE DECIDED TO FIGURE OUT WHY THEY BEHAVED DIFFERENTLY THAN THE MALES.

OUT OF THE WATER.'

forge ahead with blinders on, doing so can vastly compromise a study's findings and overlook critical aspects of biology.

So how to proceed?

To begin with, it's important to define the terms accurately to avoid confusion. Even many research articles, and researchers, refer to gender when they mean sex.

Sex is a biological trait that is determined by the specific sex chromosomes inherited from one's parents. In humans, male sex is determined (with a few exceptions) by the presence of the Y chromosome. A gene on the Y chromosome directs the differentiation of the fetal gonads into testes, resulting in the production of testosterone — which affects many of the body's tissues — early in development. People with one X and one Y chromosome, or variants like XXY or XYY, are typically male, while those who have solely X chro-

mosomes are usually female. People have a sex; animals have a sex; all tissues, including the fetal placenta, have a sex; even individual cells have a sex.

Gender, on the other hand, is socially, culturally and personally defined. It includes how individuals see themselves (gender identity), how others perceive them and expect them to behave (gender norms), and the interactions (gender relations) that they have with others. Often one's gender aligns with one's sex: Men tend to assume more masculine behaviors and traits, and to be seen as masculine by others around them, for example. But not always. Increasingly, researchers like Stefanick and Schiebinger are realizing that both men and women exhibit a spectrum of gender traits that aren't purely masculine or feminine.

Stefanick and Schiebinger refer to these characteristics as "gender variables" that are distinct from the overly broad and less helpful concepts of masculinity or femininity. They include, among others, consideration of the degree of responsibility for caregiving a person assumes; whether a person describes himself or herself as competitive or communal, empathetic or ex-

pressive; and the degree of social support one receives.

“We want to get rid of the notion that gender can be reduced to ‘masculine’ or ‘feminine’ based on a prepackaged set of characteristics,” says Schiebinger. “Instead we want to open that package to find ways to measure each characteristic individually.”

THERE ARE MANY EXAMPLES of the effect of gender, and gender norms, on health. It’s becoming well-known that the high-heeled shoes favored by many women can cause lasting damage to the wearer’s feet. Others examples are more subtle, such as the fact that American men who conform to what are perceived as traditionally masculine traits may avoid well-care visits with their physicians, drink and drive, engage in risky sexual practices or take on inherently dangerous occupations.

As a result of the interaction of these gender variables with biological factors, American men can expect to live about five fewer years than American women. They experience higher rates of mortality than do women for the majority of the 15 most common causes of death, including heart disease, cancer, accidents, suicide and homicide.

Conversely, “feminine” traits traditionally encompass the emotionally and physically stressful caregiving for children and elderly parents. Women frequently assume a greater portion of household tasks regardless of whether they work outside the home, leaving little time for exercise or other forms of self-care. Overall, they are often lower in social status, which may help explain why they are more likely to suffer from depression, recover more poorly from cardiac events and live with higher rates of osteoporosis.

The researchers conducting the Canadian study of acute coronary syndrome went beyond “masculine” and “feminine,” and instead asked the patients to answer a series of questions to derive a composite measure of gender on a scale of 1 to 100. To do so, they used a measure developed in 1974 at Stanford called the Bem Sex Role Inventory.

The lower the score, the more traits the patient displayed that are typically considered to be more masculine, such as assertiveness. Higher scores included traditionally more feminine traits, such as being more expressive. The use of the scale allowed each person to be assigned a gender on a continuum.

The researchers found that, despite the fact that men overall tend to die younger than women, those cardiac patients with more feminine roles and personality traits fared

much more poorly during the yearlong recovery period than those with more masculine identities — regardless of their biological sex.

“Basically it showed that if you are a masculine man or a masculine women, you recover more readily than if you are a feminine man or a feminine woman,” says Stefanick. “But this study used a set of questions that we feel are too limiting and based on older ideas of gender roles. Our concepts about gender have been evolving so fast that the definitions can’t keep up.”

“We really need a big rethink on gender and health,” says Schiebinger. “Sex and gender interact; gender behaviors — such as a person’s choice of shoes — can shape biology and biology certainly influences gender.”

Like gender, the influence of sex on health and biology runs deep. At the most basic level, it controls

whether, when and how our genes are made into proteins. These proteins control how a cell functions, interacts and communicates with its neighbors. There’s a hormonal aspect to sex differences, as well. Varying levels of testosterone and estrogen can affect the biology of many tissues throughout the body.

“Sex differences are important from the cellular level up,” says Stefanick. “We really need to investigate the genetics and cell biology to truly understand the implications of these differences.”

‘OUR CONCEPTS ABOUT

Or, in Braun’s case, the level of the placenta. She and her colleagues in Palmer’s lab were analyzing the effect of infection during pregnancy on the placenta and its role in supporting fetal development, brain structure and function of the resulting offspring. They were interested because there’s a correlation in humans between maternal illness during early pregnancy and the development of neurodevelopmental disorders like autism and schizophrenia in the child.

Fascinatingly, both sexes of the mice she was studying had similar structural brain abnormalities, but only the males displayed behaviors that mimicked the human disorders — a biological quirk that would have been missed if female mice had been excluded.

“I wanted to know why; I wanted to understand this,” says Braun. “What if we have accidentally mimicked something that is relevant to the human disorder? You can’t automati-

cally extrapolate your results to both sexes if you don't even test the females."

For decades, women were largely excluded from clinical trials intended to test the safety and efficacy of potential therapies. Like female lab mice, they were considered to be too complex due to monthly hormonal fluctuations. In 1977, the Food and Drug Administration issued guidelines urging against the inclusion of women of childbearing age in clinical trials to avoid unintentionally administering unproven medications to a developing embryo.

Ironically, however, these same researchers assumed that medications or interventions that got the thumbs-up after testing in men would work the same way in women. It was an insidious, and dangerous, double standard. Of 10 drugs recently recalled after approval due to adverse effects in humans, eight have been found to affect women more severely than men.

Things have been changing, but slowly. In 1994 the National Institutes of Health mandated the inclusion of women and minorities in clinical research that they fund. But although women now make up more than half of clinical trial participants, many published studies still fail to stratify their results to identify sex-specific side effects or outcomes. These problems also extend to the preclinical research on laboratory animals, tissues and cells that precede clinical trials. Often researchers neglect to even record or report the sex of the animals or cells they've used in their studies.

concluded in the report's executive summary.

"We need to debunk the myth that females are mysteriously complex," says Braun, "and we need to increase the literacy around the concepts of sex and gender. They are not the same. Frankly, I think a lot of researchers just don't want to say the word 'sex.' 'Gender' is more comfortable, and more fancy-sounding. But gender is its own biological variable, and we have to understand that and think critically about it."

Stefanick and Schiebinger have been

working to integrate sex and gender into research at

Stanford for several years, originally with a program in the Department of Obstetrics and Gynecology that focused on women's health. The WSDM Center was launched in 2013, and the center has awarded 22 seed grants of between \$20,000 and \$35,000 to Stanford researchers to encourage them to incorporate questions about sex and gender differences into their research.

"I want Stanford to be the leader in the world on this topic," says Stefanick. "We have the potential to achieve this."

In 2017 the WSDM Center awarded eight grants to researchers to investigate topics as diverse as the impact of eye disease and visual function on women's health, the differences in normal immune function between men and women, and the effect of sex on treatment strategy and decision-making in patients with inflammatory bowel disease.

The center is also raising awareness of the roles of sex and

GENDER HAVE BEEN EVOLVING SO FAST THAT THE DEFINITIONS CAN'T KEEP UP.'

"We rely on preclinical research as the foundation for translation to clinical studies; consequently, the prevailing gaps in knowledge about female biology may hinder efforts to turn discovery into health benefits for women. By studying both sexes and reporting on the results for women and men separately, scientific questions will be more fully answered, driving the development of sex-appropriate treatments," says the NIH's Clayton.

In 2001, the Institute of Medicine published a report titled "Exploring the Biological Contributions to Human Health: Does Sex Matter?" The authors of the report recommended that the effects of both sex and gender on biology and health should be studied along the human life span, and urged researchers and publishers to be clear in their language. "There is inconsistent and often confusing use of the terms sex and gender in the scientific literature and the popular press," they

gender in health among medical and graduate students. A recently piloted 90-minute training on sex, gender and sexuality will be required of Stanford medical students next year; however, Stefanick believes much more discussion on the impact of sex and gender on health outcomes is needed. Research scientists are rarely taught about it.

"Education about these topics is vital," says Schiebinger. "Information about sex and gender needs to be fully integrated into the medical curriculum. Right now it isn't."

For her part, Braun, who received a seed grant from the WSDM Center in December 2015, is continuing her investigation into the effects of maternal infection on the prenatal brain. Her results suggest that perhaps something was happening in utero to which the male fetuses were more vulnerable. They also contrast with the sometimes-floated idea

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

the cognitive differences between men and women

T W MINDS O

WHEN NIRAO SHAH DECIDED IN 1998 TO STUDY SEX-BASED DIFFERENCES IN THE BRAIN USING UP-TO-THE-MINUTE MOLECULAR TOOLS, HE DIDN'T HAVE A TON OF COMPETITION. BUT HE DID HAVE A GOOD REASON.

"I wanted to find and explore neural circuits that regulate specific behaviors," says Shah, then a newly minted Caltech PhD who was beginning a postdoctoral fellowship at Columbia. So, he zeroed in on sex-associated behavioral differences in mating, parenting and aggression.

"These behaviors are essential for survival and propagation," says Shah, MD, PhD, now a Stanford professor of psychiatry and behavioral sciences and of neurobiology. "They're innate rather than learned — at least in animals — so the circuitry involved ought to be developmentally hardwired into the brain. These circuits should differ depending on which sex you're looking at."

His plan was to learn what he could about the activity of genes tied to behaviors that differ between the sexes, then use that knowledge to help identify the neuronal circuits — clusters of nerve cells in close communication with one another — underlying those behaviors.

At the time, this was not a universally popular idea. The neuroscience community had largely considered any observed sex-associated differences in cognition and behavior in humans to be due to the effects of cultural influences. Animal researchers, for their part, seldom

BY BRUCE GOLDMAN

ILLUSTRATION BY GÉRARD DUBOIS PHOTOGRAPH BY LENNY GONZALEZ

Fig #01

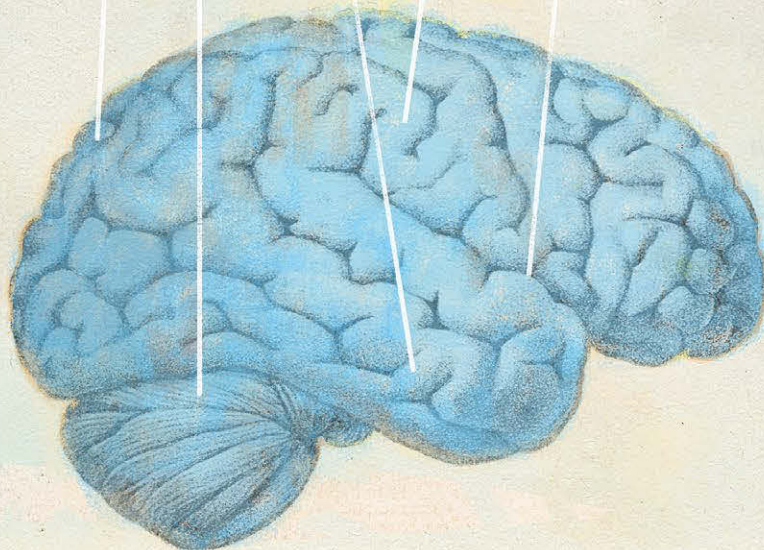
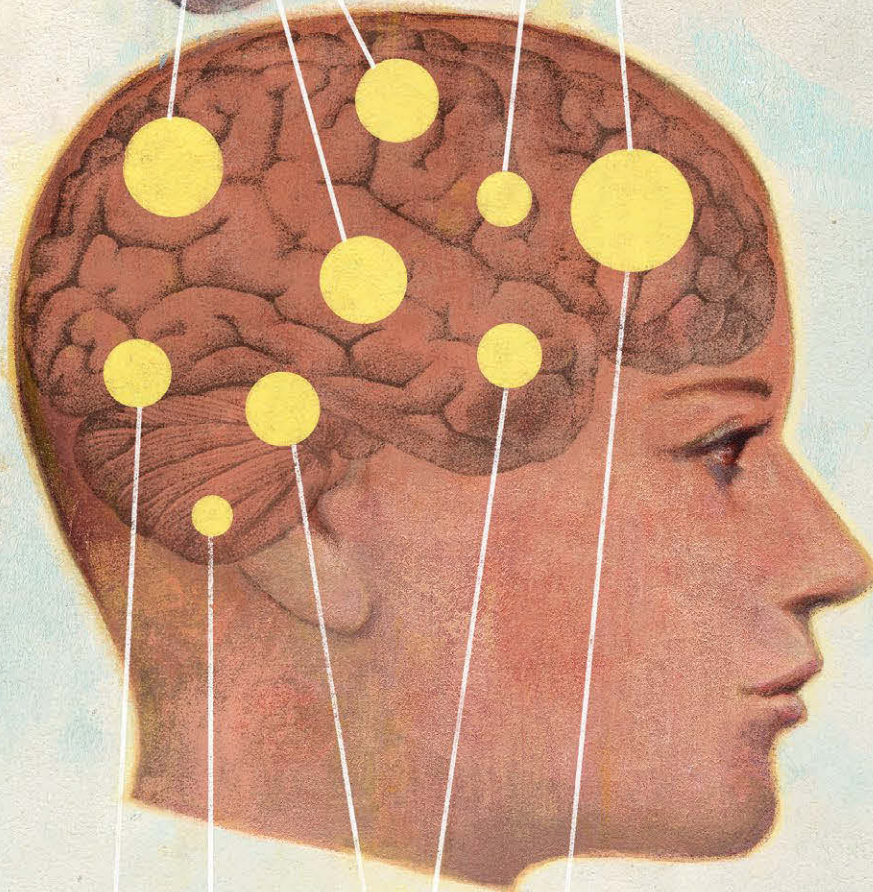
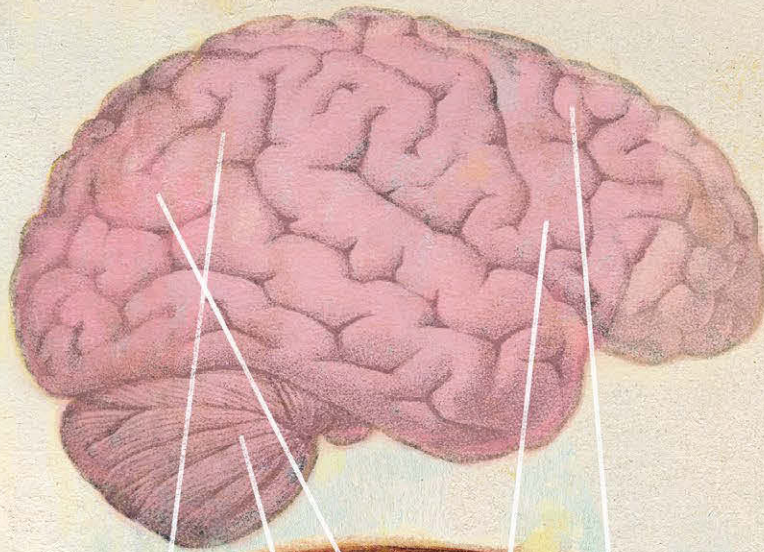


Fig #02

even bothered to use female rodents in their experiments, figuring that the cyclical variations in their reproductive hormones would introduce confounding variability into the search for fundamental neurological insights.

But over the past 15 years or so, there's been a sea change as new technologies have generated a growing pile of evidence that there are inherent differences in how men's and women's brains are wired and how they work.

Not how *well* they work, mind you. Our differences don't mean one sex or the other is better or smarter or more deserving. Some researchers have grappled with charges of "neurosexism": falling prey to stereotypes or being too quick to interpret human sex differences as biological rather than cultural. They counter, however, that data from animal research, cross-cultural surveys, natural experiments and brain-imaging studies demonstrate real, if not always earthshaking, brain differences, and that these differences may contribute to differences in behavior and cognition.

BEHAVIOR DIFFERENCES

In 1991, just a few years before Shah launched his sex-differences research, Diane Halpern, PhD, past president of the American Psychological Association, began writing the first edition of her acclaimed academic text, *Sex Differences in Cognitive Abilities*. She found that the animal-research literature had been steadily accreting reports of sex-associated neuroanatomical and behavioral differences, but those studies were mainly gathering dust in university libraries. Social psychologists and sociologists poo-hooed the notion of any fundamental cognitive differences between male and female humans, notes Halpern, a professor emerita of psychology at Claremont McKenna College.

In her preface to the first edition, Halpern wrote: "At the time, it seemed clear to me that any between-sex differences in thinking abilities were due to socialization practices, artifacts and mistakes in the research, and bias and prejudice. ...

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After reviewing a pile of journal articles that stood several feet high and numerous books and book chapters that dwarfed the stack of journal articles ... I changed my mind."

Why? There was too much data pointing to the biological basis of sex-based cognitive differences to ignore, Halpern says. For one thing, the animal-research findings resonated with sex-based differences ascribed to people. These findings continue to accrue. In a study of 34 rhesus monkeys, for example, males strongly preferred toys with wheels over plush toys, whereas females found plush toys likable. It would be tough to argue that the monkeys' parents bought them sex-typed toys or that simian

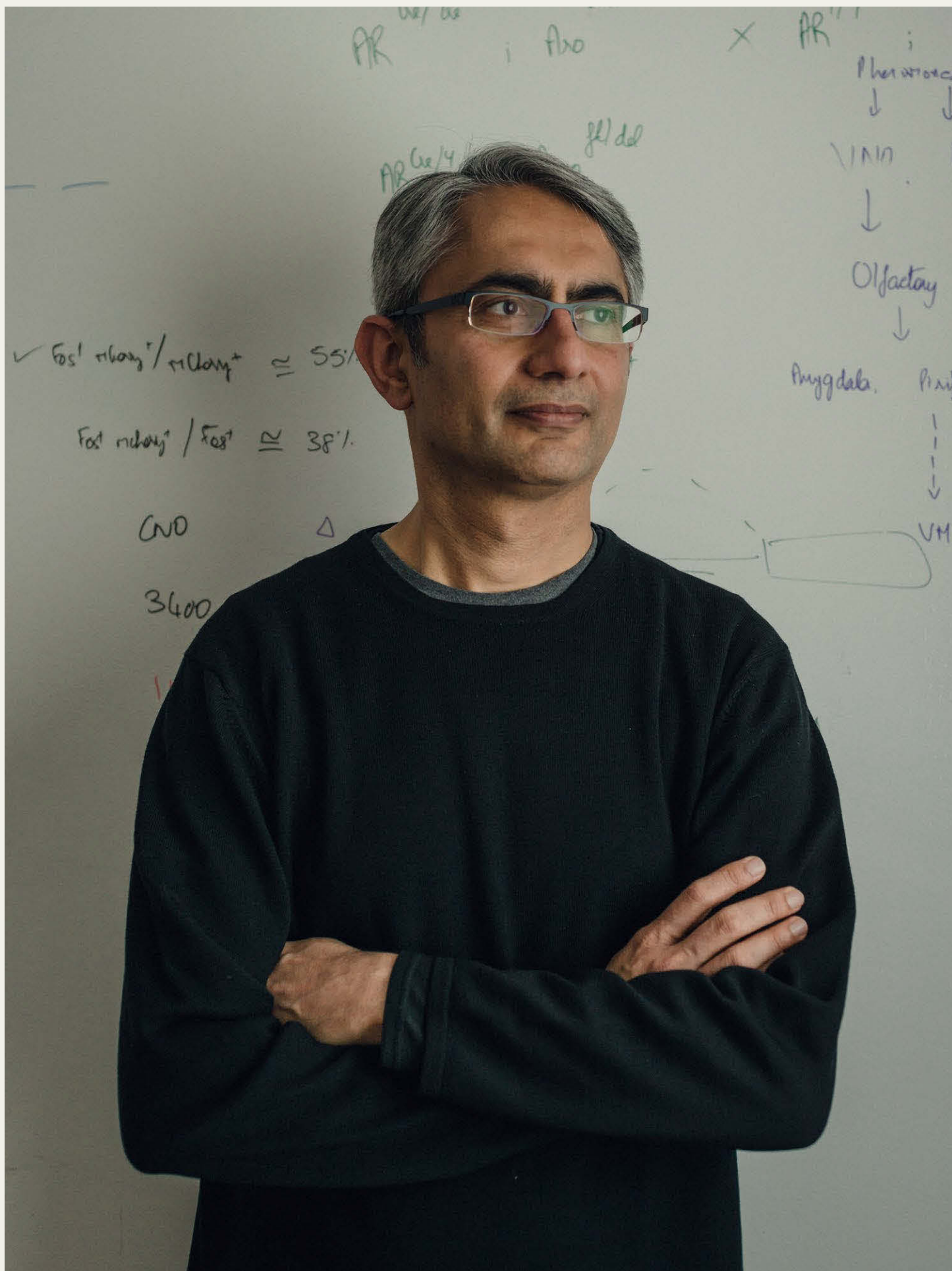
society encourages its male offspring to play more with trucks. A much more recent study established that boys and girls 9 to 17 months old — an age when children show few if any signs of recognizing either their own or other children's sex — nonetheless show marked differences in their preference for stereotypically male versus stereotypically female toys.

Halpern and others have cataloged plenty of human behavioral differences. "These findings have all been replicated," she says. Women excel in several measures of verbal ability — pretty much all of them, except for verbal analogies. Women's reading comprehension and writing ability consistently exceed that of men, on average. They outperform men in tests of fine-motor coordination and perceptual speed. They're more adept at retrieving information from long-term memory.

Men, on average, can more easily juggle items in working memory. They have superior visuospatial skills: They're better at visualizing what happens when a complicated two- or three-dimensional shape is rotated in space, at correctly determining angles from the horizontal, at tracking moving objects and at aiming projectiles.

Navigation studies in both humans and rats show that females of both species tend to rely on landmarks, while males more typically rely on "dead reckoning": calculating one's position by estimating the direction and distance traveled rather than using landmarks.

NIRAO SHAH STUDIES HOW SOME GENES AT WORK IN THE MOUSE BRAIN DETERMINE SEX-SPECIFIC BEHAVIORS.
LIKE THE FEMALE TRAIT OF PROTECTING THE NEST FROM INTRUDERS. HE SAYS
MOST OF THESE GENES HAVE HUMAN ANALOGUES BUT THEIR FUNCTION IS NOT FULLY UNDERSTOOD.



Many of these cognitive differences appear quite early in life. “You see sex differences in spatial-visualization ability in 2- and 3-month-old infants,” Halpern says. Infant girls respond more readily to faces and begin talking earlier. Boys react earlier in infancy to experimentally induced perceptual discrepancies in their visual environment. In adulthood, women remain more oriented to faces, men to things.

All these measured differences are averages derived from pooling widely varying individual results. While statistically significant, the differences tend not to be gigantic. They are most noticeable at the extremes of a bell curve, rather than in the middle, where most people cluster. Some argue that we may safely ignore them.

But the long list of behavioral tendencies in which male-female ratios are unbalanced extends to cognitive and neuropsychiatric disorders. Women are twice as likely as men to experience clinical depression in their lifetimes; likewise for post-traumatic stress disorder. Men are twice as likely to become alcoholic or drug-dependent, and 40 percent more likely to develop schizophrenia. Boys’ dyslexia rate is perhaps 10 times that of girls, and they’re four or five times as likely to get a diagnosis of autism spectrum disorder.

Could underlying biological differences — subtle though they may be for most of us — help explain these gaping between-sex imbalances in the prevalence of mental disorders and account for the cognitive and behavioral differences observed between men and women?

HOW OUR BRAINS DIFFER

The neuroscience literature shows that the human brain is a sex-typed organ with distinct anatomical differences in neural structures and accompanying physiological differences in function, says UC-Irvine professor of neurobiology and behavior Larry Cahill, PhD. Cahill edited the 70-article January/February 2017 issue of the *Journal of Neuroscience Research* — the first-ever issue of any neuroscience journal devoted entirely to the influence of sex differences on nervous-system function.

Brain-imaging studies indicate that these differences extend

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well beyond the strictly reproductive domain, Cahill says. Adjusted for total brain size (men’s are bigger), a woman’s hippocampus, critical to learning and memorization, is larger than a man’s and works differently. Conversely, a man’s amygdala, associated with the experiencing of emotions and the recollection of such experiences, is bigger than a woman’s. It, too, works differently, as Cahill’s research has demonstrated.

In 2000, Cahill scanned the brains of men and women viewing either highly aversive films or emotionally neutral ones. The aversive films were expected to trip off strong negative emotions and concomitant imprinting in the amygdala, an almond-shaped structure found in each brain hemisphere. Activity in the amygdala during the viewing experience, as expected, predicted subjects’ later ability to recall the viewed clips. But in women, this relationship was observed only in the left amygdala. In men, it was only in the right amygdala. Cahill and others have since confirmed these results.

Discoveries like this one should ring researchers’ alarm buzzers. Women, it’s known, retain stronger, more vivid memories of emotional events than men do. They recall emotional memories more quickly, and the ones they recall are richer and more intense. If, as is likely, the amygdala figures into depression or anxiety, any failure to separately analyze men’s and women’s brains to understand their different susceptibilities to either syndrome would be as self-defeating as not knowing left from right.

The two hemispheres of a woman’s brain talk to each other more than a man’s do. In a 2014 study, University of Pennsylvania researchers imaged the brains of 428 male and 521 female youths — an uncharacteristically huge sample — and found that the females’ brains consistently showed more strongly coordinated activity between hemispheres, while the males’ brain activity was more tightly coordinated within local brain regions. This finding, a confirmation of results in smaller studies published earlier, tracks closely with others’ observations that the corpus callosum — the white-matter cable that crosses and connects the hemispheres — is bigger in women than in men and that women’s brains tend to be more bilaterally symmetrical than men’s.

“To some appreciable degree, these brain differences have to translate to behavioral differences,” says Cahill. Nu-

merous studies show that they do, sometimes with medically meaningful implications.

A 2017 study in *JAMA Psychiatry* imaged the brains of 98 individuals ages 8 to 22 with autism spectrum disorder and 98 control subjects. Both groups contained roughly equal numbers of male and female subjects. The study confirmed earlier research showing that the pattern of variation in the thickness of the brain's cortex differed between males and females. But the great majority of female subjects with ASD, the researchers found, had cortical-thickness variation profiles similar to those of typical non-ASD males.

In other words, having a typical male brain structure, whether you're a boy or a girl, is a substantial risk factor for ASD. By definition, more boys' than girls' brains have this profile, possibly helping explain ASD's four- to fivefold preponderance among boys compared with girls.

WHY OUR BRAINS DIFFER

But why are men's and women's brains different? One big reason is that, for much of their lifetimes, women and men have different fuel additives running through their tanks: the sex-steroid hormones. In female mammals, the primary additives are a few members of the set of molecules called estrogens, along with another molecule called progesterone; and in males, testosterone and a few look-alikes collectively deemed androgens. Importantly, males developing normally in utero get hit with a big mid-gestation surge of testosterone, permanently shaping not only their body parts and proportions but also their brains. (Genetic defects disrupting testosterone's influence on a developing male human's cells induce a shift to a feminine body plan, our "default" condition.)

In general, brain regions that differ in size between men and women (such as the amygdala and the hippocampus) tend to contain especially high concentrations of receptors for sex hormones.

Another key variable in the composition of men versus women stems from the sex chromosomes, which form one of the 23 pairs of human chromosomes in each cell. Generally, females have two X chromosomes in their pair, while males have one X and one Y chromosome. A gene on the Y chromosome is responsible for the cascade of developmental events that cause bodies and brains to take on male characteristics. Some other genes on the Y chromosome may be involved in brain physiology and cognition.

Scientists routinely acknowledge that the presence or absence of a single DNA base pair can make a medically

important difference. What about an entire chromosome? While the genes hosted on the X chromosome and the Y chromosome (about 1,500 on the X, 27 on the Y) may once have had counterparts on the other, that's now the case for only a few of them. Every cell in a man's body (including his brain) has a slightly different set of functioning sex-chromosome genes from those operating in a woman's.

Sex-based differences in brain structure and physiology reflect the alchemy of these hormone/receptor interactions, their effects within the cells, and the intermediating influence of genetic variables — particularly the possession of an XX versus an XY genotype, says Cahill.

ZEROING IN ON NEURAL CIRCUITS

Shah's experiments in animals employ technologies enabling scientists to boost or suppress the activity of individual nerve cells — or even of single genes within those nerve cells — in a conscious, active animal's brain. These experiments have pinpointed genes whose activity levels differ strongly at specific sites in male versus female mice's brains.

What would happen, Shah's team wondered, if you knocked out of commission one or another of these genes whose activity level differed between male and female brains? They tried it with one of their candidate genes, turning off one that was normally more active in females. Doing this, they found, totally shredded mouse moms' willingness to defend their nests from intruders and to retrieve pups who had wandered away — maternal mandates that normal female mice unfailingly observe — yet had no observable effect on their sexual behavior. Torpedoing a different gene radically reduced a female mouse's mating mood, but males in which the gene has been trashed appear completely normal.

All this points to a picture of at least parts of the brain as consisting of modules. Each module consists of a neural or genetic pathway in charge of one piece of a complicated behavior, and responds to genetic and hormonal signals. These modules — or at least some of them — are masculinized or feminized, respectively, by the early testosterone rush or its absence. The mammalian brain features myriad modules of this sort, giving rise to complex combinations of behavioral traits.

Which is not to say every man's or woman's brain looks the same. Our multitudinous genetic variations interact with some of our genes' differential responsiveness to estrogens versus androgens. This complicated pinball game affects

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

As a child, Noah Wilson thought *gender* meant *boy or girl, the end*. But when they were both 14, Noah's best friend, Rory, came out as nonbinary, a person who feels neither squarely male nor female.

Noah — who had always assumed he was female, since that's what it says on his birth certificate — went home and quietly Googled “nonbinary.” (Noah and Rory are identified by pseudonyms in this story.) He was just trying to be a supportive friend to Rory, but soon realized something else was going on. The idea that people could question their gender resonated. A lot.

Maybe I'm not a girl, he remembers thinking. Worried about

Trans gender

CARING FOR KIDS MAKING THE TRANSITION

what his parents would think, he kept quiet and spent months wrestling internally with his gender identity.

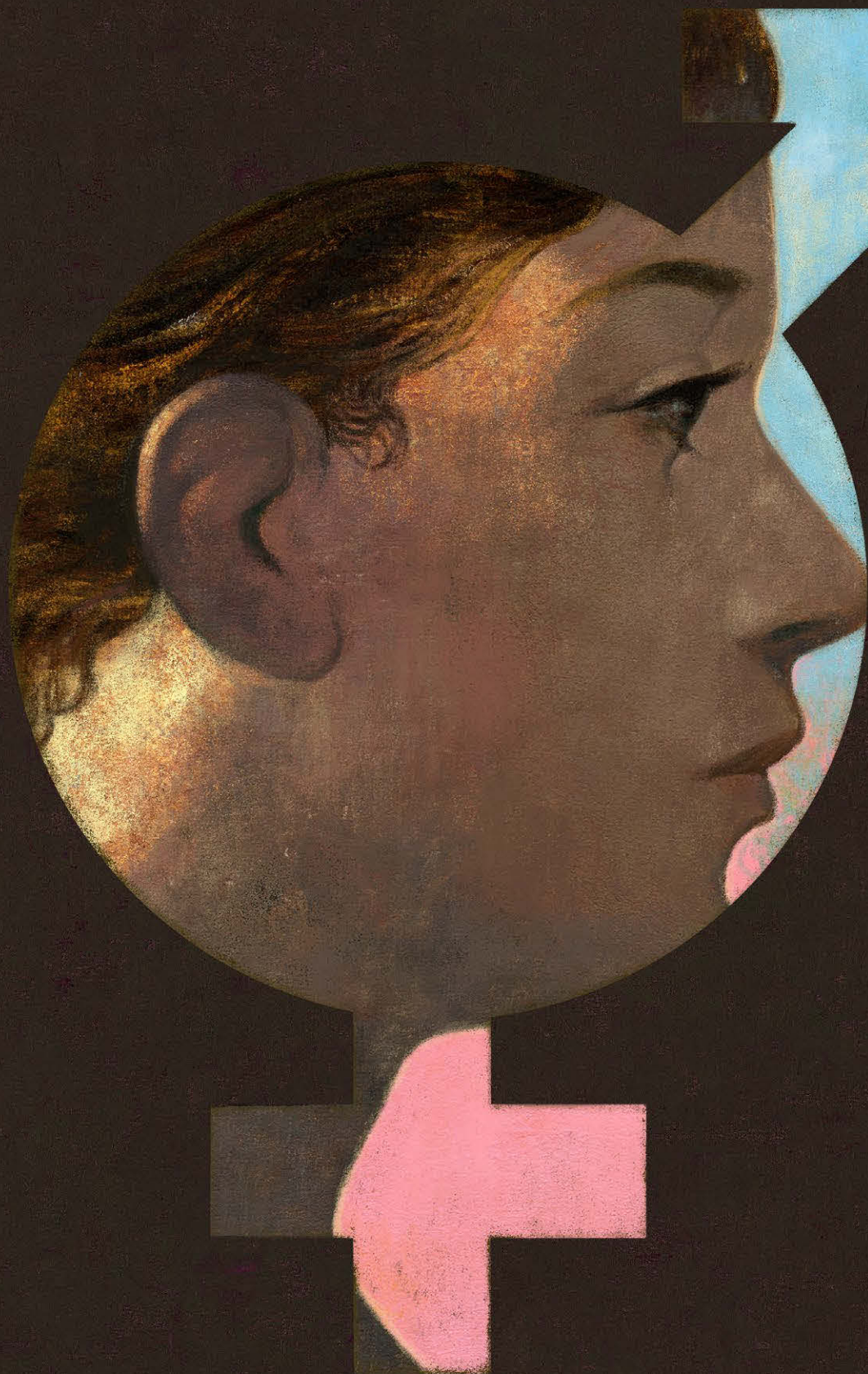
“At first, I didn't know that was a thing I was allowed to do and I didn't have the words to describe it,” he says. Over time, he became increasingly sure he was mostly male.

“Girls can be butch, but it's not just that I don't want to be feminine,” Noah says. “It's that I feel more comfortable when people refer to me as a guy.”

Late in his sophomore year, he asked Rory and a few other close friends to start calling him Noah instead of his female

BY ERIN DIGITALE

I L L U S T R A T I O N S B Y G É R A R D D U B O I S



birth name, and told them he was a nonbinary guy, more male than female.

But he was really afraid to tell his family. Even if his left-leaning parents were OK with it, his maternal grandparents might be unaccepting; they are on the conservative end of the political spectrum and had made derogatory jokes about Caitlyn Jenner when she came out as transgender. Would expressing his identity force his mom to choose between her parents and him? Could it be worse?

"I was imagining scenarios where you guys kicked me out," Noah tells his mom and dad as they sit together on their living room sofas. "It has happened to other trans kids with worse parents."

Now 17 and a high school senior, Noah has been out to his parents for almost two years. The three of them are talking about his gender transition the same way they're talking about his college plans — with hope and love, while dinner cooks in a crockpot and the family dog trots around putting her head in the lap of anyone who might scratch her ears.

This support puts Noah in a novel group: For the first time, a cohort of several thousand youths across the country are transitioning from male to female or female to male with the backing of their parents. This is almost certainly a good thing for their psychological well-being: A 2014 report by the American Foundation for Suicide Prevention found that more than 40 percent of transgender adults had attempted suicide, whereas early research suggests transgender kids with supportive parents will grow up with much better mental health.

But even the most welcoming families face big challenges as they navigate life in the vanguard of transgender childhood. That's why a growing group of physicians, social workers, family therapists, schoolteachers and scientists are learning how to help.

"These kids really feel they've been born into the wrong body, and it causes a lot of distress," says pediatric endocrinologist Tandy Aye, MD, who founded the Pediatric and Adolescent Gender Clinic at Stanford Children's Health in 2015. "They've been thinking about this for so long and trying to voice it, and often, people have been dismissive."

Aye, an associate professor of pediatrics at the School of Medicine, first worked with transgender teens as part of her research on the effect of sex hormones on brain development. Families of her research subjects asked if she could provide medical care for their kids, so Aye began seeing patients and established the new clinic. Now one of more than 30 such programs across the country, it provides help with medical and social aspects of gender transition and connects transgender children and their families to community resources, including well-informed primary care physicians.

AS NOAH STRUGGLED with how to come out, his parents felt increasingly confused. "We were kind of told pieces of the story, but I definitely remember feeling like I was missing some information," his mother says. At one point, Noah told her he liked the way he looked with a flat chest. "Why would a girl want a flat chest? I was teased for having a flat chest when I was that age," she says. "It just didn't quite make sense because I was missing the key piece: Noah is a boy."

"I remember that you had several friends who were LGBT, including one who was nonbinary, and I didn't quite understand what that meant," his father says to Noah. "Several times I thought, 'What exactly is going on here?'"

Early in high school, Noah did tell his parents he was gay, but their support of the person they thought of as their lesbian daughter didn't quell his anxiety about coming out as trans. He tried to keep it a secret.

Then his mother found a binder he had borrowed from Rory in his tote bag. A binder looks similar to a tank top; it's a garment worn around the torso to compress the breasts and make the wearer appear more masculine. But Noah's mom didn't know that.

She said, "What is this?" Noah made an embarrassed grab for the binder, fled to his room and spent half an hour freaking out. "Oh God, they're gonna find out," he remembers thinking. He decided he had to emerge from his room and explain.

After some false starts, Noah finally got the news out. "Kind of panicking, I said, 'I think I might be trans, and oh, by the way, I'm going by Noah and I'm a guy.'"

"When Noah finally told us, I was surprised," his mother says. "But I also thought, 'Oh, that makes a lot more sense. How did I not think about that before?'"

His parents saw a certain logic in Noah's coming out and loved him no matter what, but they were filled with worries. Was it safe or wise to help a teen girl live as male? Yet Noah was eager to start taking hormones that would help him develop masculine characteristics.

"Noah wanted us to get on board right away," says his father. "For me, it took a long time to mentally come around to the idea that this is a real thing, and not just something teens are going to change their minds about."

AS DRASTIC AS A GENDER TRANSITION MAY SEEM, FOR CHILDREN WHO ARE SURE THEY'RE in the wrong-gender body the consequences of doing nothing are worse, Aye says.

"If a child has been gender-nonconforming for a long time and is not allowed to transition, going through the wrong

puberty can be psychologically devastating,” she says. Helping transgender adolescents go through the medical aspects of transition carries a different meaning for Aye than treating kids with medical illnesses. “As you treat transgender teens with hormones, you’re affirming who they are,” she says. “Each time they come to the clinic, you get to see a reblossoming of this individual.”

But early in the process, ambivalence is common. Amy Valentine, the social worker at the Stanford Children’s Health gender clinic, observes the mixture of feelings Noah’s family describes in many new patients and their families. She’s part of a team of about 15, including endocrinologists, pediatricians, adolescent-medicine specialists, ob/gyns, psychiatrists, a psychologist, a urologist and nurses. The clinic is currently serving about 50 patients, with six to eight new patients coming each month.

“We want Stanford Children’s Health to be a safe haven for patients and families who are working through gender-identity issues,” says Dennis Lund, MD, chief medical officer of Lucile Packard Children’s Hospital and Stanford Children’s Health. “Helping transgender or gender-questioning children and teens is a natural goal for our children’s hospital. It’s our job to take care of patients in need.”

Before families visit the clinic, Valentine gets a comprehensive history by phone and assesses which steps the

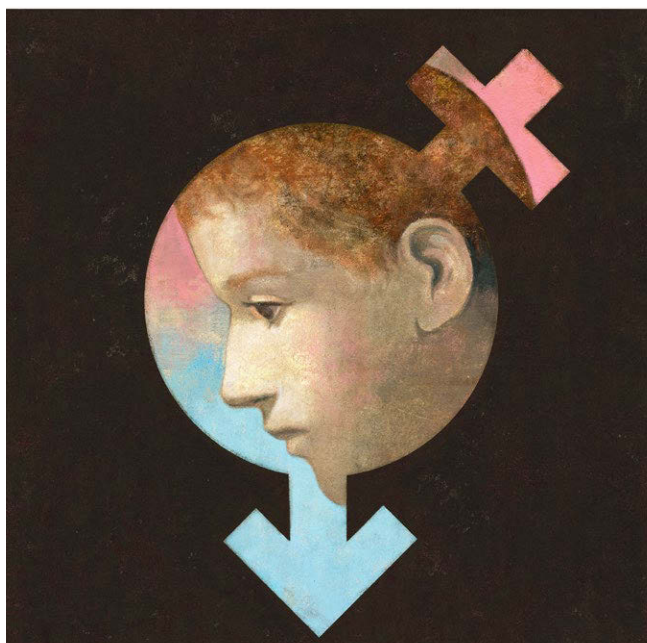
Valentine wants to know how the parents interpret what’s happening, too.

“Kids really want to be understood by their parents,” she says. “They want to feel loved and accepted for who they are and they need help from their parents to move forward. And parents come in a lot of times in disbelief, saying, ‘How did this happen all of a sudden?’”

Parents often need education in the basics of being transgender. They may not know that gender identity — one’s innate sense of being male, female, neither or in between — exists on a spectrum, and can differ from the sex on one’s birth certificate. They may confuse gender identity, an aspect of one’s self-perception, with sexual orientation, which is based on feelings of attraction to others. (Children begin forming their sense of gender identity in the preschool years, long before they give any thought to romantic relationships,

and transgender people can have any sexual orientation.) Parents may also wonder how common it is to be transgender. While statistics for children are hard to come by, one 2013 survey found that 1 percent of San Francisco middle- and high school students identify as transgender. A much more comprehensive 2016 report based on Centers for Disease Control and Prevention data found that 0.6 percent of the adult population, or around 1.4 million U.S. adults, are transgender.

Many parents also worry,



‘WHY WOULD A GIRL WANT A FLAT CHEST? I WAS TEASED FOR HAVING A FLAT CHEST WHEN I WAS THAT AGE. IT JUST DIDN’T QUITE MAKE SENSE BECAUSE I WAS MISSING THE KEY PIECE: NOAH IS A BOY.’

child may or may not have taken toward a gender-identity transition. For instance, she asks if the child has socially transitioned, which is the first step in living as their identified gender, by using a gender-congruent name, switching pronouns, and changing their hair and clothing. Therapists look for three characteristics to distinguish transgender youth: They are insistent, persistent and consistent in their gender-identity expression.

as Noah’s father did, that their child is going through a period of temporary confusion or has been influenced by peers.

Is it ever just a phase? That’s tricky to answer, and depends on the age of the child. Many preschoolers don’t fit into traditional gender categories but also don’t feel that they inhabit the wrong body. “Sometimes they seem boylike, sometimes they seem girllike, and their parents may want them to come down on one side or the other,” says Maureen Johnston, a

family therapist in private practice who works with many of the gender clinic's patients and families. Most don't ultimately come out as transgender; some later realize they are gay. "With kids who appear to be nonbinary or gender-fluid, it's very, very hard on the parents because they get a lot of pressure from outside," Johnston says. Yet squashing children into rigid gender categories can hurt them.

In contrast, many teens who have come out as transgender — and even some younger children — are certain they are in the wrong-gender body.

Though sometimes parents think their child's gender switch is about being cool, that's rarely the case, says Johnston. Teenagers are acutely aware of the stigma still attached to being transgender.

"Dyeing my hair purple — I did *that* because it was cool and my friends did it," Noah says. "But people still get bullied or killed for being trans. I don't think most people see it as cool."

AS THEY SEEK MEDICAL CARE FOR GENDER-IDENTITY CONCERNS, MANY families find that their pediatrician has never been trained on the topic. Medical support for transgender children is uneven across the country, notes Aye. While most urban areas now have well-established clinics, parents and children in rural locations may face long trips to access medical care and endure more prejudice in their communities. At a minimum, all doctors should know how to have a respectful and productive initial conversation with patients who are questioning their gender identity, Aye says. For pediatricians, that means asking children what they're feeling, what gender they identify as, and whether they have a preferred name and pronouns,

group there, his father had his first opportunity to talk with a large group of other fathers of transgender kids. "It was really awesome," he says. The other dads helped him empathize with Noah in a new way, asking him to consider how it would feel to experience a constant mismatch between his internal sense of himself and the way he looks on the outside. It transformed how he thought about his — now — son.

Before Noah's junior year of high school began in August 2015, he emailed his teachers to explain that he was transgender and ask them to use his male name in class.

His teachers agreed; other kids mostly seemed at ease. When one boy he'd gone to school with for years greeted Noah by his birth name, Noah said, "I'm going by Noah this year." The boy said, "Oh, OK, cool." Another classmate was genuinely confused at first, but soon adjusted. "No one's been mean or rude on purpose," Noah says.

During the school year, Noah and other students in the school's queer-student union asked the principal to designate a bathroom on campus as gender-neutral. "The only gender-neutral bathroom was a tiny one-stall thing in the nurses' office," Noah says. To the students' surprise, the principal quickly agreed to switch two large, centrally located restrooms to gender-neutral.

Planning how to share the news with Noah's mother's parents was a much bigger concern. His mother was worried that her parents might sever their relationship with her, or tell her she had been a bad mother to Noah. She worried about the ripple effects, too: If her parents cut ties, she'd be unable to help them as they aged, and those duties would instead fall to her brother, who lives farther away.

And Noah's parents still ask themselves what will happen when their son ventures outside the protective environment of a supportive high school in a liberal community. "I

'DYEING MY HAIR PURPLE — I DID *THAT* BECAUSE IT WAS COOL AND MY FRIENDS DID IT. BUT PEOPLE STILL GET BULLIED OR KILLED FOR BEING TRANS. I DON'T THINK MOST PEOPLE SEE IT AS COOL.'

she says. "Allow that conversation to begin and don't be dismissive. Let the child express it and listen in a welcoming way." Doctors can refer their patients to specialized gender clinics and point them to local and online resources.

Not long after Noah came out, his whole family — including his parents and his older sibling — went to a conference hosted by Gender Spectrum, a Bay Area-based advocacy organization for transgender people. At a dad's

feel pretty safe in the Bay Area but there are places I really wouldn't want Noah to go," his mother says.

Their fears aren't unfounded. *Injustice at Every Turn*, the 2011 report on the findings of the National Transgender Discrimination Survey, found that of the 6,450 U.S. transgender adults who responded, 63 percent had experienced a serious act of discrimination, including bias-related job loss, eviction, harassment at school so severe that the respondent

had to drop out, bullying by teachers, physical assault, sexual assault, homelessness, loss of relationship with a partner or children, denial of medical services and incarceration. And more than half of respondents had experienced discrimination in public settings such as retail stores, restaurants and health care facilities. (The survey was conducted by the National Center for Transgender Equality, a social-justice and advocacy organization.)

Nevertheless, Noah expects to be well-supported when he goes away to college next year — he has deliberately chosen a school known to welcome transgender students. Although he's nervous about life in a college dorm, he expects to be able to be open about his identity, a far cry from what earlier generations of transgender college students experienced.

PSYCHOLOGICAL RESEARCHERS ARE BEGINNING TO NOTE THE BENEFITS OF WIDENING FAMILY and societal support on young transgender individuals.

"We have this huge cohort of gender pioneers who are doing something we haven't done in this culture before," says Kristina Olson, PhD, associate professor of psychology at the University of Washington in Seattle. Prior generations of kids were almost universally encouraged to suppress behavior that failed to conform to their gender. Those who didn't "received incredible amounts of bullying," Olson says. "It's a unique thing that we now have kids who are openly transgender and *haven't* experienced lots of bullying."

In the past, some clinicians tried to influence gender-nonconforming children to change their behavior to meet traditional expectations, but this approach is now in disrepute. Standards of care from the World Professional Association for Transgender Health state that such treatment has been shown to be unsuccessful and is no longer considered ethical.

To figure out how social support changes the picture for younger transgender kids, Olson runs the TransYouth Project, which has recruited about 300 children aged 3 to 12 who have socially transitioned to live as their identified gender, as well as a large group of kids who are gender-nonconforming but haven't made any type of transition, and age-matched controls who are not transgender or questioning their gender. She is planning to follow them through adolescence and into adulthood.

"In past studies, gender-nonconforming kids had pretty high rates of anxiety and depression, and by the time they were teens or adults, high rates of suicidality," Olson says. A 2016 study of a national cohort of U.S. young adults followed over time found that among transgender and gender-nonconforming individuals, 52 percent met clinical criteria

for depressive symptoms and 38 percent met criteria for anxiety. In cisgender subjects — those whose gender identity matches the gender on their birth certificate — the rates were 27 percent and 30 percent for females, and 25 and 14 percent for males, respectively. Another 2016 study of more than 500 children with gender dysphoria found that they were 5.1 times more likely than cisgender children to talk about suicide and 8.6 times more likely to engage in self-harm behaviors.

In contrast, in research published in *Pediatrics* in 2016 and in the *Journal of the American Academy of Child & Adolescent Psychiatry* in 2017, Olson's team found that well-supported transgender kids had similar feelings of self-worth and rates of depression to age-matched control kids, and only slightly higher rates of anxiety. The data suggest that psychological distress is not an inevitable aspect of being transgender, Olson and her co-authors conclude.

A separate group of Dutch researchers reached similar conclusions in a 2014 longitudinal study of the psychological health of 55 transgender young adults who had gone through social, medical and surgical gender transitions in adolescence and early adulthood. A year after they completed gender reassignment surgery, the gender dysphoria that subjects had experienced before transitioning was gone. Their psychological well-being was as good as or better than that of cisgender young people in the control group.

ONCE THE TEAM AT STANFORD'S GENDER CLINIC DETERMINED that Noah had good support from his family and school, they asked for a "letter of readiness" from a mental health provider. Adolescents who want to start taking cross-sex hormones need a letter to attest that they are insistent, consistent and persistent in their gender identity; have been living as a member of their identified gender for a while; and understand the ramifications of the medical treatments.

Mental health providers also help kids untangle other problems. Noah's counselor helped him sort through his anxiety and figure out how much was due to pressures at school — despite being an excellent student, he worried he was not learning what he needed to succeed in college and adulthood — and how much came from being closeted.

"Gender does not happen in a vacuum," says family therapist Johnston, who did not treat Noah but sees teens in similar situations. Like any kid, a transgender teen may experience anxiety or depression, struggle with substance abuse or

Intro to the gender spectrum

A FREE ONLINE COURSE EXPLAINS THE BASICS OF
TRANSGENDER CHILDREN'S NEEDS

In 2011, Stanford Medicine lecturer Maya Adam, MD, had just finished teaching her undergraduate course on critical issues in child health when a student approached her with some feedback. "I loved your class, but you are missing one issue," the student said. "You need a lecture on transgender children's health."

ADAM'S RESPONSE was "You're right ... but I know so little about that." Her own medical training had never mentioned transgender children; she was unsure what challenges they faced. Adam soon realized this knowledge gap was common, not just among physicians but also among teachers and other professionals who work with kids.

In March, Stanford launched a free online course that Adam created to fill the gap. Anyone can participate in the course, which is called "Health Across the Gender Spectrum" and is available at <https://www.coursera.org/learn/health-gender-spectrum>. In 18 short videos, Adam interviews Stanford experts and gives basic explanations of concepts relevant to gender identity. In addition, several videos showcase interviews with transgender children and their families. Among the conversations: A young child tells his mom that it took four tries for him to muster the courage to tell her he was really a boy, a girl describes how she feels about looking out for her transgender little sister, a dad shares his concerns that his beloved transgender child won't be accepted by society and a mom talks about how she feels blessed to raise a transgender teenager.

"There is something magical that happens when you meet a real family and see similarities between that parent and you, between

that child and yours," Adam says. Viewers hear parents' and kids' voices under cartoon animation; the families' anonymity is preserved, but their emotions come through.

"There are themes of hope and incredible love in these stories," Adam says. "Every parent we interviewed has gone above and beyond to create an environment that will allow their child to thrive."

The course also includes interviews with two Stanford researchers who are transgender: Asian studies expert Alice Lyman Miller, PhD, a fellow at the Hoover Institution; and neuroscientist Ben Barres, MD, PhD, a professor of neurobiology, of developmental biology and of neurology and neurological sciences at the School of Medicine. They speak about their academic work and their experiences of being transgender. "We need mainstream, highly accomplished transgender role models to be more visible," Adam says.

Ultimately, she hopes the course will show that placing less emphasis on gender leaves all young people — anywhere on the gender spectrum — freer to express themselves, grow and thrive.

"We can do all our kids a service by backing off from the tyranny of the pink and blue," she says. "If you're playing a part that doesn't feel like who you really are, how can you possibly be your best self?"

have parents who are in the midst of a divorce. Such struggles don't necessarily preclude starting hormone treatments, especially if a child's distress about gender underlies their psychological symptoms, Johnston says. "So often, depression is a result of gender dysphoria, or gender dysphoria is exacerbating anxiety or depression."

Johnston sometimes must mediate situations in which a parent strongly resists the idea that his or her child is transgender. She has occasionally felt compelled to remind parents of the high suicide rates among transgender individuals who are rejected by their families.

"A lot of what it comes down to is parents saying, 'I love my child and even though I don't agree with this, I would rather have an alive, happy trans daughter than a dead son,'" she says.

Once Noah had his "letter of readiness" and had received insurance approval, he began receiving a puberty blocker, Lupron, which prevented him from going through further

maturation as a female. (It is also used to temporarily halt maturation in kids who have a condition known as precocious puberty.)

"If they identify really young as transgender, kids can receive a pubertal blocker as soon as any signs of puberty start," says Aye. "If they suppress puberty and later change their minds, they can stop taking Lupron and continue to develop their own biological puberty; there's no harm to it."

For those who transition, avoiding the wrong puberty means they will look more like members of their identified gender as adults. With the medication, trans boys won't develop breasts, for example, and trans girls won't grow as tall or develop deep voices or facial hair.

Around age 16, transgender teens can begin receiving estrogen (for those transitioning to female) or testosterone (if they're transitioning to male). "They get cross-sex hormones

so that they're going through one puberty and it's appropriate," Aye says. The patient's levels of psychological readiness and family support are always important considerations in starting cross-sex hormones, she adds. "Noah has had an easier time than many kids because of what an amazing family he has — they're so supportive."

Although the first dose of cross-sex hormones isn't a huge step medically, since the hormones' effects are slow and cumulative, the emotional significance of the first dose can be enormous for patients, Aye says. Often, at her initial meeting with a family, she feels a cloud of tension looming over everyone. Weeks or months later, when the teens receive their first hormones, the shift — the kids' relief and hopefulness at having their identity recognized by their families, and the families' happiness, too — is palpable. "I've seen so many people with tears of joy," Aye says.

Noah started taking testosterone in November 2016. His voice has already become deeper, which he likes. With continued use, he'll grow a beard and develop more malelike body composition. The hormones Noah's taking have rendered him infertile, which was a trade-off he felt comfortable making. Some transgender youth choose to pursue fertility options by freezing eggs or sperm, but they can't do this unless they have gone at least partway through the "wrong" puberty.

In adulthood, some transgender individuals also choose to have gender-affirming surgery; trans men may have "top surgery" (a double mastectomy), trans women may undergo breast augmentation or facial feminization surgery, and both men and women may have genital surgery. But many transgender people decide not to undergo surgery; the degree of function that can be obtained from genital surgery varies, and there is growing acceptance of the idea that one can live as a member of one's identified gender without it.

Aye's research team is studying the effects of pubertal blockers and cross-sex hormones in teenagers, asking what the medications do to bone, brain and body composition, and trying to determine how the hormones will affect transgender individuals' health in the long run. A recent study by researchers in Cincinnati, Texas and Maryland found that transgender people taking testosterone had increased body mass index and hemoglobin/

hematocrit (higher red blood cell count, because testosterone promotes red blood cell formation), as well as decreased high-density lipoprotein ("good") cholesterol levels. Those taking estrogen did not experience significant changes in their metabolic parameters.

"I've told Noah a lot of times that I'm still very concerned about the hormones and medical issues," Noah's father says. To Noah, he adds, "I'm OK with the idea of changing how you dress and how you present but I get really nervous about signing up for taking medication for the rest of your life. And I know not everyone takes it forever and ever, but it makes me really nervous because you're messing with the way your body normally works."

LOOKING BACK ON THE PAST THREE YEARS, NOAH'S FAMILY HAS some advice for other families in their shoes.

"For parents, you need to educate yourself as quickly as possible, and you need to process your own feelings away from your kid," his mother says. Your child needs your support, no matter what worries you have along the way, she adds.

"If you know that your parents are probably going to be accepting, come out sooner," Noah says, adding that he thinks talking with a therapist as he questioned his gender might have helped him feel less lonely. "I felt like I had to get everything exactly figured out. And yet I definitely felt relief once everyone started calling me Noah; it was a lot better."

But the whole family was still on edge about whether they would ever hear Noah's new name said in a welcoming way by his maternal grandparents.

Noah's mother worried not just about a political or philosophical gap, but also the generation gap. Had her parents ever heard of transgender people who were just regular folks, not reality TV stars or drag queens? Would old stereotypes cloud their perception of their grandchild?

However, when she explained the situation to her parents on the phone, she got a surprise. "My mom took it really well," she says. "My dad has had a little more trouble understanding it, but he has been reading about it, and he also appreciates how hard this has been on Noah and our family. They are definitely being supportive."

On her parents' first visit after they heard the news, "as soon as she got out of the car, Grandma gave him a big hug," she says.

The first words out of her mouth? "Hi, Noah." **SM**

— Contact Erin Digitale at digitale@stanford.edu

WEB EXTRA

DANI'S JOURNEY

Meet another transgender teen and his family in our video:
<http://stan.md/2paeSxb>



PURSUING

A NEW GENERATION OF FEMALE FACULTY IS GATHERING DATA

ON WHY THERE SHOULD BE MORE OF THEM

PARTY

ODETTE HARRIS WAS THE ONLY BLACK WOMAN in Stanford School of Medicine's class of 1996. Upon graduation, she became Stanford's sole first-year neurosurgery resident.

"I don't think I've ever been in a professional situation where I wasn't the first or the only," says Harris, MD, now an associate professor of neurosurgery at Stanford, the associate chief of staff for rehabilitation at the Veterans Affairs Palo Alto Health Care System and the director of brain injury programs at both institutions.

As a medical student, Harris had conducted research with Stanford neurosurgeon John Adler, MD, who likes to warn incoming residents about the grueling program they're embarking on. "He was incredibly candid with me about what people thought about me joining the residency, and he did that in a way not to freak me out or depress me, but he wanted me to have a very real perspective about what I was getting into and not be Pollyanna about it," Harris says. "He was like, 'Listen, I want you to have your guard up.' It was good baggage to carry through residency, to know that I had to be better and to do more."

She knew she was joining a department that had recently been roiled by controversy. In 1991, Frances Conley, MD, the only woman on the neurosurgery faculty — and, in fact, the first female full professor of neurosurgery in the United States — had submitted a letter of resignation after a colleague whose behavior she found demeaning was promoted to acting department chair. After a year of turmoil, the colleague's appointment was reversed and Conley rescinded her resignation, but her revelations of the treatment she and others experienced at the hands of their male colleagues — from exclusion and

BY KATHY ZONANA

P H O T O G R A P H Y B Y L E N N Y G O N Z A L E Z

THE FIRST AND THE ONLY
Odette Harris wants to inspire the
next generation.



stereotyping to lewd remarks and unwanted touching — opened up a national conversation about women and sexism in academic medicine.

Five years later, Harris didn't have much bandwidth to worry about whether she was entering an inhospitable environment. "I was very much aware of what had happened, but I think these are luxury concerns when your biggest concern is, am I going to survive this residency? Are people going to think I'm capable? Are people going to think I'm smart enough?" she says. Even in retrospect, she sees Conley primarily as the inspirational pioneer whose legacy she inherited when she joined the Stanford faculty.

"Fran went through more bullshit than Odette," says Adler, a professor emeritus of neurosurgery who considers Conley a mentor and has himself been a lifelong mentor to Harris. "There was more hostility toward Fran. I know

facts of unconscious biases and how to mitigate them, on the best way to compensate for differences in how male and female faculty tend to spend their time. After all, they say, they're scientists.

BEYOND THE PIPELINE

The gender disparity in academic medicine can no longer be attributed to the so-called pipeline problem: Women make up roughly half of U.S. medical students and more than half of those receiving PhDs in the biomedical sciences. But they make up 22 percent of the tenured faculty at U.S. medical schools, according to 2013 data from the Association of American Medical Colleges. Their proportion declines as they rise in academic rank: Women are 44 percent of assistant professors — the junior faculty position that represents the first

'WELL, SHOULD WE HIRE THIS WOMAN, OR SOME GUY WHO'S GOING TO COME IN AND DO THE WORK?'

that Odette encountered individual animosity, but it wasn't broad, across-the-department hostility."

Today, Stanford's neurosurgery faculty includes 13 women and 43 men in a variety of research and clinical specialties, not all of whom perform surgery. "Nowadays we just expect women to be in the operating room," Adler says. "But even right now, we only have a few women and we should have more. And eventually we're going to."

"Eventually" is too long to wait," says Hannah Valentine, MD, a cardiologist who served as the School of Medicine's senior associate dean for diversity for many years and is now the chief officer for scientific workforce diversity at the National Institutes of Health. At the current rate of change, without targeted intervention, Valentine has calculated it's going to take more than 50 years before women in the United States achieve parity in academic medicine.

The argument for equal opportunity in academic medicine has moved from "because it's the right thing to do" to "because it's the smart thing to do." Valentine and others who are working to bolster gender equality are increasingly marshaling data in support of their cause: on the benefits of a diverse workforce, on how underrepresented women are in the professoriate and in academic leadership, on the ef-

fects of unconscious biases and how to mitigate them, on the best way to compensate for differences in how male and female faculty tend to spend their time. After all, they say, they're scientists.

step toward tenure — but only 34 percent of associate professors and 21 percent of full professors. The only rank at which women outnumber men is that of instructor, a separate, non-tenure-track faculty line. And while women are increasingly likely to serve in medical schools' leadership, their numbers in key positions are still small. Nationwide, they make up just 15 percent of department chairs and 16 percent of medical school deans.

"What I hear a lot is, well, we just haven't had women in the pipeline long enough to essentially trickle up," says Diana Lautenberger, the director of women in science at the AAMC. "But if you look at it, women were 40 percent of medical students in 1993. Those women would be in their 50s now, and we don't see anything even close to that percentage in the faculty ranks. So instead of looking at how to get women in the pipeline, because they're already there, we're trying to look at the climate and culture factors that push them out."

Stanford's School of Medicine has made a concerted effort in recent years to increase the diversity of its faculty, including its gender diversity. In 2013, Stanford exceeded the AAMC's benchmarking data for female faculty — women were 52 percent of assistant professors, 41 percent of associate professors and 22 percent of full professors — whereas the school was below the national benchmarks a decade pri-

or. (These numbers have continued to increase; in 2016, they were 56, 44 and 26 percent, respectively.) Women are also rising in the leadership ranks: Today, 27 percent of the departments in the School of Medicine are chaired by women.

“We need to build a diverse scientific workforce so that we can serve the needs of our diverse society,” says Lloyd Minor, MD, dean of the School of Medicine. “At Stanford, we have the opportunity to be a beacon of excellence in diversity and inclusivity, just as we are a beacon of excellence in science and clinical care.”

Having a diverse faculty benefits the research, education and clinical missions of an academic medical center, says professor of pediatrics Yvonne (Bonnie) Maldonado, MD, Valentine’s successor as the senior associate dean for faculty development and diversity. “From an academic standpoint, we want to attract the best people. We know that if there are obstacles to women, you can lose up to half of your talented workforce,” she says. With respect to clinical care, patient surveys support the value of having a physician workforce that reflects the population it serves, Maldonado says. “People feel comfortable around others with whom they share common experiences or backgrounds,” she says. “Gender is a very simple one. Not to say that every woman should have a female physician and likewise for men, but giving patients opportunities to pick from a number of diverse providers is great.”

PLUGGING THE LEAKS

When Mary Hawn, MD, applied for her first faculty job at the University of Alabama-Birmingham, in 2001, a senior faculty member asked, somewhat rhetorically, “Well, should we hire this woman, or some guy who’s going to come in and do the work?”

“Ultimately, he was my biggest advocate and promoter,” says Hawn, now the chair of Stanford’s Department of Surgery. His remark has become a longstanding joke between the two of them. “He just laughs, ‘Oh, no, did I say that?’ And he knows he did,” she says.

Hawn has heard it all: “Mostly we’re told we don’t work as hard, we don’t see as many patients, and we’re going to need to double the workforce if we keep letting all these women in.” In a field where physicians frequently perform procedures, like surgery (as opposed to a less “procedural” field like family practice), those assumptions can be even more entrenched. “I think, to this day, women are discouraged from pursuing highly procedural fields because of the feeling that the time commitment is more significant and the flexibility is less,” Hawn says. “Whenever a woman declares she’s inter-

ested in being a surgeon or some other intensive specialty, it gets a lot of pushback, and I think it’s not intentional. Some of it is just the biases we all have.”

Exactly, say researchers. Everyone agrees that women should be in the operating room, but sometimes biases — unconscious ones — get in the way of hiring and promoting qualified women.

“If a woman walks into the room, you automatically have a certain set of expectations — which, by the way, both women and men have,” says associate professor of surgery Sabine Girod, MD, PhD, DDS. “For men there is a positive expectation: He’s young but he’s a great guy and he will get it done. And for a woman, it’s, well, she’s young and doesn’t have enough experience. This is very soft unconscious bias — I don’t think anybody is doing anything on purpose.”

Valentine, Girod and colleagues conducted a study, published in January 2016 in *Academic Medicine*, showing that a 20-minute educational intervention could change faculty members’ awareness of unconscious bias and their perceptions of female leaders. While she was still at Stanford, Valentine encouraged department chairs to provide this type of information at faculty meetings. “During that period of time, the hiring of women increased,” she says.

Now, every faculty search committee at the School of Medicine receives unconscious bias training at the outset of the search. “People have preconceived notions of who fits a particular job description,” says Maldonado, “and when you are able to free yourself to think a little more broadly about whether somebody who would not be a traditional choice for you can fill that position, frequently you can hit pay dirt.”

Educating search committees, Valentine says, is only half the battle. The other is to ensure women are applying for tenure-track positions in the first place. “Where in the career path do we lose people?” she asks. “It’s that transition into independent careers in academia.” Valentine notes that in the biomedical sciences, women make up almost half of post-doctoral scholars but only 25 percent of applicants for assistant professor positions. Instead, they take jobs in other fields, such as industry or policy. “This is a very scary phenomenon for academic medicine,” she says.

THE LEADERSHIP GAP

Seven years ago, when Laura Roberts, MD, was offered the position of chair of the Department of Psychiatry and Behavioral Sciences at Stanford, some counseled her not to take it. “People thought that Stanford would not be a supportive environment for a woman

'THE ISSUES THAT ARE TRADITIONALLY THOUGHT TO BE GENDER-BASED ARE ACTUALLY ISSUES THAT AFFECT ALL OF US.'



DIVERSITY DEAN
Bonnie Maldonado urges faculty to think broadly about hires.

leader,” she says. “And that’s not been the case at all. I’ve felt incredibly well-supported at Stanford.”

Case in point: Shortly after her arrival, Roberts asked for, and received, the approval of university leaders to review the compensation and faculty-line classifications in her department and make adjustments for equity. Then, she expanded its leadership team. “The people who had been leaders in the department were outstanding in every way — they were collaborative and they were lovely to me. They also happened to be from, let’s say, a narrow demographic,” she says. “They were extraordinary colleagues and I did not want to signal disrespect or disregard for their great work over many years — instead I just elevated other people around them so that our leadership team would reflect the broader perspectives,

backgrounds and strengths of our department.” The effect of her larger-than-ordinary leadership team has been salutary. “Our people can see that there are many ways to advance professionally and to become a recognized leader in the department,” she says. “We identify positions so that people can apply for them. My sense is that these efforts have lifted morale because the opportunities for promotion and leadership are merit-driven, fair and logical.”

That’s exactly the kind of transparency that’s necessary to get more women into leadership positions in academic medicine, says Girod, who, along with Roberts, represented the School of Medicine on Stanford’s Task Force on Women in Leadership. “A lot of women want to do it, but they don’t get picked,” she says. “When you hire someone for a leadership position, you tend to, because of unconscious bias, pick somebody who is like you. And there are not many women who are picking for these positions, right?”

Roberts is particularly concerned with boosting the number of female department chairs in academic medicine. Although assistant and associate deans are higher on the org chart, the financial power in medical schools is concentrated in departments. “I am happy to see women in visible leadership roles, but I admit that what I really look for is women in leadership roles with actual budgets — women who are enabled to direct resources, to set a vision and allow strategic steps to be taken,” says Roberts. “Because that’s rare.”

Moreover, chairs set the tone for their departments, “from pay equity to culture and climate,” says the AAMC’s Lautenberger. “We work a lot with the deans and the deans are very much on board, but departments are really like their own independent organizations. They have their own budgets and their own culture and their own structure. Sometimes these departments are largely untouched. It’s interesting when you get in there to find climates that are not supportive of gender equity or considering women for leadership positions.”

Ensuring a healthy climate was one reason women in Stanford’s Department of Surgery banded together and asked to participate in their department’s recent search for a new chair. “We said we are 16 female faculty; in the past 10 years we hired 12 women and 11 women left. It’s like a revolving door at the associate and assistant professor levels,” says Girod, who, with several colleagues, is completing a study on the reasons faculty

leave the School of Medicine. “The dean and the chair of the search committee were open to that argument and we actually interviewed every single candidate as a group of women. Then we wrote our recommendations to the dean.”

The result of the search: Hawn, whom Girod calls “fantastically qualified — she was really the best of everybody.”

Being selected as chair of surgery “validated my contributions were important and impactful, that a traditionally male field would aspire to have a female leader,” says Hawn. “I think for the women it’s great that they see a woman in charge. I’m curious what it means for the guys. I suspect the relationships are probably a little more formal than they would be with a male chair. But gender isn’t the only thing that aligns you with somebody or makes them feel accessible or inspirational.”

Hawn looks forward to the day when no one remarks on her gender. “To me, the goal is that there isn’t a qualifier,” she says. “That you’re not a ‘woman chair.’ That you’re not a ‘woman surgeon.’ That we say, ‘Remember the day when we were worried about women being promoted to leadership positions?’ Nobody questions a woman’s equal right to vote, or admission to college.”

CARRYING AN EXTRA LOAD

Bonnie Maldonado has three children, two of whom were born after she became a faculty member. “How do you deal with going home at night?” she remembers wondering. “How do you balance that?”

The answer came from a more senior colleague, who said, simply, “I don’t go to events on evenings and weekends.”

In that moment, “I realized it’s OK for me to say, ‘I really can’t go to that event,’” Maldonado says. “I was afraid people would say, well, she just wants to go home and take care of her kids, not be a physician-scientist. And there’s no longer a reason to say you have to be one or the other. You should be able to be both.”

“If you look at the generation before me, the majority of women who went into surgery never had children,” says Hawn, who has two. “They felt like they did have to make a choice.”

That was true for Conley, who decided with her husband early on that they would not have children. “You can only have so many lives,” she says. “I was really into my neurosurgery program, and it would have taken away from that. I was just so enthralled, to open up the skull and see the brain, the whole soul of the person opened up in front of you.”

Roberts, who has six children, calls herself a “poster child for everything you’re not supposed to do” to be successful in academia. “The decision to have a large family was contrary

to all of the advice I received when I was an assistant professor,” she says. “Now, everywhere I go, I am told that I am an ‘inspiration’ because of my dedication to both my children and my career — but at the time, it was hard not to feel like a negative outlier. I had to quickly learn to reject the idea that your personal life and professional life are a teeter-totter in which one must be sacrificed for the other. Doing both fully, and joyfully, has been my intent.”

Today, Hawn, Maldonado and Roberts say, both male and female faculty acknowledge greater interest in pursuing work and family goals simultaneously. “The issues that are traditionally thought to be gender-based are actually issues that affect all of us,” says Maldonado. “I’m an epidemiologist, and one of the things we learn in training is that outliers can sometimes tell you the key to the problem you’re looking at. Since women tended to be the primary caregivers, it seemed to be amplified for women, but it’s a problem for everyone.”

Women also do more housework, says Girod, citing a 2010 study by Stanford professor of history Londa Schiebinger, PhD, that found that female scientists performed 54 percent of core household tasks, whereas male scientists performed 28 percent. There are also studies showing that women faculty members shoulder a disproportionate share of “academic housework” — work that benefits the institution but does not necessarily advance individual careers, such as committee service, extra teaching responsibilities or student advising.

To address work-life pressures, in 2013-14 Stanford piloted a time-banking program, which provided faculty with credits for such things as serving on committees or providing mentoring. They could exchange those credits for things that would buy them time back at work or at home, such as grant-writing support, housecleaning or meal delivery. Time banking is a better fit for academic culture, Valentine says, than giving people time off in exchange for extra work, or an extra year on the tenure clock after maternity leave. “These integrative policies have to be framed as career advancing, rather than career pausing,” she says. “We were able to demonstrate tremendous return on investment.” Although the pilot has ended, the Department of Emergency Medicine has chosen to provide time banking for its faculty, and other departments may follow suit.

THE NEXT GENERATION

Olette Harris has a pair of photos of the Stanford neurosurgery faculty and residents on her office wall. One day, her two young daughters came in, saw them, and asked, “Mommy, where are the women?”

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

SIMPLY STREISAND

A CONVERSATION ON MATTERS OF THE HEART

Barbra Streisand is one of the most celebrated individuals in the history of the entertainment industry. The voice alone is considered by many to be a singular sensation. Streisand has sold more albums in the United States than any other female recording artist. Her awards are sweeping: from Oscars and Emmys to Grammys and a Tony, along with the Presidential Medal of Freedom.

Since the beginning of her career on the Broadway stage, Streisand has been a stalwart supporter of civil rights and humanitarian causes. The well-known political activist and philanthropist has donated millions to a wide range of causes for social justice. Her activism dates back to the '60s, at the start of her career. In 1965 she sang at the civil rights benefit "Broadway Answers Selma," which featured special guest the Rev. Martin Luther King Jr.

Streisand embarked on a new mission, to bring gender equity to women in health care, when she learned that women were second-class citizens in medicine and research. To change that, in 2012 she created the Barbra Streisand Women's Heart Center at Cedars-Sinai Medical Center in Los Angeles.

But she also wanted to raise awareness among women before they found themselves in the hospital, and she wanted to help drive policy change at every level — local, state and national. That's why in 2014, she joined forces with businessman and philanthropist Ronald O. Perelman to found the Women's Heart Alliance. Their mission is to prevent women from needlessly facing and dying from heart disease and stroke. WHA focuses on health differences between women and men, and promotes activities that spread knowledge and create change, whether working with local communities, college students, medical professionals or policymakers.

In this special issue of *Stanford Medicine* on gender and biomedicine, we were looking for a voice that would add distinction and passion to the subject. What better voice is there than Streisand's? Executive editor Paul Costello and Barbra Streisand exchanged emails in this Q&A.



COSTELLO Some readers may be surprised to see Barbra Streisand in a biomedical magazine, but you are a longtime advocate for gender equality in biomedical research and health care, including cardiovascular disease. What led to this focus?

STREISAND I am passionate about fighting gender discrimination in all forms and improving women's lives, a commitment that goes

RUSSELL JAMES

back to my 20s when I made a movie based on Isaac Bashevis Singer's story of Yentl, a young woman who has to pretend she's a man to get an education. Initially, multiple studios turned me down. No one believed that a woman could direct or manage a budget. That fueled my determination to help women get the same chances in life as men.

Many years later, I was staggered to learn about a problem called "Yentl syndrome," a phrase coined by cardiologist and former director of the National Institutes of Health Bernadine Healy. Dr. Healy found that women experiencing heart attacks got worse care than men. Women's heart attack symptoms often differ from men's, but unless a woman presented with symptoms that looked like a man's, too often, she was misdiagnosed or undertreated.

With heart disease, women aren't getting the same chance in life, *literally*.

COSTELLO How so? How would you describe the scope of the problem?

STREISAND Most people are stunned to learn that cardiovascular disease is the No. 1 killer of women in the United States, claiming more women's lives than all cancers combined. One in three women die of heart disease and stroke. That's one woman almost every 80 seconds — reflecting gaps in awareness, prevention, diagnosis, treatment and support. African-American women are especially at risk. And rates of heart disease in younger women are climbing.

So, CVD isn't a "man's disease." This epidemic targets women, too. And its impact is exacerbated by the lack of knowledge and awareness among some medical professionals. For example, when women having heart attacks go to the emergency room, too often they do not receive the correct diagnostic tests or treatments. It's common to hear stories of women experiencing a heart attack, receiving an antacid in the ER and being sent home.

COSTELLO Why don't more women know about their risk?

STREISAND One reason is that women aren't encouraged to share their stories of heart disease, so we don't realize how many people we know are affected. And, without that personal connection, it's harder to rally a movement to fight it. But because we aren't aware of the risk, we miss opportunities to safeguard ourselves and save the lives of women we love. It's a devastating cycle.

That's why one of our first WHA initiatives was a campaign to encourage every woman to get her heart checked — to talk with her doctor, know her risk factors, and learn how to fight and prevent heart disease and stroke.

But for those conversations to have their fullest impact, we need an enabling environment. That means improving access to and quality of care. It means curriculum reform in medical schools so that doctors and other health care professionals have a better understanding of women's hearts. It means more research on sex differences in heart disease. And it means more support to help women take up and maintain the behaviors that will make a positive difference for their heart health.

WHA is working on all these fronts, and reaching out to every

sector of society. We want to mobilize collective action on behalf of women's lives.

COSTELLO What do you mean by collective action?

STREISAND Improving heart health is everybody's responsibility — because CVD is everybody's problem. Beyond the human cost, there's an economic toll as well. Nationwide, according to the American Heart Association, the annual costs of lost productivity due to CVD are \$237 billion and growing.

Everyone has a part to play in turning this trend around. Employers can sponsor wellness programs at work; faith- and community-based organizations can help with outreach and engagement; local officials can promote heart-healthy development in their communities, such as walkable neighborhoods, public recreation space and farmers markets. Advancing women's heart health is a team effort!

This February, the WHA launched an exciting new initiative called Cities/Communities with Heart that will address women's heart health in mid-sized cities, using this collaborative model.

We're starting in Nashville, Tennessee, where we're working with Nashville's wonderful mayor, Megan Barry; the health department, as well as the city's many hospitals, health systems and clinics; academic institutions; business leaders; and faith-based and civic organizations.

Together, we identified five interventions for 2017: a program to improve the cardiovascular health of nurses at major hospitals and health systems; a clinical study on pregnancy complications and their link to CVD risk factors and CVD; a workforce health initiative to improve the heart health of female municipal workers; a screening and prevention effort in collaboration with Tennessee State University to reduce CVD and its precursors in younger women; and a community initiative centered around one or more health centers and reaching African-American, immigrant and refugee women.

COSTELLO Is there any research that you want to see undertaken?

STREISAND For starters, we need more resources put to women's heart research. Heart disease kills many more women than cancer does, yet in 2011, the NIH spent nearly \$959 million on women's cancer research, but only \$246 million on women's heart disease. I don't want cancer research funding to go down, but heart disease funding should go up!

Second, we need more women participants in clinical trials. How can we optimize diagnostics and therapeutics for women if we're not studying them in the lab?

We also need to study the differences between men and women. Take MINOCA — myocardial infarction with nonobstructive coronary arteries. People typically think of heart attacks as resulting from clogged arteries. But women's arteries are unobstructed in up to 50 percent of acute coronary syndromes. That's a real contrast with men. If we better understood what causes MINOCA, we could devise better tests, better prevention and better treatments. And that would be better for everyone.

C O N T I N U E S O N P A G E 4 5

Insurance policy

HOW
AN INDUSTRY SHIFTED
FROM
PROTECTING
PATIENTS
TO SEEKING PROFIT

JEFFREY KIVI, PHD, was receiving monthly infusions of Remicade to treat psoriatic arthritis, an autoimmune disease he'd had since childhood. The drug enabled the high school science teacher to stand all day in his classroom and to walk down the school's hallways. Each monthly infusion cost \$19,000, which his insurance covered.

Then his doctor switched hospitals.

The cost of Kivi's infusions ballooned, soon surpassing \$132,000 a month. He still wasn't responsible for any of the cost, but he was stunned. What could account for this disparity in price?

Plenty of factors, writes Elisabeth Rosenthal, MD, in her new book An American Sickness. The new hospital spent more on amenities and marketing. It held the patent on Remicade, and stood to benefit from its administration if profits were high enough. And Kivi's insurer didn't push back against the higher price — instead, it paid three-quarters of it. Kivi was so appalled he switched to a medication he could take at home.

The United States spends almost 20 percent of its gross domestic product on health care, and if we want to reduce that, Rosenthal argues, we're all going to have to be more like Jeffrey Kivi. Rosenthal, editor-in-chief of Kaiser Health News, itemizes the ills that have befallen health care, including opaque and inequitable pricing, perverse financial incentives and an ethos of putting profits before patients. She then writes a prescription for reform, including short-term strategies to reduce costs and long-term policy goals.

In this excerpt, Rosenthal explains how the transformation of the United States' health care economy began: with the creation of insurance companies and their evolution into for-profit entities.

The very idea of health insurance is in some ways the original sin that catalyzed the evolution of today's medical-industrial complex.

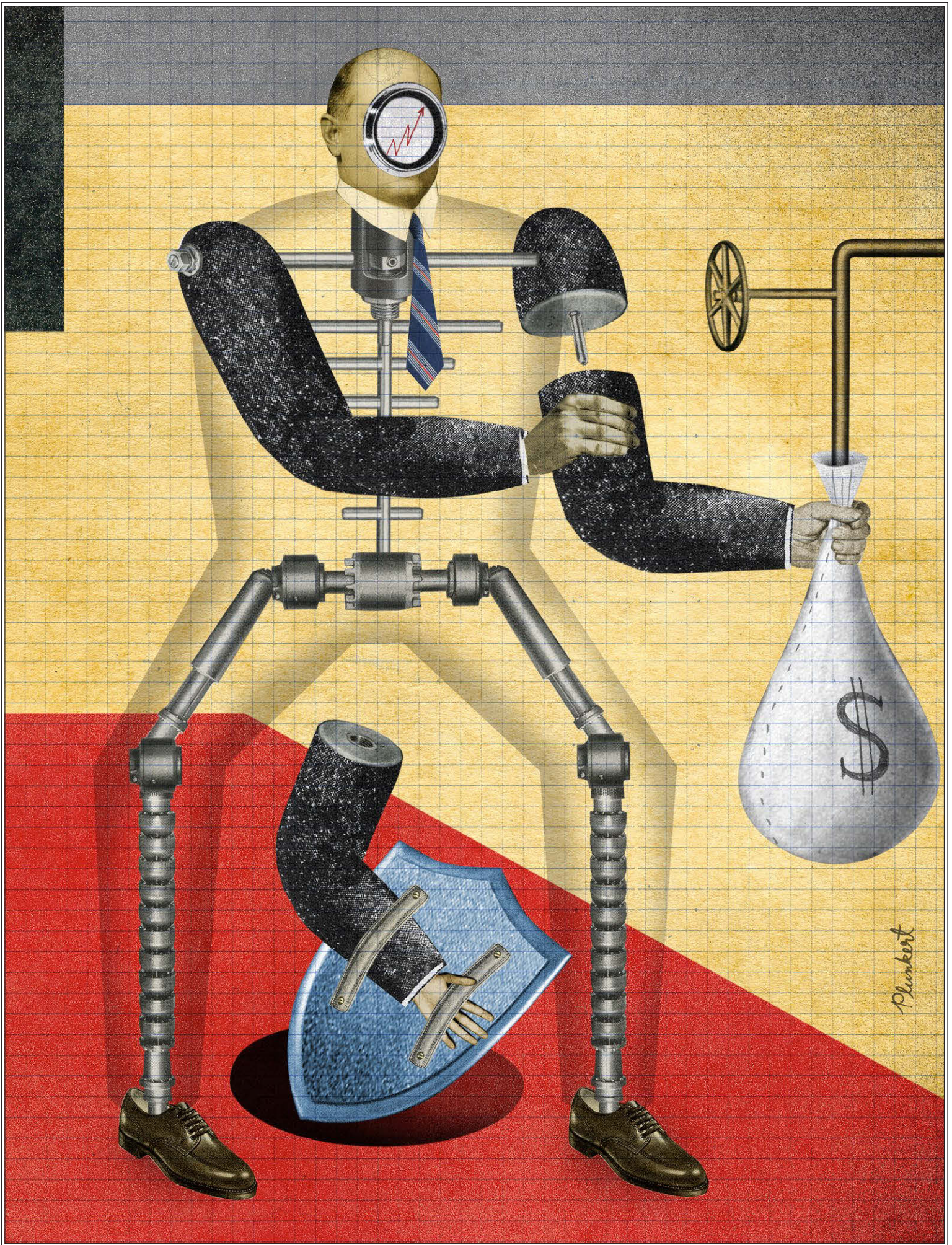
The people who founded the Blue Cross Association in Texas nearly a century ago had no idea how their innovation would spin out of control. They intended it to help the sick. And, in the beginning, it did.

A hundred years ago medical treatments were basic, cheap and not terribly effective. Often run by religious charities, hospitals were places where people mostly went to die. "Care," such as it was, was delivered at dispensaries by doctors or quacks for minimal fees.

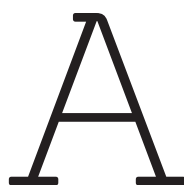
Disease was very time-consuming. Without antibiotics and nonsteroidal medicines, or anesthetics and minimally invasive surgery, sickness and injury took much longer to heal. The earliest health insurance policies were designed primarily to compensate for income lost while workers were ill. Long absences were a big problem for compa-

AN EXCERPT FROM AN AMERICAN SICKNESS

BY ELISABETH ROSENTHAL ILLUSTRATION BY DAVID PLUNKERT



nies that depended on manual labor, so they often hired doctors to tend to workers. In the 1890s, lumber companies in Tacoma, Washington, paid two enterprising doctors 50 cents a month to care for employees. It was perhaps one of the earliest predecessors to the type of employer-based insurance found in the United States today.



AS MEDICAL TREATMENTS AND KNOWLEDGE IMPROVED IN THE EARLY 20TH CENTURY, THE CONCEPT OF INSURANCE EVOLVED. The archetype for today's insurance plans was developed at Baylor University Medical Center in Dallas, Texas (now part of Baylor Scott & White Health, since it merged with another health system in 2013, forming a giant health care conglomerate), which was founded in 1903 in a 14-room mansion by the Baptist Church. A devout cattleman provided the initial \$50,000 in funding to open what was then called the Texas Baptist Memorial Sanitarium, "a great humanitarian hospital." By the 1920s, more and more Texans were coming for treatment. When Justin Ford Kimball, a lawyer who was Baylor's vice president, found out that the hospital was carrying a huge number of unpaid bills, he offered the local teachers' union a deal. For \$6 a year, or 50 cents a month, teachers who subscribed were entitled to a 21-day stay in the hospital, all costs included. But there was a deductible. The "insurance" took effect after a week and covered the full costs of hospitalization, \$5 a day, which is about \$105 in 2016 dollars.

Soon, employees for the *Dallas Morning News* and local radio stations were also signing up for what we today would call catastrophic care insurance. It was a good deal. The cost of a 21-day hospitalization, \$525, would have bankrupted many at the time. In that era, given the treatments available, within 21 days you were likely dead or cured.

Within a decade, the model spread across the country. Three million people had signed up by 1939 and the concept had been given a name: Blue Cross Plans. The goal was not to make money, but to protect patient savings and keep hospitals — and the charitable religious groups that funded them — afloat. Blue Cross Plans were then not-for-profit.

Despite this, before World War II, when most treatments were still relatively unsophisticated and cheap, few Americans had health insurance. The invention of effective ventilators, breathing machines that moved air in and out of the lungs, enabled a vast expansion of surgery suites and intensive care

units. That meant more people could be saved, including soldiers injured during the war and victims of polio outbreaks.

Transformative technologies rapidly spread across the developed world. Abbott Laboratories made and patented the first intravenous anesthetic, thiopental, in the 1930s. Massachusetts General Hospital started the first anesthesia department in the United States in 1936. The first intensive care unit armed with ventilators opened during a polio epidemic in Copenhagen in the early 1940s.

Five dollars a day and a 21-day maximum stay were no longer enough. Insurance with a capital I was increasingly needed. A private industry selling direct to customers could have filled the need — as it has for auto and life insurance. But a quirk of history and some well-meaning policy helped etch in place employer-based health insurance in the United States. When the National War Labor Board froze salaries during and after World War II, companies facing severe labor shortages discovered that they could attract workers by offering health insurance instead. To encourage the trend, the federal government ruled that money paid for employees' health benefits would not be taxed. This strategy was a win-win in the short term, but in the long term has had some very losing implications.

The policies offered were termed major medical, meaning they paid for extensive care but not routine doctor visits and the like. The original purpose of health insurance was to mitigate financial disasters brought about by a serious illness, such as losing your home or your job, but it was never intended to make health care cheap or serve as a tool for cost control. Our expectations about what insurance should do have grown.



BLUE CROSS AND ITS PARTNER, BLUE SHIELD, WERE MORE OR LESS THE ONLY MAJOR INSURERS AT THE TIME and both stood ever ready to enroll new members. The former covered hospital care and the latter doctors' visits. Between 1940 and 1955, the number of Americans with health insurance skyrocketed from 10 percent to over 60 percent. That was before the advent of government programs like Medicare and Medicaid. The Blue Cross/Blue Shield logo became ubiquitous as a force for good across America. According to their charter, the Blues were nonprofit and accepted everyone who sought to sign up; all members were charged the same rates, no matter

how old or how sick. Boy Scouts handed out brochures and preachers urged their congregants to join. By some accounts, Blue Cross Blue Shield became, like Walter Cronkite, one of the most trusted brands in postwar America.

But the new demand for health insurance presented a business opportunity and spawned an emerging market with other motivations. Suddenly, at a time when medicine had more of value to offer, tens of millions of people were interested in gaining access and expected their employers to provide insurance so they could do so. For-profit insurance companies moved in, unencumbered by the Blues' charitable mission. They accepted only younger, healthier patients on whom they could make a profit. They charged different rates, depending on factors like age, as they had long done with life insurance. And they produced different types of policies, for different amounts of money, which provided different levels of protection.

Aetna and Cigna were both offering major medical coverage by 1951. With aggressive marketing and closer ties to business than to health care, these for-profit plans slowly gained market share through the 1970s and 1980s. It was difficult for the Blues to compete. From a market perspective, the poor Blues still had to worry about their mission of "providing high-quality, affordable health care for all."

By the 1990s, the Blues, which offered insurance in all 50 states, were hemorrhaging money, having been left to cover the sickest patients. In 1994, after state directors rebelled, the Blues' board relented and allowed member plans to become for-profit insurers. Their primary motivation was not to charge patients more, but to gain access to the stock market to raise some quick cash to erase deficits. This was the final nail in the coffin of old-fashioned noble-minded health insurance.

Many of the long-suffering Blue plans seized the business opportunity. Blue Cross and Blue Shield of California was particularly aggressive, gobbling up its fellow Blues in a dozen other states. Renamed WellPoint, it is the biggest of the for-profit companies descended from the original nonprofit Blue Cross Blue Shield Association; today it is the second-largest insurer in the United States. Most of its plans still operate under the name Anthem BlueCross BlueShield, but in New York the plans operate under the Emblem brand. The insurer for New York City teachers, which reimbursed about \$100,000 for each of Jeffrey Kivi's outpatient infusions, has evolved a long way from its not-for-profit mission and \$5-a-day hospital payments.

WellPoint's first priority appears no longer to be its patient/members or even the companies and unions that choose it as an insurer, but instead its shareholders and investors. As in

any for-profit enterprise, executives are compensated for how well they perform that financial function and are compensated well. In 2010 WellPoint had intended to hike premiums in California by 39 percent, before an attorney general effectively nixed the plan. CEO Angela Braly received total annual compensation of more than \$20 million in 2012, despite the fact that she resigned under pressure that year because the company revenues were down. Joe Swedish, the new CEO appointed in 2013, is a longtime health care executive who served at the for-profit Hospital Corporation of America.

His starting salary and bonus totaled about \$5 million, not including stock options.

Then, in August 2014, WellPoint announced that it planned to change its name to Anthem Blue Cross (pending approval by shareholders), presumably to take advantage of whatever nostalgic good feelings patients had retained toward the Blues, before raising premiums on some of its California ACA policies by 25 percent in 2015. Dave Jones, California's vocal insurance commissioner, accused Anthem of "once again imposing

an unjustified and unreasonable rate increase on its individual members." Using his bully pulpit to publicly voice his objections was Jones' only recourse, since he, like many state insurance commissioners, can make only nonbinding determinations and has no legal authority to deny rates. To express their collective frustration, members gathered signatures for a MoveOn.org petition: "Anthem Blue Cross: Stop Playing Politics with Our Premiums." They urged their insurer "to stop spending corporate funds on political campaigns, disclose everything it has spent directly or indirectly on political campaigns, and use the money to lower rates for Anthem policy-holders and California taxpayers."

In 1993, before the Blues went for-profit, insurers spent 95 cents out of every dollar of premiums on medical care, which is called their "medical loss ratio." To increase profits, all insurers, regardless of their tax status, have been spending less on care in recent years and more on activities like marketing, lobbying, administration and the paying out of dividends. The average medical loss ratio is now closer to 80

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C O N T I N U E S O N P A G E 4 5

wildly frugal

MANU PRAKASH'S DREAM IS SCIENCE TOOLS FOR EVERYONE,
EVERYWHERE

Standing at the lectern in a darkened auditorium, Stanford bioengineering professor Manu Prakash told his audience that he was going to demonstrate a few low-cost scientific instruments that had been developed in his lab. He looked more like a graduate student than a professor, with his untamed hair and rumpled down jacket, as he reached into his backpack and pulled out what looked like a colorful paper bookmark.

"This is the Foldscope," he said, "a microscope made from 97 cents of materials." He pointed to a tiny spherical lens at the center, and told them that they could look through it and see microscopic objects with the naked eye.

To illustrate its magnification power, he played a video clip that had been recorded by attaching a Foldscope to a smartphone camera lens. The image of a gnat laying eggs squirmed across the auditorium's large movie screen. Its hairy body was translucent, revealing its pulsating organs. It was like a scene from an alien horror film. A few people gasped.

Next, he held up something that looked like a whirligig toy, a loop of twine threaded through two holes in a 3-inch-diameter disc. He grabbed the twisted ends, then rhythmically pulled. As the twine coiled and uncoiled, the disc spun at a dizzying speed. Prakash explained how he could attach a thin tube of blood along the radius of the disc and the spinning forces would separate, say, malaria parasites from blood cells, making it

BY KRIS NEWBY PHOTOGRAPH BY LENNY GONZALEZ

MANU PRAKASH INVENTS INEXPENSIVE SCIENCE TOOLS LIKE THE FOLDSCOPE, A MICROSCOPE MADE OF PAPER, TO BRING THE POWER AND JOY OF SCIENTIFIC DISCOVERY TO CHILDREN AROUND THE WORLD. (ADULTS LIKE THEM TOO.)



easy to detect the organisms under a microscope. This 20-cent, hand-powered device, called a “paperfuge” because of the prototype’s paper disc, can do the job of a \$1,000 commercial centrifuge.

Prakash was presenting at The Sequoias, a brainy retirement community nestled in the wooded foothills west of Stanford University. He had been invited to lecture on this February morning by resident Fabian Pease, PhD, an 80-year-old professor emeritus of electrical engineering at Stanford and a key collaborator on what may be Prakash’s most ambitious project yet: designing a scanning electron microscope that provides the basic functions of a \$60,000 model for just \$100.

The Foldscope, the simple centrifuge and the SEM all exemplify “frugal science,” designing scientific instruments that are affordable to people in resource-poor regions.

to accept me. I only had a computer science degree and I hadn’t published any papers,” says Prakash.

AT MIT, PRAKASH THRIVED. He invented a computer that used logic circuits comprised of microfluidic bubbles traveling along tiny etched canals, rather than electrons moving within metal pathways. And he worked out equations that described how water striders walk on water and how birds feed. He received his PhD in applied physics in 2008, then was awarded a Junior Fellowship at Harvard, which allowed him to pursue scholarship in any discipline for three years.

While Prakash was visiting a health clinic in India in 2010,

‘I’ve been wanting to talk to Could you help us design a \$100

Prakash is on a mission to inspire others to create tools that will ignite the curiosity of our next generation of scientists and engineers. And it seems as if he won’t stop until every child on the planet has a backpack full of frugal science tools.

OUT OF INDIA

Prakash’s love of invention began during his childhood in a small town in northern India. He grew up in a home where his mother, who had a PhD and taught political science at a local college, emphasized learning. Outside of school, he was encouraged to explore and invent. He and his brother loved spending time building rockets, dissecting animals, collecting unoccupied bird nests and assembling large science models.

“This informal, curiosity-driven learning time fueled my love of science,” says Prakash.

As an undergraduate at the Indian Institute of Technology in Kanpur, Prakash studied computer science. But he soon found that he disliked sitting in front of a computer all day. So, he began sneaking off to tinker in the robotics lab, where he built an omnidirectional walking spider-robot and a program that simulated the drawing style of children. He wanted to do more of this kind of work, and he heard that MIT was the place for inventors, so he applied and got in.

“I just got remarkably lucky. There was no rational reason

he saw a photo of Mahatma Gandhi that set his course. In the photo, Gandhi looks through a microscope to observe the bacteria that cause leprosy. Prakash loved the contrasts in the photo. It showed Gandhi in a loincloth, sitting cross-legged on the ground, using an expensive European microscope at a time when India was struggling to shed its dependence on all things European. The instrument was impractical for rural India, where, because of the humid climate, lenses often cloud over with mold. But Gandhi knew he needed this instrument to help fight disease in his country.

For Prakash, this image embodies the idea that a single person embracing science during a tumultuous time can make a difference. “This is the picture that started me on my path of frugal science,” he says. He decided to spend at least half of his time as a professor developing low-cost science tools for everyone, everywhere.

IT’S A SMALL WORLD

Pease, a lanky, British-born microscope lover with a full head of silver hair, first heard about Prakash at a June 2014 scientific conference in Washington, D.C. His former Stanford student Alireza Nojeh, PhD, told him over dinner about an extraordinary presentation he’d seen earlier in the day: A Stanford bioengineering professor had designed a working paper microscope that cost about a dollar. It was Prakash,

who had joined Stanford's faculty in 2011.

Pease had to have one, so as soon as he returned to Stanford, he phoned Prakash, who happened to work in the building next door.

"I've been wanting to talk to you, too," said Prakash. "Could you help us design a \$100 scanning electron microscope?"

"It's been tried and it can't be done. The vacuum pumps are too expensive," said Pease, who in 1964 wrote his PhD thesis on a high-resolution scanning electron microscope he had designed and built.

Electrons are small, fast and difficult to control, since they obey the strange rules of quantum mechanics. Prakash knew that Pease's expertise in harnessing electron beams would be invaluable in his pursuit of a low-cost SEM. Pease was a pioneer in developing electron beam lithography tools used to build large-scale integrated circuits. He also helped Tom

Newman, his graduate student, win Nobelist Richard Feynman's most famous physics challenge — to inscribe text small enough to fit all the pages of Encyclopedia Britannica's 24 volumes on the head of a pin. (They did it by using electron-beam lithography.)

Undaunted, Prakash appealed to Pease's love of audacious challenges: "What if we shot the electrons through a very small distance in air, so that we didn't need vacuum pumps?"

An SEM works on the same principle as a document scanner: by firing a precisely controlled beam back and forth across an object, measuring the intensity of the reflected beam and turning the beam into an image by layering dots on a screen. (It's a beam of light in a scanner and of electrons in an SEM.) But SEMs work on a much, much smaller scale, which drives up costs. Generating detailed images of microscopic bacteria and viruses requires a very fine electron beam. And to keep the beam from hitting air molecules and scattering, it is fired inside an airless chamber attached to a pump and power supply.

But instead of this costly set-up, they could shoot the beam through a sealed vacuum tube like those used in old television sets. Or they could shoot it through a very thin glass window, positioned extremely close to the desired ob-

you, too.
scanning electron microscope?



THE FOLDSCOPE'S INVENTORS ENCOURAGE USERS TO DRAW AND PHOTOGRAPH WHAT THEY SEE THROUGH THE LENS AND TO SHARE THE IMAGES WITH THE TOOL'S ONLINE COMMUNITY. HERE'S HOW POLLEN GRAINS FROM A LILY LOOK.

ject. If they didn't need a 40,000-volt power supply to drive the vacuum pumps, the other microscope subsystems could be run on a trickle charge from batteries.

For battery advice, they turned to Yi Cui, PhD, a Stanford professor of materials science and engineering. He suggested that such a battery could be made for several dollars by using conductive ink to print about 1,000 battery cells on an 8-inch-long, flexible circuit board.

The next challenge was to figure out how to create a tight beam of electrons without using an expensive, power-hungry laser. Pease called in Nojeh, who after Stanford went on to teach engineering at the University of British Columbia. Nojeh proposed that they focus an office-supply laser pointer on an array of carbon nanotubes to create such a beam.

At a certain point, Pease forgot how impossible the goal had seemed at first.

"It took me back to my childhood," says Pease. He had pulled out his old textbooks and started thinking about how to simplify everything. Now Pease is a regular fixture in Prakash's lab, joining three generations of scholars dedicated to squeezing cost out of the microscope subsystems. They currently have a working test prototype.

THE PRIMORDIAL SOUP

Many of the Prakash lab's best ideas originate at the Friday meetings where Prakash and his 13 students brainstorm and solve problems. They are primarily biologists, physicists and engineers, but past members have included a circus performer, a music technologist and several high school students. Today, roughly half of the students are developing frugal science tools. The other half study how biological organisms function.

Take *Haeteria grandinella*. Prakash brought this organism into the lab accidentally, from water collected during a Foldscope testing field trip at Lake Tahoe. At a recent lab meeting, Deepak Krishnamurthy, a tall, bearded graduate student wearing nerdy black glasses, led a discussion of the single-celled creature. The aspect that most interests him is the organism's ability to jump at speeds unheard of in the world of microbes. While he was trying to take a picture of the microbe, it disappeared from the microscope's field of view and reappeared elsewhere, almost as if by teleportation. The organism, which lives in pond scum, is spherical with a floppy tuft of hairlike projections, called cilia. It looked like it was wearing a bad toupee.



MANU PRAKASH AND LAB MEMBERS IN MADAGASCAR COLLECT SNAILS FOR A SURVEY OF A DISEASE-CAUSING PARASITE THE ANIMALS SPREAD. RIGHT: CHILDREN IN TANZANIA BUILD FOLDSCOPE MICROSCOPES FOR LESSONS ON GERM THEORY AND SANITATION.

LEFT: SAAD BHAMLA; OPPOSITE: JIM CYBULSKI

Prakash kicked off the discussion: “OK, let’s get this out of the way. Yes, the cilia on top look like President Trump’s hair.”

Everyone laughed, then Krishnamurthy launched into his slide deck. Someone asked how the organism propels itself backward so quickly. Krishnamurthy waved his arms in a breast-stroke motion to show how the cilia propel the microbe slowly forward, then spun his arms like a frenzied egg-beater to show how the cilia generate explosive backward thrust. He pulled up a graph that showed velocity over time. Then he shared a dance-step diagram that traced the microbe’s pattern of motion. People argued about the pur-



pose of the hyperspeed jumps. And for an hour, there was nothing more important than this little pond dweller.

A MILLION POINTS OF LIGHT

Toward the end of his lecture at the Sequoias, Prakash pulled up a world map with pins showing where his team had shipped Foldscopes. So far, they’ve delivered 50,000 microscopes to 135 countries, beginning in 2013 with a grant from the Gordon and Betty Moore Foundation. The prototypes were funded by a Spectrum-Stanford Clinical and Translational Science Award from the National Institutes of Health.

Prakash added, “When we ship a kit, it comes with two Foldscopes, one for you and a second one for someone who has never looked through a microscope.”

A man in the audience asked, “Is there a temptation when you invent these things to make a lot of money?”

“This is a philosophical question I think about,” said Prakash. “We do file patents, but we decided that we wouldn’t evaluate our success by money, but by how many people are carrying these tools in their hands.”

To move the Foldscope from a lab-based project to a self-sustaining initiative, Prakash and Jim Cybulski, its co-inventor and Prakash’s first graduate student, created a for-profit business, Foldscope Instruments, with a nonprofit

subsidiary, thus enabling people with resources to subsidize those without. Their next goal is to ship 1 million Foldscopes around the world by the end of 2017. Foldscope Instruments will also commercialize other innovations from Prakash’s lab, such as the paperfuge, which was announced in January 2017, and a \$5 chemistry set, announced in April 2014.

Navi Radjou, an innovation strategist and a coauthor of the book *Frugal Innovation: How to Do More with Less*, says Prakash is onto something but it could take a while for people to catch on. “The Foldscope’s first benefit is in education; it’s a great way to get kids to learn by doing,” he says. “But when I talk about the Foldscope to large medical device companies, I don’t feel enthusiasm from the audience. The idea of affordable tools is a threat to their core business models.”

Radjou adds that in the United States, there’s a perception that if something is low-cost, it’s shoddy. “It may be that the developing world will leapfrog the West in frugal innovation, because of the West’s attachment to a ‘more is better’ mentality,” he says. “The challenge is, how can Manu inspire the whole science community to embrace this concept?”

Prakash and Cybulski have learned that it’s important to have partners in each country who can help train new users and promote the adoption of frugal science tools. To that end, Foldscope Instruments is partnering with a variety of industry, nonprofit and community groups. Through the Sigma-Aldrich Curiosity Labs initiative, they will provide students in 47 cities worldwide with Foldscopes and mentoring. To begin integrating the microscopes into Indian schools, clinics and everyday life, the Foldscope team is working with the Indian government to couple micro-research grants with free Foldscopes. They recently announced a call for proposals from Indian kids, teachers and tinkerers alike.

“This was a special moment for me, since I deeply understand what a program like this might have meant for me as a kid growing up in a small town in India,” says Prakash.

Near the end of his lecture at the senior center, Prakash offered to launch a Foldscope club there. He and Pease would teach the seniors how to build microscopes; then they, in turn, could teach their children and grandchildren.

“Tell the children that everything that you touch, every experience that you have, everything that you hold, has a microscopic component,” Prakash urged them. “Every living thing is made of these living cells. And just like with astronomy, when you look through a microscope lens, there are galaxies of things crawling around.”

As the lights in the auditorium went on, a crowd of seniors rushed the stage, each clamoring for a Foldscope. **SM**

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FEATURE

Of mice, men and women

CONTINUED FROM PAGE 11

that males are more vulnerable to developing autism spectrum disorders because their brains are already tilted toward the types of thinking associated with the condition, such as systematizing data, and away from other, more interactive, attributes such as empathizing with others.

“Our perspective zooms out from any preconceived notions of differences between male and female brains, and looks at the contributions of sex differences in the placenta,” says Braun. “It’s a fresh approach that’s free from any gendered assumptions about the tissue’s nature and function.” Braun’s results suggest that the risk factors that affect boys may be fundamentally different from those that affect girls, and that those differences may arise where one would least expect.

“Amy brings an unusual depth and breadth of understanding to her work on sex differences in our mouse models of autism,” says Palmer, her adviser.

Braun is spending increasing amounts of time talking with other researchers about the importance of including sex and gender as critical variables in their work. But it’s not always well-received.

“Researchers who have already decided they are going to ignore sex as a variable don’t really want to hear about it,” she says. “People can get defensive. But sometimes I feel like a broken record, asking over and over again when people present their research, ‘Did you analyze by sex?’ ‘Did you look at females?’”

“More than once, Amy has stopped me in mid-sentence to say ‘Theo, sex is a genotype, gender is an identity!’” says Palmer. “Unlike many other researchers, Amy effortlessly reconciles these ideas in her personal and scientific life.”

“Some biologists are so far behind in their social science literacy that the

distinction between sex and gender often isn’t clear,” says Braun. “I didn’t get any education about this earlier in my grad school career. I kind of stumbled sideways into this issue and now I can’t stop seeing it everywhere.” **SM**

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FEATURE

Two minds

CONTINUED FROM PAGE 17

goings-on in at least some of the brain’s neural circuits and in whatever little piece of behavior each of these neural circuits manages.

“We think gender-specific behavior is a composite of all these modules, which, added up, give you your overall degree of maleness and femaleness,” says Shah.

Consider the genes Shah has isolated whose activity levels differ significantly in the brains of male and female mice. “Almost all of these genes have human analogues,” he says. “We still don’t completely understand their function in human social behavior. But when we looked at publicly available databases to find out what we do know about them, we found a surprising number that in humans have been linked with autism, alcoholism and other conditions.”

Bigger imaging studies and imaginative animal research now in the works promise to reveal much more about humanity’s inherent — although by no means uniform, and often not substantial — sex-associated cognitive differences and vulnerability to diseases.

Trying to assign exact percentages to the relative contributions of “culture” versus “biology” to the behavior of free-living human individuals in a complex social environment is tough at best. Halpern offers a succinct assessment: “The role of culture is not zero.

The role of biology is not zero.” **SM**

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FEATURE

Pursuing parity

CONTINUED FROM PAGE 31

“I was like, ‘What are you talking about?’” Harris says. “And I came over to look at the pictures and I was like, holy crap, you’re absolutely right.” In the photo from 2003, when Harris finished her residency, there is one other woman, and she’s a neurologist rather than a neurosurgeon. In the 2009 photo, from Harris’ first year on the faculty, there are a smattering, but again, most of them are not surgeons. In certain surgical specialties, women remain rare.

“The sense of isolation is pretty overwhelming if you don’t have the sounding board and the mentorship,” Harris says, emphasizing that she herself has felt strongly supported by the senior members of her department. “Everyone needs a sense of community to be able to thrive in this environment.” In collaboration with the school’s Office of Faculty Development and Diversity, she is spearheading a new program that will create small, supportive groups of women. The office also offers a monthly networking luncheon for all female faculty.

Outside of her work in neurosurgery, Harris has made it her mission to improve access to careers like hers, primarily through science outreach to children. “There are few jobs where you can take the time outside of work to serve on the board of a Boys’ and Girls’ Club,” she says. “Where you can bring in an entire all-girls school to volunteer for a year at the VA when you’re a neurosurgeon and some may think your time is better spent in the operating room. I have amazing bosses who authentically support that kind of vision.

And to have opportunities like that and still be a neurosurgeon is a dream.”

There’s only one workplace Harris could combine these threads, she says: academic medicine. “If I have a legacy in the next 30 years, I hope it’s my grass-roots efforts to inspire kids,” Harris says. “Someday, my children will not be the first or the onlies.” **SM**

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Q & A

Simply Streisand

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COSTELLO You’re truly a believer.

STREISAND I am. We can do this. We can beat women’s heart disease. Because, in many ways, we have the cure already. Eighty percent of the risk of heart disease is preventable. Those are encouraging odds.

Prevention is cure.

So let’s provide more proactive screening and support. Let’s equip people with the information to make heart-healthy choices — things like quitting smoking, eating healthier, keeping cholesterol in check, getting on and staying on medication for high blood pressure, and keeping physically active. And let’s take inspiration from the breast cancer fight, which has helped bring down deaths by a third from their peak. If we focus people’s minds on the battle for women’s hearts, then, together, we can save women’s lives. **SM**

*To learn more, go to
<https://womensheartalliance.org>.*

FEATURE

Insurance policy

CONTINUED FROM PAGE 37

percent. Some of the Blues were spending far less than that a decade into the new century. The medical loss ratio at the Texas Blues, where the whole concept of health insurance started, was

just 64.4 percent in 2010.

The framers of the Affordable Care Act tried to curb insurers’ profits and their executives’ salaries, which were some of the highest in the U.S. health care industry, by requiring them to spend 80 to 85 percent of every premium dollar on patient care. Insurers fought bitterly against this provision. Its inclusion in the ACA was hailed as a victory for consumers. But even that apparent “demand” was actually quite a generous gift when you consider that Medicare uses 98 percent of its funding for health care and only 2 percent for administration.

Why did EmblemHealth agree to pay nearly \$100,000 for each of Jeffrey Kivi’s infusions, even though they cost only \$19,000 at another hospital just down the street? First, it’s less trouble for insurers to pay it than not. NYU is a big client that insurers don’t want to lose, and an insurer can compensate for the high price in various ways — by raising premiums, co-payments, or deductibles. Second, now that they suddenly have to use 80 to 85 percent rather than, say, 75 percent of premiums on patient care, insurers have a new perverse motivation to tolerate such big payouts. In order to make sure their 15 percent take is still sufficient to maintain salaries and investor dividends, insurance executives have to increase the size of the pie. To cover shortfalls, premiums are increased the next year, passing costs on to the consumers. And 15 percent of a big sum is more than 15 percent of a smaller one. No wonder 2017 premiums for the most common type of ACA plan are slated to rise by double digits in many cities, despite economists’ assurances that the growth of health care spending is slowing.

To some extent insurers do better if they negotiate better rates for your care. But that is true only under certain circumstances and in a limited way. “They are methodical money takers, who take

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in premiums and pay claims according to contracts — that’s their job,” said Barry Cohen, who owns an Ohio-based employee benefits company. “They don’t care whether the claims go up or down 20 percent as long as they get their piece. They’re too big to care about you.” **SM**

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ALL DUE RESPECT

BREAKING THE CYCLE OF MED STUDENT MISTREATMENT

Nathaniel Morris, MD, well remembers being humiliated by a supervisor during his first days of surgery training as a medical student on the East Coast. Morris was learning how to stitch closed an open wound. “The surgeon told me, ‘You suture like Helen Keller,’” says Morris, who is now a resident in psychiatry at Stanford. “Then he kind of laughed.”

Far from a hidden problem, the reality is that students are routinely humiliated, belittled and harassed by supervisors while in medical school, according to data collected annually by the American Association of Medical Colleges.

“It is something that most medical students experience at some point,” Morris says.

Doctors will tell you it’s a tradition perpetuated by the profession’s hierarchical structure — attending physicians above residents above interns. And medical students, who are at the bottom, often face social pressure to “appear strong” and just deal with mistreatment. Though the humiliation is decried, it continues.

“Once the learners become the teachers, the cycle of mistreatment often repeats with residents and physicians treating students as they were treated,” wrote a group of Stanford educators in an article published in *Academic Psychiatry* last spring.

In 2009, notes the article, the dean of Stanford’s medical school saw that the rate of mistreatment reported by Stanford’s graduating medical students had increased above the national average, leading him to heighten efforts to break the cycle. New programs included receiving monthly feedback from students about problems, and educating students on ways to report problems without fear of reprisal.

“When we started this mistreatment initiative in 2010 it was a program ahead of what other medical schools were doing,” says Rebecca Smith-Coggins, MD, lead author of the paper and associate dean for medical student life advising. “We wanted other schools to have an example of a program to help develop their own.”

The authors report that the program is making progress, citing data collected from the AAMC medical school graduation questionnaire.

The study reports that by 2014, students were half as likely to cite fear of reprisal as the reason they failed to report an episode of mistreatment.

In addition, from 2012 to 2014, smaller percentages of students reported experiencing mistreatment, according to the study. In 2012, 55 percent of the 63 students who responded reported experiencing mistreatment; in 2013, the figure dropped to 52 percent of the 64 students who responded; and in 2014, it dropped again to 34 percent of the 48 students who responded, Smith-Coggins says.

“It’s been our goal to help our educators find respectful ways to teach, and to help our students understand the culture of medicine, and to make sure issues are addressed without fear of reprisal for the student,” says Smith-Coggins.

Additional efforts include a policy for addressing claims of mistreatment that includes disciplinary action if necessary, and a series of educational videos depicting behavior that students may interpret as mistreatment.

Since the study was published, representatives from about a dozen medical schools have asked Smith-Coggins for advice on how to set up similar programs, she says.

“We are focusing on this so intently in medical school so our future residents and attending physicians will change,” Smith-Coggins says. “Culture change is such a difficult beast. But that’s the hope.” — TRACIE WHITE



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Memory lane

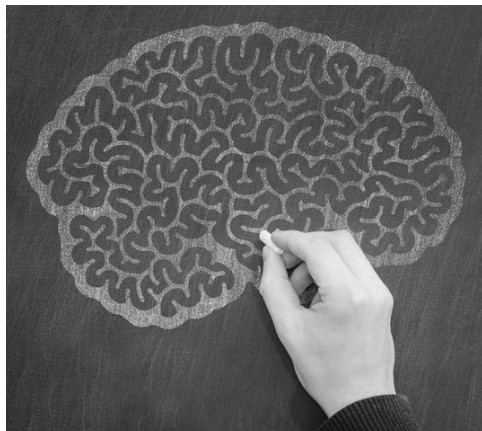
HOW USING LANDMARKS BOOSTS MEMORIZATION ABILITY

Ever wish you were one of those people who could quickly memorize the order of all the cards in a deck? You can be, according to researchers from the Stanford School of Medicine and from the Donders Institute for Brain, Cognition and Behavior in the Netherlands.

Their study, published in March in *Neuron*, examines the memorization techniques of 23 “memory athletes,” each of whom had scored in the top 50 in the World Memory Championships. Many of the memory athletes attributed their prodigious memorization skills to a mnemonic system called the “method of loci,” in which the athlete pairs each item to be memorized with a visual recollection of a landmark along a familiar route, such as a walk to the grocery store.

In baseline testing, memory athletes who were asked to memorize a list of 72 words could correctly recall an average of nearly 71 after 20 minutes. Non-athletes recalled about 40, on average.

The researchers then divided non-athletes into three groups. One group received six weeks of training in the method of loci; a second was trained in a technique to improve working memory, or the ability to briefly juggle several pieces of data in your head; and the third received no training. The group trained in the method of loci — and only that group — became nearly as skilled in recalling words as the memory



athletes. Four months later, they were still able to show off their memorization prowess with a new list of words. Using fMRI, the researchers could see that their brains had changed: While they were at rest, the patterns of activity in regions implicated in memory more closely resembled those of memory athletes than they had before the training.

“Training normal humans to be memory athletes bulks up the brain’s memory networks,” says the study’s senior author, Michael Greicius, MD, associate professor of neurology and neurological sciences.

But even memory athletes have been known to forget something important from time to time. “If you were to ask one of them if their skill spills over into other aspects of their lives, they would say no,” says Stanford medical student William Shirer, one of the study’s co-lead authors. “They lose their car keys as frequently as you and I do.”

— BRUCE GOLDMAN

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