STANFORD MEDICINE

Spring 2011

special report

BIOETHICS
NO EASY ANSWERS

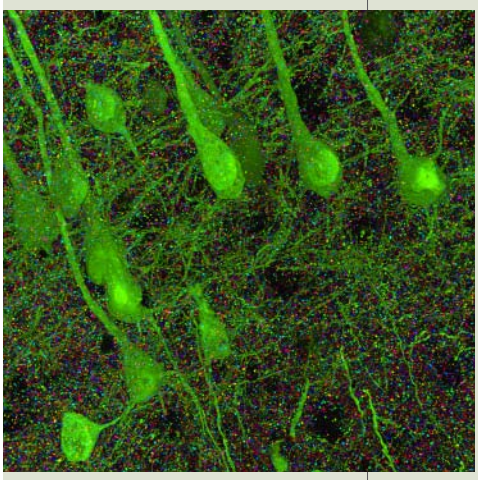
STANFORD MEDICINE

Spring 2011

high-res head shot

A NEW WAY TO SEE THE BRAIN'S CONNECTIONS

It's mind-boggling. A typical human brain contains about 200 billion neurons linked to one another via hundreds of trillions of tiny connections called synapses. These connections form the circuits behind thinking, feeling and moving — yet they're so abundant and closely packed that getting a precise handle on what's where has defied scientists' best attempts. • But here comes a solution. Stephen Smith, PhD, professor of molecular and cellular physiology, and Kristina Micheva, PhD, a senior staff scientist in Smith's lab, have invented a technique that quickly locates and counts the synapses in unprecedented detail, and reveals their variations. They described the imaging system, called "array tomography," in the Nov. 18, 2010, issue of *Neuron*. • Attempting to map the cerebral cortex's complex circuitry has been a fool's errand up to now, Smith says. "We've been guessing at it." Synapses in the brain are crowded so close together that they cannot be reliably resolved by even the best of traditional light microscopes, he says. • In particular, the cerebral cortex — a thin layer of tissue on the brain's surface — is a thicket of prolifically branching neurons. "In a human, there are more than 125 trillion synapses just in the cerebral cortex alone," says Smith. That's roughly equal to the number of stars in 1,500 Milky Way galaxies, he notes. • Here's how Smith, Micheva and their colleagues carried out the technique for the demonstration published in *Neuron*: A slab of tissue — in this case, from a mouse's cerebral cortex — was carefully sliced into sections only 70 nanometers thick. These ultrathin sections were stained with antibodies designed to match 18 different synapse-associated proteins, and they were further modified by conjugation to molecules that respond to light by glowing in different colors.



This visual reconstruction shows the synapses in the mouse somatosensory cortex, the region responsive to whisker stimulation. Neurons are depicted in green; multicolored dots represent separate synapses.

The antibodies were applied in groups of three to the brain sections. After each application, huge numbers of extremely high-resolution photographs recorded the locations of different fluorescing colors associated with antibodies to different synaptic proteins. The antibodies were then chemically rinsed away and the procedure was repeated with the next set of three antibodies, and so forth. Each individual synapse thus acquired its own protein-composition "signature," enabling the compilation of a very fine-grained catalog of the brain's varied synaptic types.

The team created software that virtually stitched together all the slices in the original slab into a three-dimensional image that can be rotated, penetrated and navigated. The researchers were able to "travel" through the resulting 3-D mosaic and observe different colors corresponding to different synaptic types just as a voyager might transit outer space and note the different hues of the stars dotting the infinite blackness.

This level of detailed visualization has never been achieved before, Smith says. "The entire anatomical context of the synapses is preserved. You know right where each one is, and what kind it is," he says.

Observed in this manner, the brain's overall complexity is almost beyond belief, says Smith. "One synapse, by itself, is more like a microprocessor — with both memory-storage and information-processing elements — than a mere on/off switch. In fact, one synapse may contain on the order of 1,000 molecular-scale switches. A single human brain has more switches than all the computers and routers and Internet connections on Earth," he says. — BRUCE GOLDMAN

COURTESY STEPHEN SMITH

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COVER: ILLUSTRATION BY GERARD DUBOIS

letter from the dean

Starting out in a career as a pediatric oncologist and HIV specialist, I soon encountered serious ethical questions that medical school classes had not prepared me to answer.

At what age should children learn they have a life-threatening disease? At what age should a child be expected to give informed consent or assent for the treatment of a serious disease, and what should be done if a child refuses potentially life-saving treatment? Is it moral to test drugs on a vulnerable population such as children? Is it moral *not* to test drugs on children when, after all, it's only through such clinical trials pediatricians will learn what works? I hasten to add that some of these questions are still not fully resolved.

Medical education for my generation was by and large a matter of learning medical facts and gaining practical experience. At the end of the 1960s, when I was a medical student, bioethics was in its infancy. When my generation became physicians and scientists, we often relied on our internal moral compass when faced with ethical quandaries — a strategy that in hindsight did not always result in the best decisions.

That's changing today, and I think that is a good thing. As medical treatments and delivery have become more complicated and society has become more diverse, ethical dilemmas have come center stage. With these challenges emerging from every facet of medicine, more and more we rely on systematic analysis to guide our responses. That's why today bioethics should be a part of medical school education for future physicians.

No matter what specialty students choose, they will face difficult ethical questions, which will grow only more common in the years to come. One area of health care already posing challenges is genetic medicine. If the genomic revolution bears fruit and personalized medicine becomes part of ordinary health care, we'll face challenges to our privacy and will see greater potential for genetic discrimination.

The primary question for academic medicine is how to prepare future doctors. Most U.S. medical schools teach bioethics, but the specifics and time commitment vary widely. At Stanford, all medical students study the subject in the Practice of Medicine course during their first two years. They can explore the area further through additional courses and seminars and by choosing a concentration in biomedical ethics and medical humanities, one of eight in-depth study areas. The unusual program combines research and clinical experience; its students make valuable contributions to scholarship with the potential to direct future policies and protocols.

Bioethics began coalescing as a field in the 1970s, spurred in part by public debate over demands by the parents of coma patient Karen Quinlan to remove her feeding tube, in part by in vitro fertilization breakthroughs and in part by outrage over the Tuskegee syphilis study. Today, several thousand people in the United States make bioethics the focus of their teaching, clinical practice or research.

LESLIE WILLIAMSON

Ultimately, what is most important for assuring ethical medicine of the future is that medical schools imbue physicians and scientists with the knowledge and sensitivity to recognize when they have entered an ethical gray zone, and the wisdom to ask for guidance when the time comes, as it inevitably will.

Sincerely,
Philip A. Pizzo, MD
Dean
Stanford University School of Medicine
Carl and Elizabeth Naumann
Professor, Pediatrics, Microbiology and Immunology

upfront

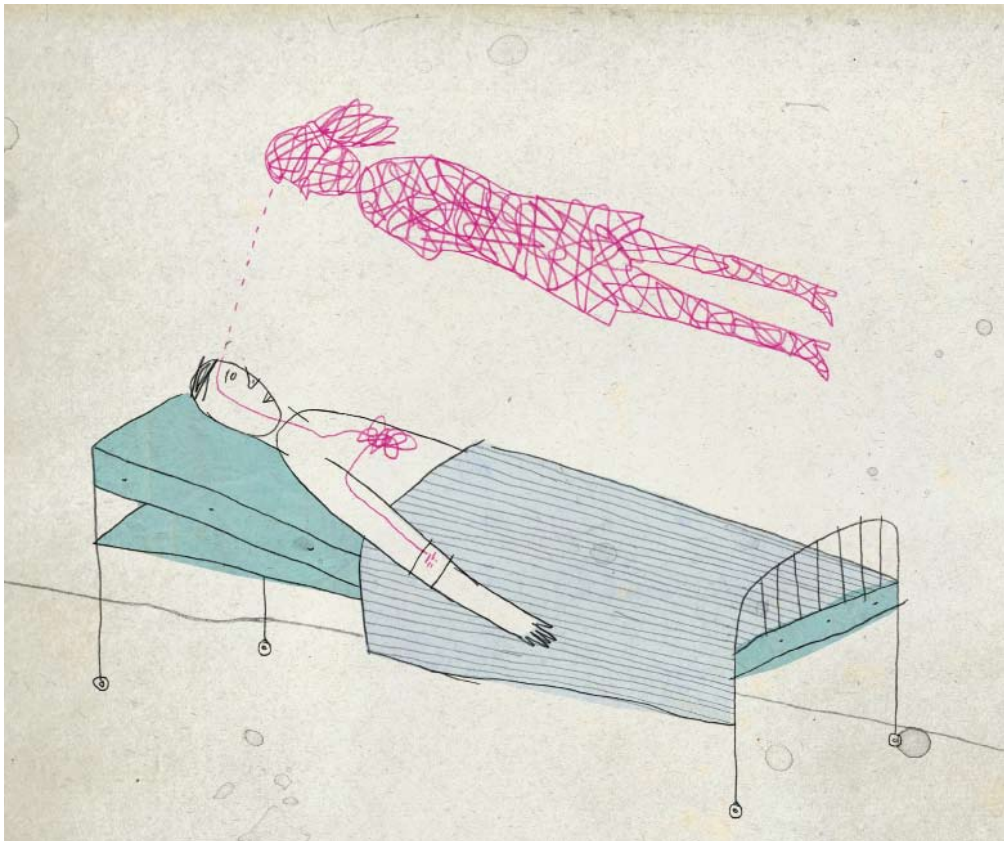
A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD UNIVERSITY MEDICAL CENTER

Turn on relief

IT'S TRUE WHAT THE SONG SAYS: Love *is* the drug, especially if you're in pain. The intense feelings of love provide an amazingly effective balm, says professor of anesthesia Sean Mackey, MD, PhD, senior author of an Oct. 13, 2010, report in the journal *PLoS ONE* about this discovery.

The researchers recruited 15 undergraduates (eight women and seven men) for the study. "We specifically were not looking for longer-lasting, more mature phases of the relationship," says Mackey. "We wanted subjects who were feeling euphoric, energetic, obsessively thinking about their beloved, craving their presence. We posted fliers … and within hours we had undergrads banging on our door."

Each was asked to bring in photos of the beloved and photos of an equally attractive acquaintance.



BRIAN REA

The researchers then successively flashed the pictures before the subjects, while heating up a computer-controlled thermal stimulator placed in the palm of their hands to cause mild pain. At the same time, their brains were scanned in a functional magnetic resonance imaging machine.

The undergraduates were also tested for levels of pain relief while being distracted with word-association tasks such as: "Think of sports that don't involve balls." Scientific evidence has shown that distraction causes pain relief, and researchers wanted to make sure that love was not just working as a distraction from pain.

Results showed that love and distraction reduced pain equally, and they did so much more effectively than concentrating on the photo of the attractive acquaintance. Interestingly, the two methods of pain reduction used very different brain pathways.

"With the distraction test, the brain pathways leading to pain relief were mostly

"One of the key sites for love-induced analgesia is the nucleus accumbens, a reward center for opioids, cocaine and other drugs of abuse. The region tells the brain that you really need to keep doing this."

cognitive," says co-author Jarred Younger, PhD, assistant professor of anesthesia. "The reduction of pain was associated with higher, cortical parts of the brain. Love-induced analgesia is much more associated with the reward centers. It appears to involve more primitive aspects of the brain, activating deep structures that may block pain at a spinal level — similar to how opioid analgesics work.

"One of the key sites for love-induced analgesia is the nucleus accumbens, a reward center for opioids, cocaine and other drugs of abuse. The region tells the brain that you really need to keep doing this," Younger said.

"This tells us that you don't have to just rely on drugs for pain relief," says another co-author, Arthur Aron, a professor of psychology at State University of New York at Stony Brook. "People are feeling intense rewards without the side effects of drugs."

— TRACIE WHITE

The study was funded in part by the Chris Redlich Pain Research Fund.

A gene test fails

A GENETIC MARKER touted as a predictor of coronary artery disease is no such thing, according to a massive international study led by Stanford researchers.

The study analyzed the data from more than 17,000 patients with cardiovascular disease and 40,000 others to assess whether carrying a particular variant of the KIF6 gene indicated a greater risk for coronary artery disease. The disease can lead to chest pain as well as heart attacks, which are often fatal.

The study, published online Oct. 7, 2010, in the *Journal of the American College of Cardiology*, found essentially no association between the gene variant and the risk of coronary disease. "This study puts the nail in the coffin," says Tom Quertermous, MD, professor of cardiovascular medicine and the study's senior author. "This is such a big study — if there was a significant association between this variant and coronary disease, we would have found it."

Celera Corp., which pioneered the mapping of the human genome, owns the assay and currently performs the majority of the testing services.

Previous studies of the variant were less conclusive because they were based on fewer patients with coronary artery disease, says the new study's leader, assistant professor of medicine Themistocles Assimes, MD, PhD. These earlier studies had suggested a 22 to 55 percent greater risk for those who had the variant. "We are showing that the additional risk is almost certainly nil in subjects of European ancestry. If it is not nil, it is at most 2 percent," Assimes says.

The study pulled together data from research groups around the world that have genetically fingerprinted individuals with coronary disease as well as subjects with no known disease. Most of the data were from people of European descent, but a lack of association was also noted in a smaller number of subjects of non-European ancestry. The Stanford researchers' co-authors include more than 130 scientists, clinicians and administrators at over 70 research organizations in Europe and North America.

The study offers good news to patients whose KIF6 test result had indicated they were at risk for heart attacks. "They don't need to worry so much," Quertermous says. "If they are on medications strictly because of their KIF6 test result, they should ask their doctor to reconsider the need for these medications."

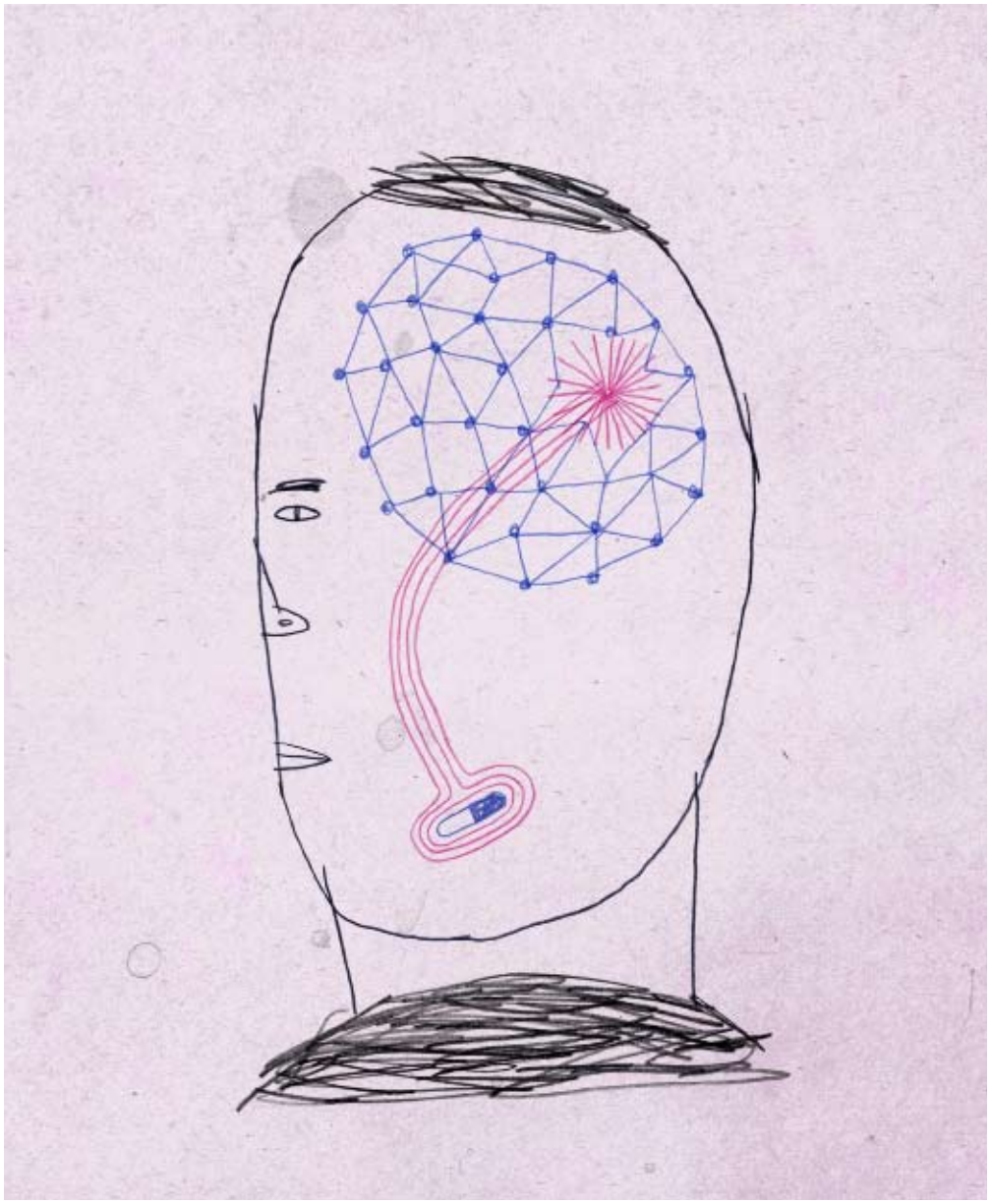
The finding's larger message is that more caution is warranted when using genetic markers to guide health care. "We know from previous experience that a positive association between a genetic variant and a common disease, such as coronary disease, needs to be consistently observed in many human population studies before it can be believed," says Assimes.

— ROSANNE SPECTOR

The data collections used in this study were supported by more than 30 institutions including government and nonprofit agencies and the following companies: Astra Zeneca, Berlin Chemie, Boots Healthcare, deCODE genetics, Glaxo-Smith-Kline, McNeil Pharma, MSD Sharp & Dohme and Pfizer.

Brain gain

SCIENTISTS HAVE FOUND A single protein that directs the growth of blood vessels into brains — a discovery that could help enhance blood vessel growth to fight stroke, or choke it off to starve brain tumors.



BRIAN REA

Calvin Kuo, MD, PhD, associate professor of medicine, and his team discovered the protein's role in studies of brain development in mouse embryos, which as mammals share many biological features with humans. Kuo is the senior author of the report on research, published Nov. 12, 2010, in *Science*.

When the researchers started the experiment, led by Frank Kuhnert, PhD, a research associate in Kuo's lab, they knew the protein, called GPR124, played a part in blood vessel development, but they didn't know what it was.

What they did know was that the protein is a member of a family of proteins called G-protein-coupled receptors that span the membrane that covers cells. Each receptor has a protein partner called a ligand that is secreted into the spaces between cells — usually by a different cell. When a ligand binds to its receptor, it causes a cascade of events within that cell. In this way, the ligand allows cells to "talk" to one another across distances to coordinate many aspects of development and metabolism.

The researchers began by looking to see where in an adult mouse the receptor was normally expressed. They discovered that GPR124 is found almost exclusively on the endothelial cells of the brain and the central nervous system. (Endothelial cells line blood vessels throughout the body and help blood flow more smoothly.) When the researchers bred mice lacking the ability to express GPR124, they died as embryos after about 15 days of gestation. Looking at cross-sections of their brains, it was easy to see why.

"These embryos did not have any blood vessels entering their forebrains or developing spinal cords at all, and the effects were very specific for the nervous system since all other organs had normal blood vessel development," says Kuo.

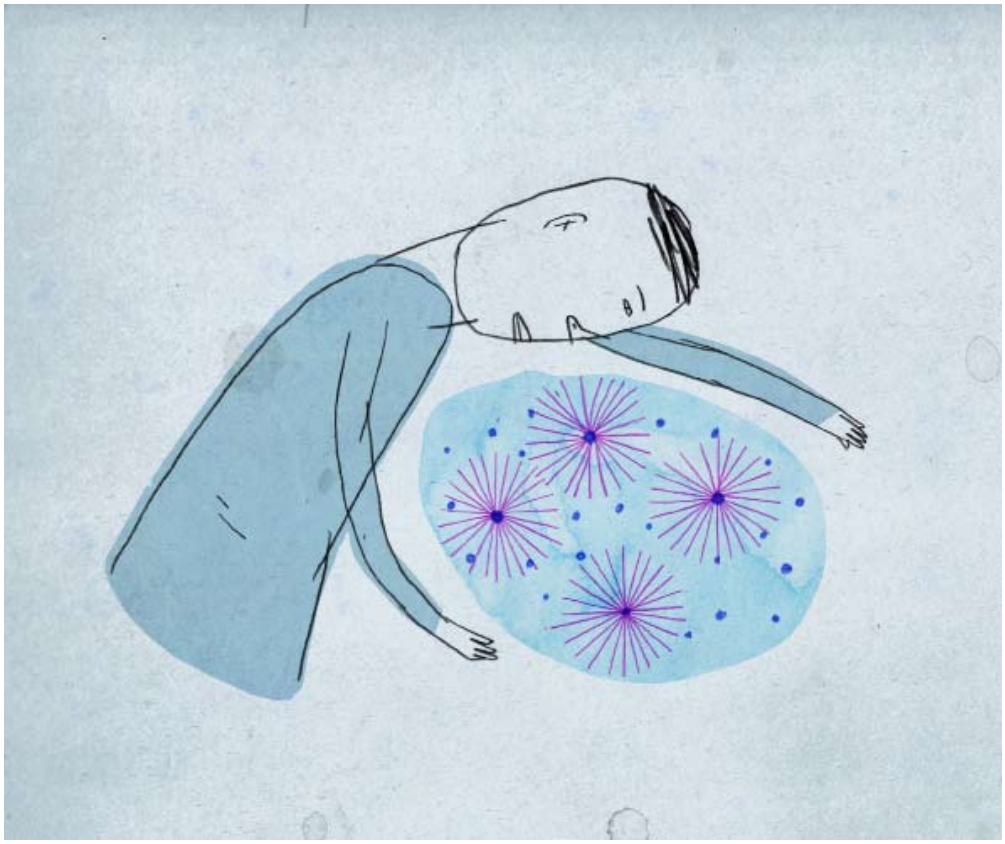
In contrast, control mice embryos, with normal expression of GPR124, had already begun developing brain blood vessels after about 11 days.

In the future, the researchers plan to use mice in which they can toggle the expression of GPR124 on and off to examine its role in brain tumor development and stroke. They also hope to learn more about whether

GPR124 is involved in the formation of the blood-brain barrier.

"There are a tremendous number of disorders that could be affected by GPR124 expression," says Kuo. "We're excited to begin those studies." — KRISTA CONGER

The research was supported in part by the Stanford Center for Children's Brain Tumors, the National Institutes of Health, American Heart Association, U.K. Medical Research Council, Brain Tumor Society and Goldhirsh Foundation.



BRIAN REA

Picking winners

RESEARCHERS HAVE FOUND A WAY to predict within just two days after a human embryo's fertilization whether it will develop successfully. Since two-thirds of all fertilized eggs fail to make it, the technique could be put to good use, especially at in vitro fertilization clinics.

"It completely surprised me that we could predict embryonic fate so well and so early," says Renee Reijo Pera, PhD, the senior author of a paper about the technique, published Oct. 3, 2010, in *Nature Biotechnology*. *Time* magazine named the discovery one of the 10 medical breakthroughs of 2010.

Professor of obstetrics and gynecology Reijo Pera and her team conducted their study on 242 frozen, one-cell human embryos from an Illinois in vitro fertilization program. When the clinic closed in 2002, the patients gave their consent for their embryos to be used in research.

One of the research team's aims was to reduce the need for multiple transfers. Because fertilization attempts fail so often, most patients try to increase their chance of success by having more than one embryo transferred into their womb at a time. Yet, multiple transfers lead to other problems. If more than one embryo develops successfully, chances of miscarriage are higher. If a woman has a selective abortion to reduce the number, she improves the survival odds for those remaining — but most women would prefer to avoid such a choice.

Another goal was to cut down on the time embryos spend growing in culture. Nowadays, clinicians usually grow the embryos in culture for three to five days and then pick those that look healthiest to implant or freeze for later use. But this method doesn't work very well, and concerns are mounting that during culture genetic changes accumulate that can harm the fetus.

The researchers used time-lapse video and computer software they created to track the development of a subset of the embryos from the Illinois clinic — which were ideal for this particular study because they had been cultured for less than a day before being frozen. They followed the embryos through the development of a hollow ball called a blastocyst, which typically occurs within five to six days after fertilization. A blastocyst is usually an indication of a healthy embryo.

"Our findings are a call to action for the health-care system. We need a nationwide strategy for reducing harm from medical care."

They found that 38 percent formed normal-looking blastocysts — about the same proportion that would be expected to be successful in normal pregnancies. Because they had tracked the embryos' development so closely, they were then able to go back and identify specific parameters that were associated with successful blastocyst formation, among them the time that the embryos took to make their first division from one cell into two, as well as how long that division took.

If an embryo's development fit certain parameters, it had a 93 percent likelihood of developing successfully into a blastocyst.

As part of the project, the researchers created an automated algorithm for clinical use that could assess these time-lapse microscopy videos and determine with high accuracy which of these very early embryos would be successful. Stanford has licensed the technology exclusively to Auxogyn Inc. Reijo Pera and the other co-authors of the manuscript own or have the right to purchase stock in the company. — KRISTA CONGER

The research was funded by an anonymous donor, the March of Dimes and the Stanford Institute for Stem Cell Biology and Regenerative Medicine.

Not safe yet

SINCE A 1999 Institute of Medicine report sounded the alarm about high medical error rates, most U.S. hospitals have made changes in operations intended to keep patients safer. But a look at 10 hospitals' safety records reveals bad news: Over a recent five-year period, no decreases in patient harm were found at these randomly selected hospitals in North Carolina, a state that has shown a particularly strong commitment to patient safety.

"Our findings are a call to action for the health-care system. We need a nationwide strategy for reducing harm from medical care," says Paul Sharek, MD, an associate professor of pediatrics, and co-author of the report.

The research was published Nov. 25, 2010, in the *New England Journal of Medicine*. The study's lead author is Christopher Landrigan, MD, assistant professor of pediatrics and of medicine at Harvard.

To perform the study, the team used the Institute for Healthcare Improvement's Global Trigger Tool. Trained investigators scanned patients' charts for "trigger" events that suggested harm had occurred. For instance, a prescription for the anti-opioid drug naloxone could suggest an overdose of morphine or a related opioid medication. When reviewers find such an event, they examine the patient's entire medical record to look for evidence of harm.

The reviewers used this method to examine medical charts from 2,341 randomly selected hospital admissions at 10 randomly selected hospitals in North Carolina between January 2002 and December 2007. The analysis turned up evidence of 588 instances of harm to patients. More than 80 percent of the harms identified were temporary. About half of the temporary harms prolonged the patient's hospital stay.

Most of the harms were minor or reversible but some were more serious: 50 were classified as life-threatening, 17 incidents resulted in permanent harm to a patient and 14 deaths were attributed in whole or in part to medical errors.

Total harm rates remained the same throughout the study, at about 25 harms per 100 hospital admissions. Separate analysis of different types of harms — more versus less severe and preventable versus non-preventable — did not uncover any subtypes of harm that changed during the study. However, the study did not have the statistical power to evaluate changes in the rate of the most serious harms.

The findings beg the question: Are safety measures useless? Sharek says no. "Implementation of best practices shown to improve patient safety is very difficult and takes time," Sharek says. Adding to the challenge is the paucity of evidence-based best practices identified in the medical literature for hospitals to implement. More research is needed to separate useful safety interventions from those that do not reduce medical errors, Sharek says.
— ERIN DIGITALE

The research was funded by a grant from the Rx Foundation and by funds from the Institute for Healthcare Improvement.

BIOETHICS AT MIDLIFE

the dilemmas facing a field in flux

BY SUSAN IPAKTCHIAN

ILLUSTRATION BY GÉRARD DUBOIS

The resident is seated at the conference table giving her colleagues an overview of a patient in one of Stanford Hospital's ICUs. The unconscious man with no ID had been brought in the previous day after being found in a pool of blood. He had vomited an additional 5 liters of blood and his condition remained unstable. If he begins to bleed again, the resident says, the medical team feels there's little more that can be done. • Next to her at the table is David Magnus, director of Stanford's Center for Biomedical Ethics and a regular participant in the weekly ICU interdisciplinary rounds, along with physicians, social workers, nurses, respiratory therapists, dietitians and clergy. At these sessions, the participants review the status of all the patients currently in the medical ICU. "Who is making the decision to discontinue medical care?" Magnus asks the resident. • "Well," she replies, "we are." • "You can't do that," Magnus points out, explaining that for an unresponsive patient with no designated representative to make a decision, an ethics consult is required. The ethics team would assess the situation and make a recommendation to the hospital's chief of staff,

who would then make the decision. "So, are you requesting an ethics consult?" Magnus asks with a gentle smile. The resident assents, and Magnus writes himself a note to follow up on this case.

A clinical ethics consult — which addresses situations such as how to protect a patient from the harmful acts of a family member or whether a psychiatric patient can refuse treatment — allows a small, multidisciplinary team to gather relevant facts from all of the involved parties, elucidate values and make recommendations in which those values are prioritized. In highly wrought, emotional circumstances when there may be conflicts between the desires of the patient, the patient's family and the doctors and nurses providing care, the ethics team works to provide thoughtful, respectful and evidence-based guidance. The team approach is a stark contrast to the early days of medicine when doctors alone made the decisions, often without consulting the patient.

No longer relegated to the background, bioethics has become a strong team player in the medical establishment as society wrestles with such high-profile issues as the role of stem cell research and how to handle end-of-life care. And in these situations, bioethicists wear many hats. They give scientists and clinicians practical tools and advice for dealing with the ethical, legal and social ramifications of their work. They also play roles in educating the public, protecting the rights of patients and giving a voice to vulnerable populations.

"The world of medicine has been washed up in this tsunami of commercial health care, and it makes it very difficult to see each patient as a person," says Albert Jonsen, PhD, one of the early bioethicists and author of *The Birth of Bioethics*, among other books. "That's what bioethics is supposed to do."

Bioethics' reach extends far beyond the bedside and the practice of clinical ethics. Its primary purpose is to inquire, reflect and debate the ethical issues associated with medicine, bioscience and health. Somewhere between 2,000 and 6,000 people in the United States focus on bioethics as their primary area of research, teaching or clinical practice, says Magnus. Their debates play out in a variety of venues, from the courts, to the halls of government, to the media.

And yet, despite the field's growth since the 1970s, bioethics is still maturing. Its practitioners face skepticism from those who believe bioethicists have built-in biases and an overly "American" approach that lacks a true understanding of other cultures' values. The field also has internal struggles: Should its training programs share a common curriculum? And — a biggie — should clinical bioethicists be certified?

"Bioethics is a field that is always evolving because it exists in relation to newly emerging moral questions in society," says bioethicist Laura Roberts, MD, professor and chair of psychiatry and behavioral sciences at Stanford. "The field itself struggles — we are always trying to make sense of things and to understand and resolve complex issues in ways that rely on more than mere intuition."

And though the struggles may take time to resolve, bioethicists are doing what they do best — rolling up their sleeves, gathering as much information as possible and going where the evidence leads them.

TWO DAYS AFTER Magnus steered the ICU resident toward an ethics consult for the unconscious patient, a hospital social worker learns the man's identity and tracks down his brother. With a family member involved, the ethics consult is no longer necessary. Examinations show the patient, in his 40s, suffered significant brain damage and among other problems is in liver failure. While the hospital will continue to treat him, the man's family signs a do-not-resuscitate order which means that there will be no attempts to revive him if his heart or breathing stop.

Just 40 years ago, a request for an ethics consultation, now routine, was rarely an option. Few hospitals or academic medical centers had bioethicists on staff. Jonsen notes that when he accepted a position at the University of California-San Francisco in 1972, he was only the second bioethicist on the faculty at any U.S. medical school. The 1976 case in which Karen Anne Quinlan's parents went to court to remove her feeding tube was among the first to stir public debate about the ethics of withholding life-prolonging treatment. The field's reach soon broadened to the research world with the 1978 publication of the Belmont Report, establishing principles for protecting patients enrolled in clinical trials. Jonsen,

'WE ARE ALWAYS TRYING TO MAKE SENSE OF THINGS AND TO UNDERSTAND AND RESOLVE COMPLEX ISSUES IN WAYS THAT RELY ON MORE THAN MERE INTUITION.'

IN THE THICK OF IT

Stanford's bioethicists serve as resources for researchers

When Lauren Milner arrived at Stanford this past September to begin her postdoctoral fellowship in biomedical ethics, she knew she'd be sitting in on discussions involving the ethical implications of research projects. She was pleasantly surprised to find out that she'd also have the opportunity to participate in ethics discussions in Stanford's hospitals, listening as doctors and other health-care providers wrestled with decisions involving their patients.

"Watching these doctors and other people try to hash out the best decision is really heartening, and that's what this is all about — individual people with individual problems that need guidance," says Milner, PhD, whose background is in behavioral genetics.

The interplay of clinical and research ethics makes Stanford's Center for Biomedical Ethics and its fellowship program unusual. While many medical schools have bioethics centers that address academic or research-oriented questions, they often focus solely on conducting their own research. But the members of Stanford's center play leadership roles in the hospitals' ethics committees, acting as resources for physicians as well as patients and their families in making difficult decisions under stressful circumstances. In addition, the center in 2004 initiated a "benchside" consult service for researchers that is now operated through Spectrum, the medical school's center for clinical and translational research.

Stanford's training program is funded by a federal grant received in 2004 to create the Center for the Integration of Research on Genetics and Ethics. CIRGE is one of six centers funded by the National Human Genome Research Institute to explore the ethical, legal and social implications of genetic research.

Mildred Cho, PhD, the principal investigator for the CIRGE grant and associate director of the bioethics center, says the students in the postdoctoral program come from a variety of backgrounds — primarily from a bioscience field but also from law and social science. The postdocs spend the two to three years of their fellowship filling in the gaps in their backgrounds to become bioethicists. For those with science backgrounds, that means masatering the methodology of social science research (such as conducting interviews, coding the responses, and looking for trends) as well as learning basic ethical theory and spending time getting exposure to clinical ethics.

"It's very overwhelming during the first few months of the fellowship," says Cho, who earned her PhD in pharmacology before moving into the bioethics field. "This is very different for trainees, especially if they've come from a laboratory science. They're used to cutting up mice, whereas the social science methods that we use tend to be more observational."

The strength of Stanford's postdoctoral program is reflected in the success of its first three graduates, all of whom earned tenure-track faculty positions upon completing the program. "It's hard enough to get a faculty position, and in bioethics there aren't that many slots," Cho says. "It speaks not just to the quality of the people selected for our program but also to the demand for bioethicists who have science training."

Jen McCormick, PhD, who graduated from the program in 2008 and is now an assistant professor of biomedical ethics at the Mayo Clinic and College of Medicine, remembers feeling that she had stumbled upon a whole new world when she began her postdoctoral training. McCormick, who describes herself as a policy nerd, had already spent a year teaching science policy, doing research and writing a book after earning her doctorate in biology. Still, making the transition to bioethics "uncovered a huge gap in my knowledge. But it was one of the best things that ever happened to me," she says.

As someone still making that transition from lab science to social science, Milner can attest to the magnitude of difference between the bench and bioethics. She laughs as she recalls a recent conversation with a colleague who asked if she thought qualitative or quantitative data would be better for a research project. "And I said, 'What's qualitative data?'

"I originally thought that bioethics would be just like science, only on social issues — but it's really not," she says. "I'm starting to understand that the way I learned to do research in a lab is not going to be productive in the field of ethics. These are issues that you can't put in a beaker and run on a gel."

one of the report's authors, says that by the 1980s most medical schools saw the need for bioethicists. However, many of the programs that emerged in subsequent years operated primarily as think tanks and had little involvement with the clinical and research cases arising on their own campuses.

As the field reaches middle age, though, the think-tank approach is changing. An increasing number of U.S. bioethics centers have begun emulating Stanford and other pioneering programs by providing both clinical and research consulting services in addition to conducting their own research. The growing need for research guidance is due in part to a National Institutes of Health initiative to streamline the process of turning lab findings into therapies. This program, the Clinical and Translational Sciences Awards, requires medical schools that receive CTSA funding to offer bioethics consultations to its researchers. Stanford's bioethics center had been offering benchside consults since 2004, and the center is now providing those services through Spectrum, the program that administers Stanford's CTSA grant.

SOCIOLOGIST Renee Fox, PhD, of the University of Pennsylvania is in the unusual position of being both a participant in and observer of bioethics since its inception. Fox has spent her career conducting first-hand studies of the sociology of medicine as well as medical education, research and ethics. Because of her expertise, she was named to the founding board of the Hastings Center, the first U.S. bioethics center.

One of Fox's main criticisms of bioethics is that its U.S. practitioners don't always seem aware of just how "American" the field's foundational values are. For instance, bioethics places heavy emphasis on individual rights, including the ability of informed individuals to freely make decisions for themselves. That focus, says Fox, doesn't always give enough weight to other crucial values, such as the connection between individuals and others, kinship, community and the common good. It also doesn't adequately reflect the values of other cultures, which have largely imported the bioethics model developed in the United States. "Bioethics has become global without becoming international," she says.

It's important, Fox and others say, for bioethicists to continually challenge their own assumptions about the values underlying their approach as well as the issues they study.

Stanford's Roberts, a longtime practitioner of evidence-based ethics in support of her work with vulnerable populations, says relying on evidence is critical for bioethicists to understand the impact of their decisions. "Reality is so much more complicated and rich than what we can imagine ourselves," Roberts says. "Evidence can help resolve certain kinds of questions that good, well-intentioned people might naturally disagree upon. When ethicists have opinions and beliefs that are not grounded in the real experiences of the people whom they are advising, they can do harm despite their desire to help others."

This point was driven home early in her career when psychiatry researchers questioned the ethics of enrolling people with schizophrenia in clinical trials aimed at finding treatments for the disease. The prevailing wisdom was that people with severe mental illness were incapable of providing informed consent for trial participation, but when Roberts interviewed patients she found this was not uniformly the case. While some clearly fell into that category, she saw others who, though ill and experiencing symptoms such as hallucinations and delusional beliefs, were also "rational, intelligent, wonderfully altruistic, thoughtful and aware."

"So if there are arm-chair philosophers who are not attuned to the strengths of people with serious illnesses, whether it be cancer or schizophrenia, there is the potential to underestimate, stigmatize and discriminate against them."

LIKE MANY bioethicists of her generation, Mildred Cho didn't even know what the field was about until she unintentionally wandered in. She began moving toward it when she enrolled as an undergraduate in biology at MIT in 1980 and learned that just a few years earlier the Cambridge, Mass., city council had imposed a three-month moratorium on recombinant DNA research. City leaders were concerned about what the

'AT ITS BEST, BIOETHICS CAN HELP RESEARCHERS DO BETTER RESEARCH AND IT CAN HELP TRANSLATE THAT RESEARCH INTO PRACTICAL APPLICATIONS.'

"people in white coats" would do with this frightening new capability to combine DNA from two or more sources.

"That got me interested in science policy," says Cho, PhD, associate director of Stanford's bioethics center. That interest persisted through Cho's doctoral work in developmental biology at Stanford, and led to a fellowship at UCSF's Institute for Health Policy Studies.

A big part of her work since joining Stanford's faculty has been getting researchers to welcome bioethicists into the lab setting, in the same way that clinicians had come to value clinical ethics input over the years. Stanford's bioethics center was one of the first to offer a benchside consulting service, and has one of the most active such services in the country. Cho, who oversees the lab consults, believes that "at its best, bioethics can help researchers do better research and it can help translate that research into practical applications."

As an example, Cho says one of the big problems in research involving human subjects today is how to handle "incidental" findings, such as when the analysis of a person's genome for a clinical trial turns up unexpected results. How should the study participant be told about this? While the trial's principal investigator may not have considered such a situation, bioethicists have. As a result, Stanford's bioethicists have helped develop language now included in the informed-consent documents signed by clinical trial subjects addressing how such incidental findings will be handled.

One of the inspirations behind Stanford's benchside consulting service was a request for advice from Irving Weissman, MD, director of Stanford's Institute for Cell Biology and Regenerative Medicine. In 2001, he asked for recommendations about creating animal models to study human brain diseases, such as Alzheimer's and Parkinson's, that do not normally occur in animals. To do that, he posed the possibility of inserting human neural stem cells derived from patients with a brain disorder into the brains of fetal mice, thereby creating a cellular chimera — an organism made up of two genetically distinct types of cells. Mindful of possible concerns from the public about creating this kind of mouse, Weissman wanted some guidance.

A team of bioethicists researched the case and advised him on how they thought such work could proceed. For instance, they suggested that Weissman conduct the least controversial work first and move slowly to ensure that the brains in the mice didn't take on human characteristics. So far, Weissman has done some preliminary work by creating mice in which about 1 percent of the brain cells were human.

"Ethics isn't just about things like informed consent; it's also about doing research that's of value to the research participants and to the populations that are supposed to be served by the research," Cho says. "We can help identify those values and communicate them to the researchers."

ALTHOUGH MANY medical schools offer training programs and classes in bioethics, the field is still developing a core curriculum.

"In engineering, you can't have different ideas of how to build a bridge," Jonsen points out. "Right now, there's no common curriculum for training bioethicists."

The lack of consensus about the prerequisites for qualifying as a bioethicist also troubles Fox, who notes that there isn't agreement on how much philosophy, religion, sociology, anthropology, law and other training students should receive in master's and doctoral programs. "I really don't know what they're learning at Stanford compared with what they're learning at Penn, for example," she says, adding that she believes students also need in-depth training in research methods before conducting field interviews and observations, and clinical and psychological training before offering counsel at a patient's bedside.

And should the curriculum be focused solely on the theories and social-science research methods that underlie the discipline, or should it include training in clinical ethics as well? And should there be a formal accreditation process for bioethics programs?

At Stanford, for instance, students and postdoctoral trainees have the option of participating in the clinical ethics rounds at the two hospitals. The training was particularly useful to former postdoctoral trainee Holly Tabor, PhD, who was hired in 2008 as an assistant professor of pediatrics in bioethics at the University of Washington and a scholar at the Trueman Katz Center for Pediatric Bioethics at Seattle Children's Hospital. Tabor says that during her time at Stanford, she began shadowing Magnus on the clinical rounds and enjoyed it so much that she trained to become a full-time, on-call ethics consultant at the hospitals. She now does clinical and research consultations as well as studying issues surrounding whole-genome sequencing, such as how the genetic test results are interpreted and delivered to patients. "The clinical work will always be an important part of what I do," Tabor says.

FOR YEARS bioethicists have debated how far to go in professionalizing the field — particularly clinical ethics. Currently, there is no certification process, but Magnus and others think the field is moving toward some kind of credentialing for those who

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JESSE'S LEGACY

A CONVERSATION WITH PAUL GELSINGER

Eleven years after his son's death, the heartbreak in Paul Gelsinger's voice is clear. Jesse Gelsinger would have been 29 today. Instead his name is synonymous with the colossal failure of a clinical trial.

Jesse Gelsinger was born with a rare and sometimes fatal metabolic disorder, ornithine transcarbamylase deficiency syndrome, which causes ammonia to build up in the blood and can cause liver and nerve damage, lethargy and coma. Jesse's case was not severe, and he was able to live a relatively normal life, controlling the disease through medication and diet. At 18, on Sept. 9, 1999, he entered a clinical trial run by the University of Pennsylvania aimed at developing gene therapy for infants born with the illness. His motive was pure altruism, as any treatment from the trial would most likely have had no impact on his life. Eight days later he was dead, apparently having suffered a massive immune response to the virus that was a component of the trial's injections. Jesse Gelsinger became the first person ever publicly identified to have died in a clinical trial for gene therapy.

An investigation by the federal Food and Drug Administration found widespread problems. These included conflicts of interests, researcher misconduct and the failure to tell the young man and his family about the potential hazards of participation in the clinical trial.

If a young person's death can ever be said to have meaning, Jesse's did — it forever changed clinical research. His legacy is a warning to all researchers about the dangers of clinical trials with human subjects.

Gelsinger spoke about clinical trials and ethics with Paul Costello, the School of Medicine's chief communications officer.

Costello: ***Eleven years after your son's death, do you think that human subjects are any safer?***

Gelsinger: The system hasn't changed dramatically — not enough for me to be comfortable with it.

Costello: ***Why do you say that?***

Gelsinger: I worked at this for seven, eight years, and I became really frustrated with the lack of change. The only changes that came about were at institutions where they got caught — institutions that were found to be lax in their ethical review and conduct in research. The University of Pennsylvania has a model program now, but it's only because of what happened to Jesse there and the awareness it brought about. Unless this happens at many more institutions, and we have some concise guidelines for ethical conduct, I'm not really comfortable that things have changed enough.

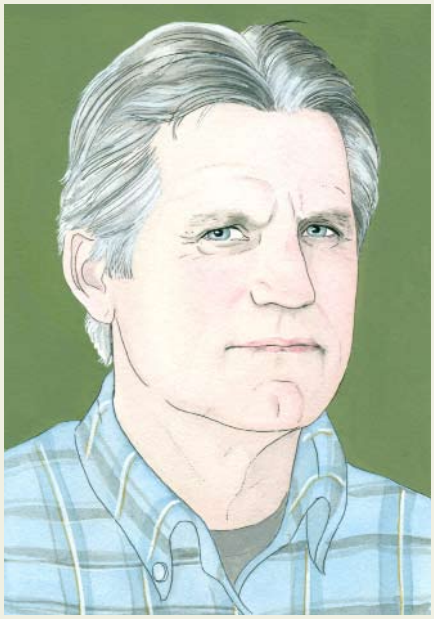
Costello: ***What do you think are the most significant gaps that need to be addressed?***

Gelsinger: For me, the primary one is conflict of interest related to financial matters. A lot of researchers have a financial stake in what they're working on — they're involved with companies that have a stake in the outcome of the research. And a lot of the medical institutions have ownership in these companies. The money puts blinders on people. Going after prestige is part of it too, but primarily it's the money.

In my case, I came to see that these were not bad men who did this; these were very qualified scientists. It's the companies pushing for these technologies. They want results, and they put pressure on these researchers, and so the researchers push the envelope further than they should.

Costello: ***I'm sure people have sought advice from you over the years about whether they should participate in clinical trials. What do you tell them?***

LARA TOMLIN



Gelsinger: I try to steer away from giving advice, but if it's somebody I know personally, then I just advise them: Be very careful. There are a lot of hidden things going on that you're most likely not aware of. Try to get an advocate, somebody who's got a lot of medical knowledge and can be there to ask the right questions and find the answers that you need.

Costello: *What's your message to those in government who oversee clinical trials?*

Gelsinger: The whole system should be spending a whole lot more money on the ethical oversight of research, and they should be pushing for it all the time.

Costello: *What has your experience with clinical trials taught you?*

Gelsinger: I never will trust the system again. It was my first and only experience with clinical research, and you can be sure that I will not participate in a clinical trial, probably even if it would save my life.

Costello: *You wouldn't ever, ever participate in a clinical trial?*

Gelsinger: The system's not trustworthy yet. We need to get walls up to prevent financial conflicts of interest. Companies that want to do research shouldn't be the sponsors, directly, of that research. They should not be able to have any communication with the researchers directly. There should be intermediaries that handle the money and the information. We should get this thing so it's right and ethical. But I don't see that happening. I think the laws that are in effect are there because of pressure from the financial interests that stand to benefit.

I'm a far less trusting person than I used to be, and that's a shame. I want to trust people, and especially the medical profession, and it was just such a disappointing, disheartening experience. I still rely on doctors. I just had knee surgery this year, but I ask a lot of questions that have doctors raising their eyebrows at me.

Costello: *What do you ask?*

Gelsinger: Well, I get into, "So, how did you come to use this technology?" and "How many patients have been treated?" and "What kind of negative effects is it having?"

Costello: *I read that you scattered Jesse's ashes at Mt. Wrightson, outside Tucson where he grew up. I wondered if you ever return up there and if you do, what are your thoughts when you're standing there?*

Gelsinger: I haven't been there in about four years because my knees started giving me so many problems. One of my goals is to be able to hike up to that mountain again. And I know they had to do clinical research to develop the implants that would make that possible.

Costello: *So your message isn't stop clinical trials. Your message is get it right.*

Gelsinger: Absolutely. Get it right. Go about it with the same intent that my son had. He had a heart of gold. What he did wasn't for himself, it was for others. Hopefully the system can work the same way he did.

This interview was condensed and edited by Rosanne Spector.

Peddling hope

BIOETHICS
NO EASY ANSWERS

Unproven stem cell treatments for sale in a country near you

BY KRISTA CONGER
ILLUSTRATION BY GÉRARD DUBOIS

ON THE SURFACE IT SEEMS EASY. Overseas stem cell "clinics" peddling unproven treatments to desperate and dying patients, charging tens of thousands of dollars for the privilege of being injected with mysterious concoctions of cells meant to cure almost every ailment: What's not to hate? But for many patients, the issue is more complex than it may at first seem. To them, the fact that a treatment has not been thoroughly tested and approved by the U.S. Food and Drug Administration is a minor detail, with hope trouncing logic in a world where mainstream medicine can sometimes neither cure nor alleviate suffering. The result is a booming international business that is growing every year, thanks in large part to the Internet and the savvy marketers who prey on patients' fears. • "What we're hearing on these websites promoting these unproven treatments is that regulatory agencies like


A17
mexico
300
CLINICS
travel
Treatment
diabetes

the Food and Drug Administration and the pharmaceutical industry don't want you to get better," says Douglas Sipp, the manager of scientific communications at RIKEN Center for Developmental Biology in Kobe, Japan, and an international expert on the marketing of such treatments around the world. "And this resonates with people who are, in many cases, seriously ill, and who are frustrated by the perceived lack of progress in established medicine."

With people who are so sick, comes the opportunity and risk of exploitation, says Ezekiel Emanuel, MD, PhD, director of the National Institute of Health's Department of Bioethics and special advisor for health policy in the White House's Office of Management and Budget. "These overseas clinics are charging a very vulnerable population a lot of money for treatments that are unproven and are operating with no oversight and no monitoring," says Emanuel.

And in fact, there's really no way to know exactly what patients are receiving as part of their "treatment."

This tension between patients who believe they have the right to undergo any procedure they hope will help them and the government agencies and scientists who wish to bar practitioners from providing unproven treatments is not going to be easily resolved, in part because "right" answers in cases like these are hard to come by. What seems clear-cut on paper — experimental treatments shouldn't be marketed for large amounts of money to desperate patients — can be upended in the presence of a person with a life-threatening illness whose personal risk-versus-benefit equation is so different from your own.

"It's a much more complex set of decisions than you might imagine," says Stanford bioethicist Christopher Scott, who directs Stanford's Program on Stem Cells in Society. "Our devotion to clinical trials doesn't acknowledge that, for the most part, enrolling in a trial is an act of altruism. Early phase trials are designed to test safety, not to benefit participants."

In contrast, stem cells appear the stuff of magic and miracles; their existence taps into a deeply held awe about the nature of what it means to be human. The advances that they could bring about for medicine are mind-boggling, and we're now seemingly on the cusp of promises delivered. But, in this arena, every legitimate advance carries with it an unavoidable cost.

"When we report something good about stem cells, it gets picked up in the media, or in a blog that patients read," says Jeanne Loring, PhD, director of the Center for Regenerative Medicine at the Scripps Research Institute in La Jolla, Calif. "It gives them more ammunition to say that the FDA is stupid for denying access to treatments that seem like they should work."

Indeed, the fact that there are a number of ongoing clinical trials testing the ability of embryonic and adult stem cells to treat a variety of human diseases appears to validate the use of these treatments. And the proponents of untested treatments can be very persuasive and appear to have good credentials. Sifting fact from fiction can be difficult even for trained scientists, in part because the claims proponents make often hover just on the edge of believability: Your body uses stem cells to heal itself (yes); stem cells can be purified from blood and other tissues (yes); these stem cells, when injected back into the body, can heal wounds or repair damaged tissue (er, sometimes?).

Most laypeople would not spot the flaw in the preceding argument — namely that, in contrast to the embryonic stem cells or laboratory-generated induced pluripotent stem cells often featured in the media, most stem cells found in the body (called "adult" stem cells) are highly tissue-specific. A bone stem cell can't churn out replacement neurons, and a blood stem cell can't make new skin. This tendency of so-called stem cell clinics to tip over the edge into the realm of speculation and circumstantial evidence has no place in commercialized treatments, say observers.

Furthermore, a lack of follow-up and the absence of standardized guidelines for these procedures make it impossible to meaningfully assess the outcome of patients who receive purported embryonic or adult stem cell treatments. Recent reports of at least four deaths associated with such procedures overseas have fanned the flames of opposition to such clinics. And, because there's no way to tell what patients of these clinics are actually receiving, they are subsequently disqualified from participating in any legitimate clinical trials in this country.

"Tens of thousands of patients are being mistreated," says Irving Weissman, MD, director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine and immediate past president of the International Society for Stem Cell Research, or ISSCR. "In some, the treatments will disqualify them from receiving therapies that we know are at least somewhat effective. Also, failures of these unproven treatments will undoubtedly affect the public and private support of legitimate stem cell science."

"Harm is being done at a lot of levels," agrees Loring. "But on the list of things that offend me, the false hope they offer to patients is at the top."

'IT'S A MUCH MORE COMPLEX SET OF DECISIONS than you might imagine. Our devotion to clinical trials doesn't acknowledge that, for the most part, enrolling in a trial is an act of altruism.'

But the hope is cleverly packaged. "These clinics never promise a patient will be healed," says Sipp. "They'll say things like, 'most patients experience an improvement.' And, when you've spent a lot of your own money, or money that was given to you by friends or relatives, the incentive to report that the treatment helped is very strong. There's a lot of room for the placebo effect."

Thanks in part to efforts of organizations like the ISSCR, the phenomenon of what's been termed stem cell tourism has gained attention during the past year.

(Sipp, who is an ISSCR member, discourages the use of this phrase because it trivializes the patient experience and because travel is not always required.) In response, Costa Rica recently shut down a popular clinic called the Institute of Cellular Medicine that claimed to have treated at least 700 patients during the past five years. The company still operates in Panama under the name Stem Cell Institute. Last March, India launched a review of stem cell medicine in that country, and the Chinese Ministry of Health in 2009 vowed to tighten regulation of stem cell therapies. Yet the number of providers continues to grow.

"It's a worldwide industry," says Sipp, who estimates there are about 300 clinics that offer what they claim to be stem-cell-based treatments for everything from autism to diabetes, from ALS to cancer. "And recently we've been seeing a growing complement of places in the United States that either refer people to nearby international clinics in Mexico or the Dominican Republic for the treatment, or even perform procedures domestically."

By tracking the number of patients some of the bigger clinics state they have treated, Sipp has concluded that tens of thousands of people may have received unproven stem cell treatments worldwide during the past decade, which indicates a market size approaching $1 billion.

In June 2010, the ISSCR launched a website called "A Closer Look at Stem Cell Treatments" devoted to public education about stem cells and medicine. The website encourages people to submit names of suspect clinics for investigation by the ISSCR, but because the organization won't evaluate the safety or efficacy of any treatment — only whether the clinic is supervised by an official regulatory agency such as the Food and Drug Administration or the European Medicines Agency and whether a medical ethics committee was involved to protect patients' rights — its usefulness to patients may be limited.

Although ISSCR representatives say there are several ongoing investigations as of January 2011, no results have yet been posted.

It's no surprise, really, that Americans in particular would bristle at being denied access to what may seem to be the most promising clinical advance in generations.

We have freedom of speech, freedom to bear arms, freedom to worship as we please and the freedom to choose how to educate our children. Why can't we also choose our own medical treatment? After all, the outcome of such a choice is intensely personal in its repercussions. We live or we die. We get better or we don't. What's it to anyone else?

"I do think there are still, when you are dying, better or worse ways to die," responds Emanuel. "There is this phenomenon of preying on people who would otherwise be very competent and rigorous in a moment when they are weak and not necessarily having them get all the information they need. You can certainly be made sicker or worse off by some of these treatments."

"It's clear that a patient can't make an informed choice

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BIOETHICS

NO EASY ANSWERS

GENDER X the battle over boy or girl

BY DIANNE KLEIN ILLUSTRATIONS BY GÉRARD DUBOIS

When Aaron Thompson recalls cutting the umbilical cord between his wife and their firstborn child, it's not the joyful symbolism of welcoming a daughter into the world that makes him cry. It's the voice he still hears, at once banal and foreboding, of a delivery room nurse in Orange County, Calif., who looked between his newborn's pudgy legs and simply uttered, "Huh." • Thompson, which is not his real name, repeats the sound of that voice, low and flat, and more tears flow. "I started paying attention then," he says. "Then another nurse looked and said the same thing, in the same way. Then they called the doctor, who says, 'There's something wrong with your daughter, but I've got a C-section to do, so I've got to go.'" • What was "wrong" with the Thompsons' daughter — a potentially life-threatening form of the endocrine disorder congenital adrenal hyperplasia — wouldn't be medically diagnosed for a few more days. One of its effects, however, was immediately apparent: genitalia that could have been mistaken for male, or, owing to a malformed vagina, something in between.

"I was in shock," says the child's mother, Samantha. "I remember later one of the doctors saying, 'Have you named the baby yet? You might want to wait.'"

Until that night in the maternity ward where his daughter was born, Aaron Thompson, a police officer, says he wasn't aware that what were popularly called hermaphrodites even existed beyond the realm of mythology. Yet now he knows his daughter's so-called ambiguous genitalia place her within a broad and unsettled diagnostic grouping known as disorders of sex development, or DSDs.

Deciding how, or even if, DSDs should be treated is trying the skills, minds and hearts of all concerned. A jagged divide has opened between those who believe in surgery to "fix" a baby's sex and those who say — barring medical necessity — a child's genitals should be kept intact. The arguments touch on the complex nature of gender and sexual identity, on what makes up a person's sense of self, and who — or what — decides what that might be. The issues are roiling the community of pediatric bioethicists to such an extent that today many of its members are hesitant to publicly express their opinions for fear of hardening the divide. "Everybody's got a dog in this fight," says one.

Even the nomenclature is a minefield of confusion, anger and hurt. Terms used include intersex, DSDs, true hermaphrodite, female or male pseudohermaphrodite, sex reversal, or simply the medical names of some 30 specific conditions, each with its proponents and detractors. And that's just the clash over words.

The Thompsons' daughter, now a beautiful 5-year-old who wears a medical alert bracelet for congenital adrenal hyperplasia, is by every medical indicator a girl. Like her younger sister, she has XX chromosomes, ovaries, a uterus and Fallopian tubes. But because her adrenal glands lack an enzyme to make the hormones cortisol and aldosterone, her body produces more androgen, a type of male sex hormone. In utero, this caused her genitals and, many medical authorities believe, her brain, to become "masculinized," which, in turn, is associated with behavior typically linked to males. Today she must take daily hormone medication to stay alive.

Her parents call her a tomboy but are quick to point out that her mother was one, too. And their daughter's genitals, they say, now look like those of any other little girl. At the age of 6 months, she had surgery to reduce the size of her clitoris and open her partially fused labia. At least one follow-up surgery, around the time of puberty, will likely need to be performed to counteract narrowing of the vaginal canal.

Samantha Thompson, an accountant, says before she and her husband agreed to the surgery, she researched the pros and cons on the Internet, recalling how "some people called it mutilation," and how adults with DSDs who underwent genital plastic surgery as infants warned that their sexual organs and their psyches remained horribly scarred. Many such adults have begun speaking out about what they say was medical ignorance and hubris, and their parents' sense of shame.

Even given a marked improvement in today's surgical techniques and an increase in psychosexual awareness, surgeon Linda Dairiki Shortliffe, MD, chair of urology at the Stanford School of Medicine, says, "There is no right answer in many of these cases. That's why it's so hard to give advice to parents. We really don't know what that person is going to be when they grow up."

Katrina Karkazis, PhD, senior research scholar at Stanford's Center for Biomedical Ethics, who authored the 2008 book *Fixing Sex: Intersex, Medical Authority and Lived Experience*, says narrow ideas about gender, societal and medical discomfort with such ambiguity, and distraught parents' belief that they must surgically make their child normal as soon as possible have led to avoidable mistakes. "If we slow things down and think about it more," Karkazis says, "better decisions would be made."

But to parents such as the Thompsons, who say their daughter's genital masculinization was not especially pronounced, there is little debate about the benefits of choosing surgery. "The doctors said if she didn't have it, she might have trouble menstruating and there could be other problems, like bladder infections, and an enlarged clitoris can

'HAVE YOU named the baby yet? You might want to wait.'

be painful if erect," says Samantha Thompson. "Plus it could be visible in a bathing suit."

"It's a physical birth defect," adds her husband. "If it were webbed feet, wouldn't you fix that? She's not going to remember it. It was a no-brainer. It is not a sexual orientation question."

BOY OR GIRL? At its basest level, our sexual markers chart our identity as human beings. Outside of some plants and invertebrates, there is no true third way; no animal has a complete set of both male and female sex organs, tissue and chromosomes. There are, however, a variety of sexual combinations that arise in humans, even within the recognized normal range for hormones, organs and genes. Not unlike the astounding variation in, say, the shape of people's noses, the appearance of human genitalia varies too. Locker room talk and pornography aside, there is no gold standard that can determine what works best.

But what if something goes "wrong"? In the seventh week after conception, the complex process of sex differentiation begins in the human embryo. Within the chain of interactions among genetic, molecular and physiological processes, the possibilities for biological detours are vast. A so-called true hermaphrodite, for example, might be born with an ovary and a testis, or a combination of the two known as an ovotestis. The child might have an external organ that looks like a penis, or an enlarged clitoris, or a variation of the two that could be described as a clefted lump of tissue with a nubbin in front.

This is not something polite company talks about, nor even within the scientific community is it studied much. Often owing as much to the stigma as to the relative rarity of occurrences, there are no hard numbers on which research might be based, as yet no national surveys or database. Longitudinal medical studies that gauge how adolescents or adults have fared after genital plastic surgery as infants are sparse.

Categories are also ripe for dispute. Do hypospadias, the common congenital anomalies in which the opening of the urethra is somewhere other than the tip of the penis, fall under the umbrella heading of DSDs? Some medical researchers say they don't; others adamantly disagree. As such, estimates on the frequency of intersex conditions in the United States range from one in every 2,000 live births to about half that.

Cleft lip or palate, which occurs about once in every 550 live U.S. births, is one congenital anomaly to which ambiguous genitalia are often compared. Says one prominent pediatric urologist who does frequent genital surgeries on infants, "I see all these photos in the *Wall Street Journal*, kids with holes in their faces; they're pleading for money to fix cleft palates. Well, I can't show these penises, which look absolutely terrible. People would say it's child pornography."

It's the secrecy, the whiff of tawdriness, that still sets medical and social treatment of DSDs apart.

IN A PRIVATE DINING ROOM at Stanford Hospital in the fall of 2010, pediatric endocrinologist E. Kirk Neely, MD, flanked by university colleagues and two DSD patients' rights advocates, talks of the "Balkanized medical care" that intersex children and their parents receive. He refers not only to Stanford, but to the patchwork and inconsistency that is the norm nationwide. This is the fourth meeting of Stanford's fledgling DSD team, its formation spearheaded by bioethicist Karkazis, and the effort is still so unformed that members go around the table to introduce themselves.

But already there is consensus that to end what Neely, a clinical professor of pediatrics, calls the "general catch-as-catch-can" approach to treating infants with DSDs, Stanford needs a more formal team. He hands out raw census data on possible DSD cases at Lucile Packard Children's Hospital for the past year, about 50. Next he passes around his laptop, which displays a full-screen photograph of the latest case of ambiguous genitalia in the intensive care unit.

Says child psychiatrist Richard Shaw, a professor of psychiatry, "Longer-term, ours should be a model program, a nationally recognized program." Heads nod all around.

Pediatric endocrinologist Avni Shah, MD, a clinical instructor in pediatrics, offers that she was pleasantly surprised to learn that pediatric and adolescent gynecologist Paula Hillard, MD, a professor of obstetrics and gynecology, seated beside her, had been summoned to consult on two intersex babies within the past two months. But, as those around the table agreed, that was a matter of chance: A pediatric urologist who routinely performs plastic surgery in these cases — genitoplasty — might just as easily have been called.

In an earlier interview, Hillard, who spent 23 years at Cincinnati's Children's Hospital, recalled an adolescent patient who had her clitoris amputated in infancy. "How can I think anything other than, 'Why was this done?'" she asked. This and several other surgical outcomes in patients she has treated have cemented her belief in a measured, team approach to treating infants with DSDs.

THE MOST MEDICALLY INFLUENTIAL case in the annals of intersexuality didn't stem from an intersex birth, but from a horribly botched circumcision in 1966. Bruce Reimer's penis was burned beyond repair when he was 8 months old. Numbed by the news that their son would never sexually function as a typical man, his parents agreed with psychologist John Money, PhD, of the newly established Gender Identity Clinic at Johns Hopkins Medical Center, to "transform" Bruce into Brenda at 22 months.

With his identical twin brother unwittingly acting as a control, Bruce would go on to test Money's theory that with surgery, hormone treatment and gender-specific socialization, gender identity could be successfully, and unambiguously, switched. Despite mounting evidence to the contrary, the case of John/Joan as Money called it in his research papers was trumpeted as an unqualified success. Coming from a leading authority on intersex conditions and the psychological ramifications of ambiguous genitalia, the findings, backed by Money's earlier research, lent global legitimacy to the practice of sex reassignment in infants. Money's implicit message to pediatric urologists and endocrinologists was that they could, in essence, surgically or hormonally channel an intersex child into whichever gender they chose.

Then Brenda, at the age of 15, learned the truth behind her tortured existence within a life that never fit. After refusing one last time to undergo surgery that promised to complete her anatomical transformation, Brenda's father told her about the genesis of her forced femininity. The adolescent immediately switched back to male, adopting the name David and demanding male hormones to speed the process. He had his breasts surgically removed and a rudimentary penis attached all before he was 16 years old.

But David Reimer, despite having married a woman and adopting her children, despite having told his story publicly in the hope of sparing other children a similar tragedy, killed himself in 2004. Money, now deceased, never admitted that the success of the Reimer sex reassignment was anything but.

With the help of Reimer's supervising psychiatrist, a rival researcher, Milton Diamond, PhD, now retired from the University of Hawaii at Manoa, tracked down Reimer to document the disastrous outcome. "The evidence seems overwhelming that normal humans are not psychosexually neutral at birth," Diamond wrote.

But what of children born with ambiguous genitalia? Are they, according to the Freudian notion still prevalent today, dependent upon a penis or a lack thereof to define their gender identity? How often is this view imposed on infants through genital surgery? What's right, and whose call is it to make?

A leading researcher on DSDs, William Reiner, MD, a pediatric urologist and psychiatrist at the University of Oklahoma, says the answers still largely depend on where a child is born. Outside of a handful of teaching hospitals, UC-San Francisco, the University of Michigan and the University of Pittsburgh among them, few U.S. institutions have any established protocol for the always surprising, and often shocking, event of an intersex birth.

"There is no standard of care," says Reiner, also on staff at

Johns Hopkins. "Usually the approach is determined by who you happen to see first. In the Western world, everybody expects to have a perfect child to begin with. So if they aren't perfect, they're all upset. Most of what has evolved (in the treatment of DSDs) over the last half of the 20th century has more to do with people's ideas and views and thoughts and biases than it has to do with any kind of data."

WHEN LISETTE DICKINSON, which is not her real name, was born in 2004 she had several strikes against her. She came from an unstable home in a hardscrabble area of the deep South, her twin sister died shortly after birth and Lisette herself was in poor enough health that when social workers removed her from her biological mother a few weeks later, they placed her in a foster home for medically fragile kids.

The reason state adoption officials labeled her a "special needs" child, however, was her sex. Nobody could say with any certainty what it was. Her biological mother called her a girl like her twin, but, as Lisette's adopted mother explains, the child had what looked like a normal-sized penis as well as a vagina. At the hospital where she was born, they'd called her a boy. Medical tests later confirmed a small uterus, one teste and an ovotestis.

"Here's this absolutely beautiful kid, but social workers couldn't find a family for her," says Lisette's adopted mother, a psychiatrist in South Carolina. "They removed her from one foster home and put her in another. But there were problems with the other children in the home, and that mom told people about [Lisette's] condition. They were afraid too many people would find out."

As such, the state Department of Social Services called what amounted to an emergency hearing to determine what to do about this odd and fascinating case. An endocrinologist testified that the child wouldn't be adoptable without an easily identifiable sex and advocated surgery, says Lisette's adopted mother. A pediatric urologist, also favoring surgery — and soon — said the child's gender could go either way.

For reasons that the girl's adopted mother says are still not clear, a family court judge ordered that Lisette be surgically transformed into a girl, usually the easier surgical option. So when the child was 16 months old, her phallus was shaped into a clitoris and her testicular tissue removed. Today she is left with half an ovary and a uterus, and surgically created labia. She will likely be infertile.

"I wasn't privy to the hearing," says her adopted mother. "Her case worker told me after the fact. I was devastated. And so we got her at 20 months. We took her to a developmental pediatrician. We thought she might be mentally retarded; she wasn't walking, not talking. Now she's normalized out of that. But I always thought she should have been a boy. Her testosterone level is so high."

Her mother says friends of Lisette's siblings, noticing the masculine clothes the 6-year-old often favors and the tools and cars with which she plays, ask if she is a boy or girl. Lisette simply grins and declares she's a girl.

"She is the coolest kid," says her mother. "I don't want her to be angry. I want to be careful not to make her angry that they did this surgery. My gut says that it was really stupid, and it makes me angry. But I don't want to bias her that way.

"But she's asked me, 'Will I be a man when I grow up? And I say, 'Yeah, you might be.'"

USING TECHNOLOGY to shape ourselves and, without their consent, our children, has been a mainstay of bioethical debate for decades. Circumcision, foot-binding, growth hormone therapy and even tattoos and body piercings spring to mind. When it comes

'HERE'S THIS absolutely beautiful kid, but social workers couldn't find a family for her.'

to treatment of DSDs, however, the term *debate* underplays the vitriol. Activists complain of medical arrogance, of being ignored and belittled. Many, including the 3,000 members of the International Intersex Organization, are loathe to accept the very phrase "disorders of sex development," which was adopted by mainstream clinicians after the American Academy of Pediatrics published its *Consensus Statement on Management of Intersex Disorders* in 2006. Activists say disorder implies pathology, and that people with atypical variations in sexual organs, hormones and genes are, by nature, freaks.

"People are surprised that I'm well-adjusted, that I'm confident and happy about who I am," says Hida Viloria, who was born intersex 42 years ago and has never had surgery or hormone treatment. "I refuse to let bigotry influence my self-esteem."

Since testifying before a hearing investigating "the medical 'normalization' of intersex people" convened by the San Francisco Human Rights Commission in 2004, Laurence Baskin, MD, chief of pediatric urology at UCSF, rarely speaks publicly about the complex decision to surgically assign a gender to an intersex child.

"I thought they were going to shoot me," he says of his experience at the hearing.

But Baskin, like many other surgeons and medical clinicians who treat these children, is acutely aware of how much remains unknown about the long-term ramifications of assigning gender in infancy. In a recent review article in *Pediatric Urology*, he and his co-authors called for further study to assess sexual function and psychosexual development in people on whom genital surgery was involuntarily performed.

Baskin says he empathizes with adults now suffering from bad surgical outcomes, and wishes they had had the same level of care available today. "And in 10 or 20 years, it will be better," he says, moments after performing an infant genitoplasty himself. "But most of those who are talking out now come from split families, and some of it centers on the fact that they were born with terrible problems. But I've seen kids with terrible problems who have really good families. With love and empathy and proper care, these kids do fine."

Pediatric urologist Hsi-Yang Wu, associate professor of urology at Stanford, notes that an established surgical technique that pulls the clitoris under the pubic bone — now known to cause painful orgasms — is no longer used. Using a surgical textbook to illustrate, he speaks in an interview of a preferred, nerve-sparing, technique used since the mid-1990s in which the erectile portion of the clitoris is removed.

While he called the surgery "not particularly difficult," like his colleagues, Wu was quick to add that the long-term outcome remains unknown. "But I have a concern about waiting, too, about letting the child make the decision, as if that would be easier. I'm not sure it is. What I tell parents is, 'You have to make decisions for your kids on everything, all the time.'"

Physicians argue that torn between cultural norms and expectations, the complexity of gender identity, and a dearth of hard research data, they strive to offer the best medical advice they can. And there are small differences, they note, that have gone a long way toward humanizing medical treatment during stressful times.

Says nurse practitioner Angelique Champeau, who coordinates UCSF's DSD clinic, "We used to be very quick to assign a gender. We don't do that anymore, and we've taught the nursing staff not to call a baby *it*. We have a list of baby names that could go either way. And for the first time two years ago, we sent home a child without assigning sex. The parents actually bonded with their baby, not with their baby's sex."

But alliances within the loosely connected network

'PEOPLE ARE surprised that I'm well-adjusted, that I'm happy about who I am.'

of researchers, clinicians, parents and adults with DSDs continue to shift, groups splinter and dissolve, and the level of mistrust even among advocacy groups remains high. Some groups demand an end to all cosmetic genitoplasty on children with DSDs at least until the child is old enough to give consent; others warn that alienating physicians will not help their cause. Adding to the chill is a nascent effort to hold physicians and hospitals legally accountable for genital surgery that, years later, has left their former patients unable to sexually perform or even experience sexual sensation.

THE FALL MEETING of the Stanford DSD team was, in many ways, emblematic of the dilemmas involved in delivering the best care to DSD patients and their parents during a time when social concerns hold such sway. Even here, among generally like-minded colleagues, questions percolated about which pediatric urologist to ask to join the team; some were known to favor early surgeries, while others were not. And in an age of rising costs and more restrictive insurance coverage, the group wondered who would pay for personalized, long-term medical and psychosocial treatment of DSDs; the scramble for funds for more recognized conditions is already fierce.

At the meeting, bioethicist Karkazis spoke of making better decisions about genital surgery; about full disclosure; about helping families who have been misinformed or lied to; about humanizing medical, social and psychological treatment during high-stress times. Before the group broke up, assignments were made and schedules checked. They met again in January, their team now complete, and gathered again in February to begin discussing cases.

BEFORE MEREDITH and Lyle Stevenson (not their real names) decided to bring home the little boy who had languished on a Chinese adoption site for more than a year, they did a lot of soul searching. There was the matter of his ambiguous genitalia, which on that basis alone had relegated him to the category of "special needs," and then there was the fact he would be their fifth child.

But the Stevensons — she's a stay-at-home mom and he works in the software industry — also live in a small town in the Pacific Northwest. And the message from the pulpit of the close-knit church in which they worship is anything but ambiguous when it comes to matters of sex. Meredith describes it as conservative and unyielding: Man marries woman and, God willing, children result.

"So this was one other thing that entered the picture," Meredith says. "My husband and I had to think long and hard about our feelings toward homosexuality. Say we raised him as a boy and he falls in love with a boy. It could mean we picked the wrong gender. Or it could mean he's homosexual. We had to make sure we were fine with homosexuality because we didn't know for sure where he fell on the gender spectrum."

What slight research exists shows little, if any, direct link between homosexuality and intersex conditions. Still, the connection persists. Anecdotes abound about children presumed to be one gender behaving in ways typically associated with the other. And the notion that exposure to prenatal hormones can shape sexual orientation goes back decades. What studies there are do show, for example, that women exposed to high levels of androgens when they were in utero have a slightly higher rate of bisexual and homosexual orientation than those who were not.

None of this — now — means much to the Stevensons. Their little boy, 4 years old, who has XY chromosomes like a typical male, but no testicles, happily sings in the background as his mother explains. Against the advice of a pediatric urologist who urged at least the application of topical testosterone on what he called the smallest penis he'd ever seen, the couple have decided to simply let their child grow into who he is, without surgery or other treatment, without adopting fears over the stigma of a male unable to urinate standing up.

When, during a family vacation, the child begged his parents to buy him a dress, they did — and allowed him to wear it throughout a flea market despite stares from passersby.

"I felt it then," Meredith says. "That was the only point that it felt a little weird. But, you know, considering this whole thing, I think maybe I couldn't have done this with my first child. When it's your first, you have all sorts of expectations. But by your fifth child, you've filled all the holes in your own life and you just let the kid be who he is." **SM**

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FUNDAMENTALS
ETHIC
regulatory risks inherent
DEBATE OVER
HUMAN
TRANSPLANTS
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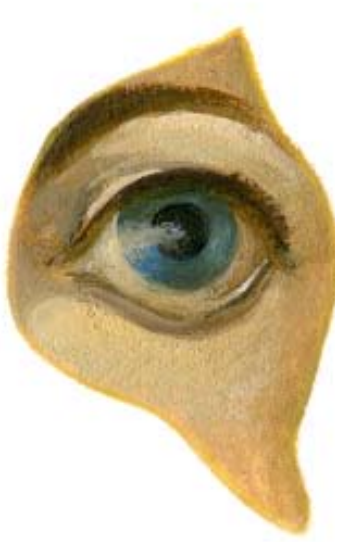
practices



when are you dead?

a resurgent form of organ transplantation raises a new question

By John Sanford
ILLUSTRATION BY GÉRARD DUBOIS

The young man had fallen off a cliff while hiking. Now he was in a coma. His doctors in Stanford's intensive care unit determined that he had suffered massive, irreversible brain damage and would never make a meaningful recovery. His parents, who knew their son would not have wanted to remain in the zombie-like limbo afforded by a mechanical ventilator, decided to withdraw life support. They also wanted to donate his organs.

"It was an incredibly altruistic gesture in the midst of a tragedy," recalls Carlos Esquivel, MD, PhD, chief of Stanford's Transplantation Division, of the seven-year-old case.

But Esquivel also recognized that organ donation helps many parents cope with their grief over the loss of a child. So he was upset when David Magnus, PhD, director of the Stanford Center for Biomedical Ethics, arrived at the scene to inform the transplant team that the procedure could not go forward. "It was just the thought that we couldn't fulfill the parents' wishes," Esquivel says.

Magnus, who is occasionally summoned to the hospital to advise doctors on end-of-life issues, including the advisability of organ donation, recalls the scene as "very tense." At the time, Stanford permitted the removal of organs only from voluntary living donors — a mother donating a kidney to her daughter, for example — and from non-living donors whose deaths were based on the loss of all brain function. But this young man's brain stem was still active, albeit barely, so donation was not an option.

A LITTLE MORE THAN 40 YEARS AGO, a partially functioning brain would not have gotten in the way of organ donation; irreversible cardiopulmonary failure was still the only standard for determining death. But during the 1970s, that began to change, and by the early 1980s, the cessation of all brain activity — brain death — had become a widely accepted standard. In the transplant community, brain death was attractive for one particular reason: The bodies of such donors could remain on respirators to keep their organs healthy, even during much of the organ-removal surgery.

Today, the medical establishment, facing a huge shortage of organs, needs new sources for transplantation. One solution has been a return to procuring organs from patients who die of heart failure. Before dying, these patients are likely to have been in a coma, sustained by a ventilator, with very minimal brain function — a hopeless distance from what we mean by consciousness. Still, many people, including some physicians, consider this type of organ donation, known as "donation after cardiac death" or DCD, as akin to murder.

Critics of DCD contend that some patients may still be alive five or even 10 minutes after cardiac arrest because, theoretically, their hearts could be restarted, and some of their brain function might still remain. In such cases, critics assert, the patients were clearly not dead because their condition was reversible. Advocates of DCD counter that do-not-resuscitate orders from a patient or family render the argument about irreversibility moot.

In any case, there would be little debate about DCD if organs in a body remained viable for transplantation 20 or 30 minutes after heart and lung failure. But they become damaged quickly, so surgeons have to act fast — ideally, within about 10 minutes of cardiac arrest.

According to the Uniform Determination of Death Act, which was drafted about 30 years ago and has since been adopted, in some form, by all of the states, you can be declared dead in one of two ways: Your brain can irreversibly cease functioning, or your heart and lungs can irreversibly stop working. "Irreversibly," in this context, has fueled the controversy. Does it mean the heart is unable to spontaneously start by itself? Or does it mean that even resuscitation efforts fail to restart the heart?

To be certain that a heart does not have the capacity to start beating again on its own, most organ procurement organizations, including the California Donor Transplant Network, require that doctors observe patients for five minutes after cardiac arrest before declaring death and admitting the transplant team into the operating room. (Five minutes is the amount of time recommended by the Institute of Medicine, even though under typical end-of-life conditions no adult heart is known to have started beating again by itself two minutes after stopping.)

Ironically, not long before the injured hiker arrived at Stanford Hospital, Magnus had proposed creating a policy that would allow DCDs here. Magnus, who earned his doctorate in philosophy from Stanford in 1989, recognized that without a protocol, donation after cardiac death was fraught with ethical pitfalls.

In the end, that patient became brain dead, so he was allowed to be a donor. Several months later, the hospital's board of directors approved the DCD protocol, which Magnus, Esquivel and other Stanford physicians helped craft. Nevertheless, Magnus is confident it was right to forgo DCD in that case.

"There's no doubt Carlos was frustrated, but I think we eventually won him over," Magnus says. "It was never a good idea to let a transplant team go in half-cocked, without a protocol."

Indeed, as both would soon discover, half-cocked DCD efforts can end in criminal charges. But we're getting ahead of the story.

More than 100,000

potential organ recipients idle on the waiting list maintained by the United Network for Organ Sharing, which manages the U.S. transplant system. An average of 18 people on the list die each day because of a shortage of donor organs. Meanwhile, demand for organs continues to grow, but the pool of brain-dead donors remains largely static, thanks in part to better automobile-safety measures, such as seat belt laws and air bags, as well as advances in treating neurological trauma.

DCD has gained popularity over the past two decades as a way of increasing the pool of potential donors. In 1995, only 1 percent of dead donors nationwide were DCD donors. That figure increased to almost 11 percent in 2008, according to the Scientific Registry of Transplant Recipients. The significant increase is probably due to greater awareness of DCD among members of the medical profession, as well as the procedure's official sanction in the intervening years by influential medical organizations, including The Joint

'In order to be dead enough to bury but alive enough to be a donor, you must be irreversibly brain dead.'

Commission and the Institute of Medicine.

Yet some hospitals, including several dozen in Northern California — Dominican Hospital in Santa Cruz, Saint Francis Memorial Hospital in San Francisco, Sequoia Hospital in Redwood City, for example — refuse to act as a venue for DCD. And despite the success seven years ago of the first DCD procurement at Stanford, one respiratory therapist involved in the case refused to participate, citing ethical concerns.

David Crippen, MD, a critical care specialist at the University of Pittsburgh Medical Center, probably would have understood this kind of reaction. Crippen, who has written about end-of-life issues in ICUs, has been critical of how death is defined in the practice of DCD. He argues that whole-brain death is the only clear standard; it is based on the widely accepted definition of death as the irreversible cessation of the integrated functioning of an organism, in which the brain, as chief executive of the nervous system, is the key integrator.

In a 2008 article in the journal *Critical Care Medicine*, he faulted the "unfortunately vague" guidelines of the Uniform Determination of Death Act for opening the door to what he describes as the "creative interpretation" of death. The problem, as Crippen sees it, is that no one in 1980, when the act was formulated, was thinking about how "irreversible" cardiopulmonary failure would be interpreted in light of DCD.

"In order to be dead enough to bury but alive enough to be a donor, you must be irreversibly brain dead," Crippen says in a telephone interview. "If it's reversible, you're no longer dead; you're a patient. And once you start messing around with this definition, you're on a slippery slope, and the question then becomes: How dead do you want patients to be before you start taking their organs?"

Crippen acknowledges the rising demand for organs and the importance of transplantation in saving lives. But, in the article, he argues "history has shown that where there are rules, there are usually reasons." He continues: "The passionate and highly publicized desire for organs promotes utilitarian workarounds of the rules to obtain these organs."

Magnus, a cautious advocate of the procedure, notes that even though the term DCD did not always exist, it was the de facto method of procuring transplant organs from dead donors until the 1970s. The notion of brain death did not even exist until about 1960 and, in the United States, was not formally recommended as an alternative method of determining death until 1968.

"DCD can be done ethically," Magnus says, but must follow a strict protocol. Stanford's protocol, which took effect in 2004, resembles most other hospitals' in its basic outline.

First, the patient's family must decide to withdraw life support. To avoid the appearance of conflict of interest, the physician caring for the patient must not propose or discuss the possibility of organ transplantation with the family. If family members want to talk about it, the physician must refer them to the California Donor Transplant Network.

Then a team of doctors must assess whether the patient would make a suitable DCD donor. If yes, Stanford Hospital's Ethics Committee must submit its approval, and a representative of the donor network must explain the process to the family, including the fact that, prior to withdrawal of life support, doctors inject the patient with heparin, a blood thinner crucial to the health of organs removed for transplantation.

The patient is then wheeled into the operating room, given some heparin and detached from the respirator. If the patient's heart does not stop beating within about an hour, he is brought back to the ICU to die; his organs, which would likely be damaged because of the decreased amount of oxygen they're getting from the ebbing heartbeat, will not be viable for transplant. But if the patient's heart stops for five minutes, the attending physician declares the patient dead and asks family members to leave the room. Then the transplant team enters to procure the organs.

"We have a very stringent protocol and a robust informed consent process," Magnus says. "If we didn't, that could be asking for trouble."

Ruben Navarro was 9

when he was diagnosed with adrenoleukodystrophy. The rare wasting disease, the focus of the 1992 film *Lorenzo's Oil*, damages the nerves and eventually leads to death. There is no cure. In late January of 2006, two weeks before his 26th birthday, Navarro was found unconscious at the assisted-care home where he lived in San Luis Obispo, Calif. The disease had ravaged his mental and physical health; he weighed only 80 pounds. He was rushed to nearby Sierra Vista Regional Medical Center and hooked up to a ventilator. Doctors determined that he had suffered irreversible brain damage. His mother, Rosa Navarro, agreed to allow his organs to be donated once life support was withdrawn.

On Feb. 3, the California Donor Transplant Network dispatched a San Francisco-based team to the hospital. It included Hootan Roozrokh, MD, a young surgeon who several months before had completed a transplant fellowship at Stanford School of Medicine and was now on the staff of Kaiser Permanente, and a senior surgeon, Arturo Martinez, MD, then-director of Kaiser's kidney transplant program for Northern California. When they arrived at Sierra Vista, Navarro was wheeled into the operating room. But there was confusion among members of the hospital and transplant teams about their various roles, court records show. Sierra Vista had no DCD protocol, and no staff at the medical center had any training in the procedure, according to the records. In any case, after life support was withdrawn, Navarro remained alive for about eight hours, making his organs unsuitable for transplant.

One-and-a-half years later, Roozrokh found himself facing three felony charges. San Luis Obispo prosecutors accused him of prescribing large quantities of a painkiller and sedative in an effort to hasten Navarro's death. (State law prohibits transplant surgeons from directing the treatment of potential organ donors until they have been declared dead.) During the trial, the defense argued that hospital staff members had failed to perform their duties and that Roozrokh stepped in only to try to relieve the patient's suffering. Navarro had developed a tolerance to the drugs, which he had used to manage pain caused by his neurological disease, and so needed a relatively large dose to get any relief, Roozrokh's lawyer said.

The judge in the case threw out two of the charges — administering harmful substances and prescribing controlled substances without a legitimate medical purpose — and the jury found Roozrokh innocent on the remaining charge: dependent adult abuse. In rendering its verdict, the jury included a note advising that the case "identified that donation after cardiac death is in desperate need of further identification of prescribed policy in order to continue successfully as a viable option for organ donation in this country."

Roozrokh, now a transplant surgeon at Loma Linda University Medical Center, vows he will never go near a DCD case again. He says there should be a national DCD protocol and liability protection for physicians who perform the procedure in good faith. "It was a terrible ordeal for my family, and the cost of my defense was enormous," he says.

Roozrokh, who has received a number of humanitarian awards, speaking invitations and professional awards, including the 2010 Northern California Kaiser Permanente Patients Recognition Award for Outstanding Service, says his reputation nevertheless has suffered because of the accusations. "Just Google me," he says. "As a doctor, your reputation is pretty much all you've got."

To Magnus,

the Navarro case serves as a cautionary tale, and the jury's note is the moral. The need for a protocol is especially important in DCD, Magnus says, because "there is no bright line" indicating the moment a person becomes a corpse. Magnus drew the analogy to how we define adulthood as beginning at 18. "We know that's not how human development works — that at 17 years and 364 days you're immature and the next day you're magically a mature adult," he says. "But we need that distinction for policy reasons. The same thing goes for death."

For all the controversy around DCD, however, it has not been the panacea many donor advocates thought it would be, Magnus says. Stanford Hospital considers about one potential DCD donor a month. Over the past seven years, only three have actually made it as far as surgery, and only two of these successfully provided organs — kidneys in both cases.

"It's a rare occurrence," Magnus says. "The hope that UNOS [United Network for Organ Sharing] initially had was this might make up as much as 30 percent of all successfully recovered cadaveric organ donations." While DCD was used for some 11 percent of dead donors in 2008, it accounted for only 7 percent of organs recovered from dead donors. (A DCD donor usually provides fewer organs than does a brain-dead donor.)

One reason DCD procurements haven't risen more is that the majority of transplant centers will accept DCD organs only from donors who are middle-aged or younger — and, on occasion, the vigorous 60-year-old who runs marathons. This is because the organs must be healthy enough to withstand the dying heart's decreasing blood flow, followed

by a complete lack of oxygen for several minutes after cardiac arrest. (In almost all cases, hearts cannot be recovered in DCD procedures because they suffer too much damage during this process.) Then the organs must survive in a cold solution, which helps slow their deterioration, for at least several hours, but often much longer. Brain-dead patients, on the other hand, can be donors into their 80s: They remain on a heart-lung machine during most of the surgery, giving their organs all the oxygen-rich blood they need.

There is no 'bright line' indicating the moment a person becomes a corpse.

ANOTHER REASON FOR THE low numbers of potential DCD donors is simply that fewer young people die — because they are, well, young. And when a young person dies, family members may have trouble coming to grips with the loss and so neglect or scorn end-of-life considerations, such as organ donation. That's unfortunate not only for potential recipients but for the family of the deceased, says Nikole Neidlinger, MD, the medical director of the California Donor Transplant Network.

"A lot of people think that it's all about the organ recipient, but really, I think, the donors' families get the biggest benefit," Neidlinger says. "They have spent perhaps weeks dealing with the hardship of seeing loved ones on life support and coming to terms with their death. And the fact that the donor gets a chance to help another person live — it's a legacy that counts so much for families."

In 2005, the day after Thanksgiving, Pierre Bobet Erhard, 25, dined on leftover turkey and stuffing with his mother, Nancy Erhard, at her home in Stoneham, Mass. Bo, as everyone called him, had led a troubled adolescence. In seventh grade, he was arrested several times for minor delinquencies, such as vandalism, shoplifting and marijuana possession. He was expelled from school. "Bo had no sense of safety, but he was a likable, funny kid," Nancy says. "He was like Robin Williams." With the support of his family, Bo turned his life around. He graduated from high school and became a plumber.

After dinner, he said goodbye to his mom and drove to a house he shared with two friends in Billerica, a town along the Concord River, about 22 miles northwest of Boston. They had recently moved in together and were throwing a housewarming party. Around midnight, Bo was in his room, talking with some friends, when he collapsed and stopped breathing — suddenly and for no apparent reason, witnesses said. An ambulance rushed him to the hospital.

"When I got to the emergency room, it was practically empty, except for Bo," Nancy says. "He was in a bed, intubated, with the guardrail down. He was completely motionless. I felt this sense of doom."

Doctors said a tear on the inside wall of his carotid artery had caused a massive stroke. He had suffered severe brain damage and was breathing only with the help of a ventilator. Nancy asked a resident in neurology whether he had treated patients in this condition, and the resident said that he had, many times. She asked if any of these patients had survived. "No one," the resident replied, and looked at the floor.

"I need to speak to the organ bank," she said.

Several days later, as Nancy waited for doctors to remove Bo from life support so he could become a DCD donor, she recalled a conversation she once had with him in his late teens: "We were driving in the car, and I told him, 'You have had more help than everyone else in town put together, and someday you have to give back.' And he turned to me with a big smile and said, 'Don't worry, Ma. Someday I will.'

"The chances of families saying yes to DCD are about 50-50," continues Nancy, who since her son's death has volunteered for the New England Organ Bank. "More and more people are doing it, though, because more and more people realize the kind of gift it is. I know what Bo would have said about this situation. He would have said, 'Mom, do some good.'" **SM**

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The case of the disappearing liver disease

UNCOVERING AN ORDINARY ANTIBIOTIC'S SECRET POWER

by Erin Digitale
portrait by leslie williamson

IT WAS THE TYPE OF CASE THAT MAKES DOCTORS FEEL HELPLESS.

The 15-year-old boy's lab tests indicated his liver function was badly impaired. He had a double whammy of two serious gastrointestinal diseases, both lacking cures. On top of it all, his colon was infected with an aggressive bacterial strain, *Clostridium difficile*. • Although pediatric gastroenterologist Kenneth Cox, MD, had little to offer for the teen's other problems, he could at least treat the infection. He prescribed the antibiotic vancomycin. • And something very strange happened. The liver-disease symptoms vanished. • "At first I thought it was a coincidence," says Cox, now chief medical officer at Lucile Packard Children's Hospital, recalling the moment in 1993 when he saw the first hint of improvement. Maybe he had misattributed symptoms of infection to liver disease, he thought. "But then I stopped the antibiotic, and the liver disease came back, even though the infection was gone." • So Cox, who is also associate chair of pediatrics and senior associate dean for pediatric and obstetric clinical affairs at the Stanford School of Medicine, gave a second round of vancomycin. Once again,

the teenager's appetite returned, his pain disappeared and his liver tests normalized.

Cox tried vancomycin in a handful of other patients who shared the teen's liver and colon diagnoses but had never had *C. difficile*. These kids had been told that their liver disease, primary sclerosing cholangitis, was untreatable. Even a liver transplant was not a guaranteed cure — the disease could recur and destroy a new organ. Yet with vancomycin, the PSC disappeared.

The discovery left Cox in an unusual position. A coincidence — a serendipitous colon infection, of all things — left him holding a potential silver bullet for a devastating and poorly understood pathology.

"The problem is that I'm dealing with a very small group of kids with an unusual disease," he says. "How do I get the science to prove that vancomycin works, so that all of my colleagues would say, '*This* is the therapy'?"

UNEXPLAINED DESTRUCTION

PSC starts in the "biliary tree," the tree-shaped network of tubes that carry newly manufactured bile from the liver through the bile duct to the intestine, where bile aids digestion and absorption of dietary fat. In PSC, for reasons no one understands, the tubes become blocked by inflammation. So bile backs up, destroying liver cells and eventually causing cirrhosis.

The rare disease, which occurs in about 10 people of every million, leaves patients feeling severely unwell, with abdominal pain, itching, jaundice, poor appetite, deep fatigue and signs of malnourishment. It can hit people of any age. About three-quarters of PSC patients — including the 15-year-old who started Cox's research odyssey — also have the more-common diagnosis of inflammatory bowel disease, another poorly understood condition, which is characterized by inflammation and ulceration of the intestine, diarrhea, abdominal pain and a host of other problems.

Cox and his Stanford collaborators believe that if they can figure out how vancomycin alleviates PSC, they'll solve two mysteries at once. Not only will they have the evidence to convince other physicians that vancomycin is a good PSC treatment, but by finding out how the drug works, they may also learn how PSC begins — which may open doors to better therapies.

Although the research task is daunting, beneath Cox's caution about its challenges is a definite sense of excitement.

"Most discoveries come by careful observation. I feel lucky that I've made this observation," he says. "The remarkable part is, not only do the liver tests get better, but the children also feel so much better. If you take a look at these children before and after therapy, they don't look like the same child."

RESCUING A TODDLER'S LIVER

One of the most dramatic vancomycin-induced transformations came in 2005, after Cox's team suggested the drug to Lyn Woodward and Melissa Hartman. Their little girl had been through the diagnostic wringer.

Things began to go wrong for Ellery Woodward-Hartman at 8 months of age, when her growth started to lag behind that of her twin brother, Robert. Her liver function gradually worsened; no one could figure out why. By the time she turned 2, Ellery's liver was scarred with cirrhosis and she was badly jaundiced. Before Cox saw her, other physicians had tested Ellery for everything from cystic fibrosis to lymphoma to HIV. None of those diagnoses fit, and her liver was getting worse. Woodward and Hartman were told to anticipate a liver transplant.

"I thought, this can't be happening," Hartman says.

In late October 2005, Cox's pediatric gastroenterology fellow, Anca Safta, MD, read Ellery's chart. The symptoms lined up with PSC, Safta and Cox agreed. Safta proposed vancomycin treatment to the family.

"She said, 'I know about Ellery; we have something that can help her,'" Woodward says, recalling her first conversation with Safta.

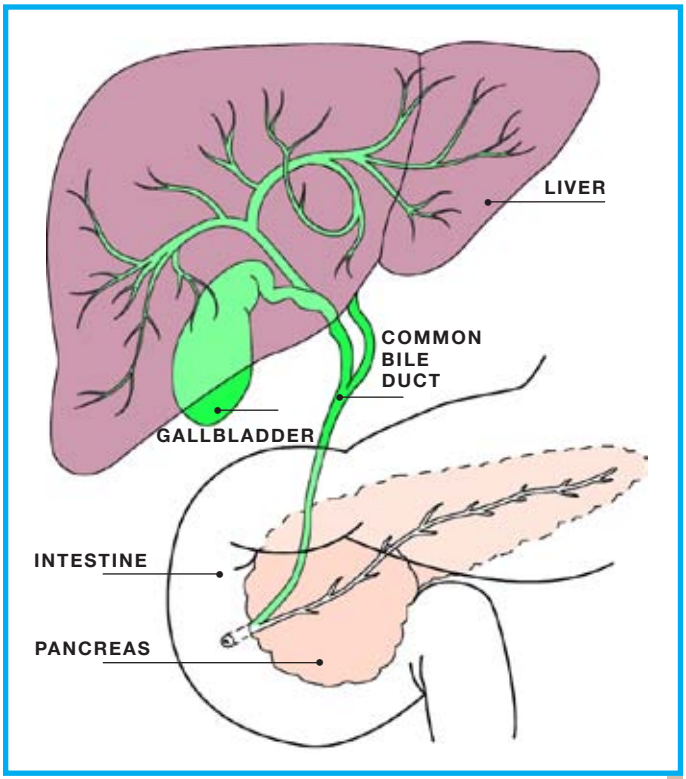
"There's a line from Emily Dickinson: '*Hope is the thing with feathers*,'" Hartman says. "I thought of that poem. It was such a relief."

Cox wasn't sure a child as sick as Ellery would benefit from the therapy; his other patients had mostly been at earlier stages of PSC illness. Maybe the antibiotic would at least give her a few months to get stronger before a transplant, he told Woodward and Hartman. Cox wrote the prescription and told the family he would follow up with them soon.

CLUES FROM THE CLINIC

Since 1993, Cox has tried vancomycin on every PSC patient he's treated, slowly accumulating evidence for the drug's effects. In 2008, he published clinical observations of the first 14 pa-

'MOST DISCOVERIES COME BY CAREFUL OBSERVATION. I FEEL LUCKY THAT I'VE MADE THIS OBSERVATION.'



Bile normally moves from the liver through the branching network of ducts to the intestine, where it digests dietary fat. In primary sclerosing cholangitis, a rare liver disease, inflammation blocks the ducts. As a result, bile backs up, damaging the liver.

tients, showing the drug caused improvement in blood markers of liver failure. The index patient, now an adult, is no longer in Cox's care, but last Cox knew, he continued to do well. To date, 33 of Cox's patients, plus a handful of others cared for by colleagues around the country, have received the drug. But it's still largely unknown as a PSC therapy.

Funding has been one obstacle to advancing the research. So far, the work has proceeded without traditional funding sources such as NIH grants. Instead, patients' families have financed the research via a parent-launched nonprofit, the Children's PSC Foundation. Cox is now working to secure pharmaceutical company funding for a multicenter study to enable researchers to try the drug in a larger group of adults and children.

FILLING THE KNOWLEDGE GAPS

In spite of the limited resources, Cox has assembled a multidisciplinary team of Stanford collaborators to figure out how vancomycin works. The scientists are starting from one important clue: They know oral vancomycin, the drug formulation Cox uses for PSC, is not absorbed from the intestine. Yet PSC's trail of destruction starts with inflammation outside the intestine, in the tubes that drain bile from the liver to the gut. The drug must be acting at a distance — but how?

One hypothesis is that PSC arises when pathogenic bacteria in the gut backflow into the bile duct and start a destructive inflammatory response. Normally, everything moves down the duct in one direction, from liver to intestine.

"Essentially, this would be regurgitation of bacteria into the bile drainage system," says project collaborator David Relman, MD, a professor of infectious diseases and of microbiology and immunology at Stanford.

Another possibility is that bacteria somehow escape from the gut to the blood, then travel through the blood to the bile duct and trigger inflammation.

Under these hypotheses, which Relman's laboratory is starting to investigate, vancomycin would resolve PSC with its antibiotic action, killing gut bacteria. To determine if that's happening, the researchers are first taking a census of the bacterial communities in healthy children's small intestines.

"Almost everything we know so far about the usual gut microbe community is based on adults," Relman says.

The researchers plan to compare gut microbes in healthy kids to those in PSC patients before and after vancomycin. Their major obstacle — indeed, the reason we know so little about kids' gut microbes — is the difficulty of sampling the small intestine's contents. It would be unethical to perform invasive endoscopy on children who have no medical indication for the procedure, so the control samples in Relman's new study will come from kids receiving endoscopy to investigate non-PSC complaints such as chronic abdominal pain. It's also challenging to find "control" children who have not received recent courses of antibiotics. "That we *know* messes with the normal picture," Relman says.

Still, he is optimistic about the lab's prospects for cataloguing the gut microbes of kids with and without PSC. If kids with PSC have "different" bacteria before vancomycin treatment and return to a normal bacterial profile with the drug, it would provide strong circumstantial evidence that bacteria initiate PSC. And it would be a good starting point for studies of how the bacteria incite disease.

AN UNEXPECTED MODUS OPERANDI

Another possibility, however, is that in PSC vancomycin is acting as more than an antibiotic. Though textbooks label it a bacteria-killer, the Stanford team suspects vancomycin is also changing patients' inflammatory response.

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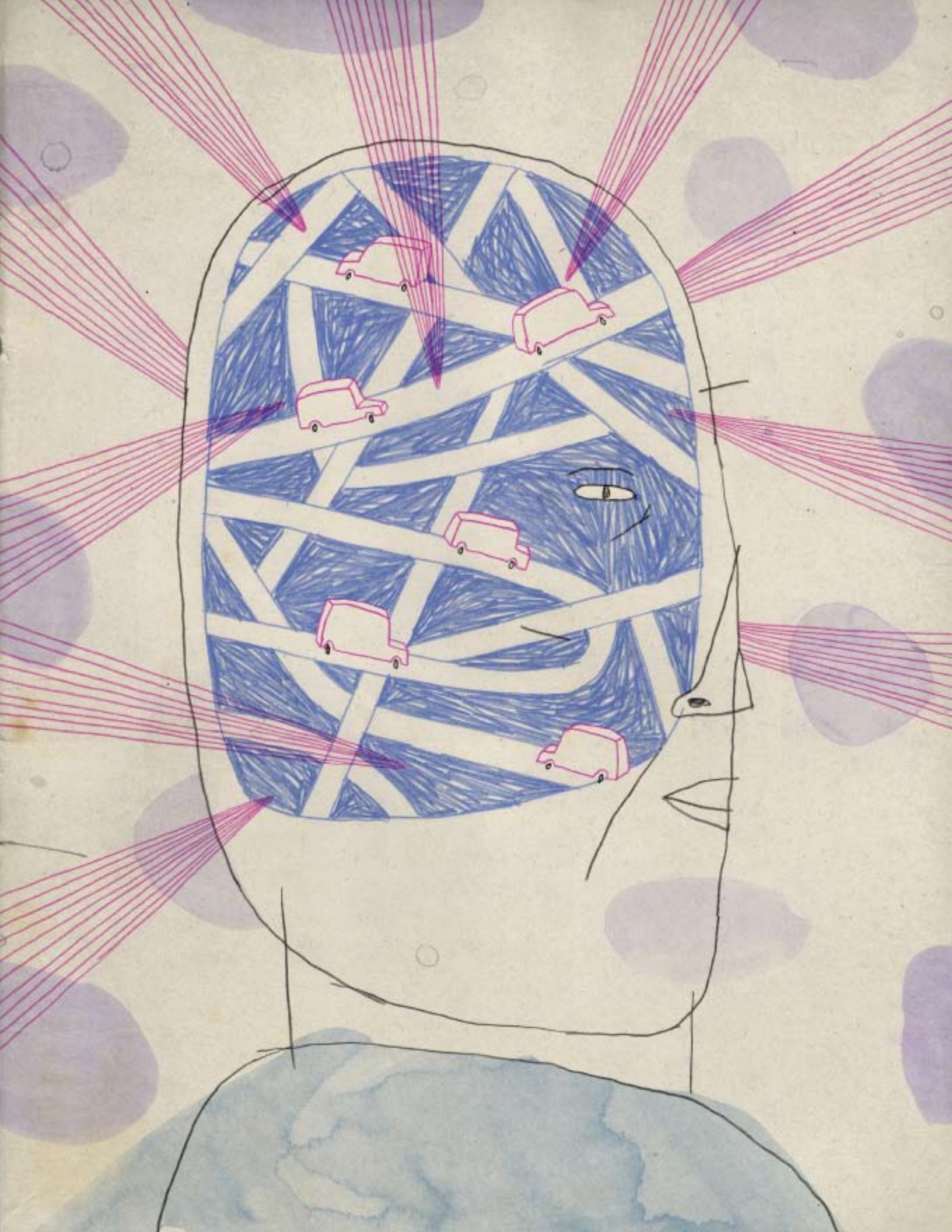
head lights

MIXING FIBER OPTICS WITH GENETICS HAS CREATED A REVOLUTIONARY TOOL FOR STUDYING THE BRAIN

BY BRUCE GOLDMAN
ILLUSTRATION BY BRIAN REA

The brain wears many hats. It thinks and dreams, it loves and hates, it recollects and predicts, it directs our moods and our movements. But it's a tough nut to crack. • "The human brain is probably the most complicated object in the universe," says Karl Deisseroth, MD, PhD, who has hit on such an effective way to finally discover how it works, colleagues say it could win him a Nobel Prize some day. • A most marvelous instrument, the brain comprises on the order of 200 billion nerve cells, or neurons, each of which may connect to 10,000 other neurons. Pulses of information in the form of electrical signals race along nerve fibers like sports cars on a speedway. • Yet what do you see when you look at a brain? Inscrutability. A shimmering, gelatinous mass of fatty fibers, snaking and threading and heading who knows where. • What if you could install traffic signals along the neurons threading through a living brain, so that you could start or stop traffic on them and observe the effect? Maybe you could learn something. • Deisseroth, an associate professor of bioengineering and of psychiatry and behavioral sciences, and his colleagues have created just such a system. The new technology, called optogenetics, mixes optics, genetic engineering and several other disciplines. It literally uses lights to control the messages zinging along our nerves: The go signal is blue, and the stop signal is yellow. Both are photosensitive proteins called opsins, originally discovered in microbes.



OPTOGENETICS HAS taken neuroscience by storm. Since Deisseroth published the first paper describing how it works in 2005, thousands of researchers around the world have started using it to define the deficits behind schizophrenia, autism, addiction, Parkinson's disease and more. In December 2010, the peer-reviewed *Nature Methods* named optogenetics the journal's "method of the year." That same month, *Science* magazine kicked off a roundup of 10 "insights of the decade" with a nod to Deisseroth.

"Optogenetics is the solution to our long-standing problem of lack of precision," says Anatol Kreitzer, PhD, a UC-San Francisco neuroscientist who recently collaborated with Deisseroth on a study of Parkinson's disease. "It lets us selectively inhibit or activate exactly the cells we're interested in. Karl's work is really revolutionary."

Deisseroth is a practicing psychiatrist as well as a researcher. The patients he sees suffer from severe, debilitating mental disorders such as autism, schizophrenia and depression. He hopes to find a way to give them their lives back — and he's painfully aware of psychiatry's limited ability to help him do so.

"Psychiatry has a long way to go," he says. "That's not because psychiatrists are anything but thoughtful, well-trained and observant. It's because we've lacked the tools to tease apart the component circuits that make up a working brain and examine their functions, one by one."

In the absence of such tools, it's even tougher to learn what's wrong with a brain that isn't working so well. Until now, most brain studies have relied on electrodes or drugs. Electrodes work fast. But they stimulate in a non-predictable way, igniting many different nerve-cell types in many different circuits. Plus, even though the stimulation is local, nerve fibers innocently passing through can get stimulated and trigger consequences far away. And while electrodes can activate neurons, they can't inhibit them, which is just as critical to studying brain function.

Drugs can selectively activate or inhibit neurons, but not always just the ones you want (that's one reason they produce side effects). Plus, they ooze everywhere and can't be mopped up quickly, making them lousy on/off switches.

Without precise techniques, how are you ever going to make sense out of 100 billion sentient spaghetti strands winding to and fro like midday traffic in some 3-D Manhattan?

Nothing to lose

IN 2004, DEISSEROTH was a new assistant professor at Stanford. He was eager to improve the lives of patients with psychiatric disorders, and dissatisfied with brain scientists' inability to map the malfunctioning nervous circuitry behind those disorders.

Here's what he was thinking: Neurons transmit electrically coded information down long, skinny fibers that project to other neurons near and far. What if you could coat their surfaces with photosensitive molecules so that when light hit those fibers, it would make them propagate — or resist propagating — electrical waves on demand? Suppose further that you could control which set of neurons would carry those molecules on their surfaces, and that you could direct the light to just the place you wanted. Then, at the flick of a switch, you'd be able to turn on or turn off the flow of impulses in the neurons of interest, and learn a huge amount about what they're doing.

Deisseroth knew that photosensitive molecules called opsins had been isolated from microbes such as *Chlamydomonas reinhardtii*, aka pond scum. Opsins are porelike proteins that open in response to particular wavelengths of light, allowing currents consisting of electrically charged particles to flow either in or out (depending on the particular type of opsin) across cell surfaces.

In theory, opsins were made to order for Deisseroth's approach. In practice, few had tried it and nobody had pulled it off, for plenty of reasons.

In living cells, proteins are created using recipes carried on genes. These days, plucking a gene (say, for an opsin) from one organism and plunking it into another organism's genome is a standard technique. But getting that gene into a living organism's brain without deleterious consequences is hardly a no-brainer. And it doesn't guarantee the protein the gene specifies will actually get made. (All your cells have virtually the same DNA inside them, yet skin cells, for instance, make entirely different batches of proteins than liver or blood cells do.)

Plus, the opsin molecules have to show up not just anywhere inside of neurons, but on their surfaces where all the electronic impulse-passing action is. Proteins aren't pets. Once made, they don't simply go where you want them to because they love to make you happy. They go where myriad biochemical imperatives direct them. Whether microbial opsins would really wind up on the surfaces of mammals' neurons — the only place where they could do any good — would be a bit of a crapshoot.

On top of all that, proteins are complex and finicky, working well only under the right conditions (heat, acidity and the companionship of chemicals called cofactors). Mammalian cells' biochemistry differs in numerous ways from that of microbes. Would an opsin molecule work as well in a mammalian neuron as it does in a pond-scum cell?

Another nail-biter: Microbial proteins on mammalian cell surfaces are sitting ducks. If the immune system, which abhors foreign substances, sees them, it just might chew the neurons they're sitting on into shreds, or at least

produce profound inflammation.

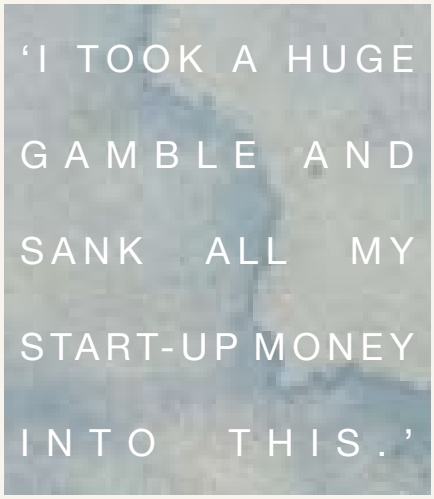
It added up to one risky proposal. "I was turned down for funding by a lot of people who thought this couldn't possibly work," Deisseroth says. "They figured if it worked it would have been done already. People had known about opsins for decades."

But he wanted to take a shot at it. He was young, with nothing to lose — no competing projects in urgent need of completion or renewal, no inventory of expensive equipment whose costs had to be amortized via other studies. He had a brand-new federal grant, and the support of the chairs of both departments he worked in. "I took a huge gamble and sank all my start-up money into this."

Deisseroth recruited two grad students, Feng Zhang and Ed Boyden. Zhang knew chemistry, molecular biology and virology. Boyden was adept at electrophysiology. They plunged in.

"Karl's lab was completely empty," says Zhang, now an assistant professor at MIT. He recalls having to go door to door in the building housing Deisseroth's lab, asking to borrow equipment from neighbors and hustling to get it back in time for the owners to use it in their own scheduled experiments.

A researcher at the Max Planck Institute had recently found an algae-derived gene coding for an opsin that, when stimulated by blue light, passed electrical current in a way that, in principle, could cause neurons to fire. Deisseroth got hold of the gene and suggested that Zhang try to fit it into some kind of system that could shuttle it into living mammalian neurons.



"I guess I didn't know any better," Zhang says. "It seemed worth a try."

Zhang's closest colleagues were trial and error. Eventually he settled on a defanged virus. If there's one thing a virus is good at, it's breaking into cells and commandeering their genetic machinery. To use a virus as a genetic-engineering tool, you take away its disease-causing weapons and replace them with a gene or genes you've taken from somewhere else. Then you inject your customized gene shuttle into an experimental animal. When the virus gets inside a cell's nucleus, it delivers the alien gene into that cell's own genome.

To ensure that just the right cells would produce the protein, Zhang affixed a kind of bar code to the opsin gene. Typically, genes have short "come hither" sequences of DNA right in front of them that tell cells' gene-reading machines which genes to perch on and when to make the proteins they specify. These little DNA tags are called promoters, and gene-readers in different cell types are attracted to different promoters. A gene — say for hemoglobin — with a particular promoter sequence may get hit on all the time by the gene-reading machines in a red blood cell, but never in a skin cell.

Deisseroth's team surmounted every hurdle. They succeeded in virally delivering opsin-encoding genes into rodents' nervous tissue. They were able to restrict opsins' production to neurons, or even just a selected type of neuron. The protein popped up on nerve-cell surfaces as hoped, and they bioengineered it further so it would do so more readily. Blue light made selected neurons fire.

To test this in live, freely moving, opsin-injected rodents, Deisseroth's group inserted a customized tube, or cannula, into the rodents' brains. During experiments, they threaded an ultra-thin optical fiber (outer diameter one-tenth of a millimeter) through the cannula. This way they could, at will, send pulses of laser light through the fiber to exactly the desired brain area. It worked like a charm, eventually.

As for the immune-reaction heebie-jeebies, a tight seal called the blood-brain barrier appeared to exempt experimental animals' brains from patrol by bulky antibodies and cellular cops. The suspicious molecules, like the proverbial falling tree thumping to the ground in an empty forest, apparently went undetected.

The Deisseroth group published their results with the excitatory blue-light opsin in 2005 in *Nature Neuroscience*. Not long afterward, they got an inhibitory, yellow-light-sensitive opsin, isolated from yet another one-celled organism, to work. Labs around the world are now routinely using both of them.

Optogenetics, applied

WHILE THE NEW methodology has terrific potential in psychiatric research, it has obvious limitations. Experiments that introduce foreign genes for light-responsive, nerve-impulse-triggering proteins into human beings aren't safe just yet. That's where experimental mice come in.

But when you're watching a mouse, it's a whole lot easier to observe its movements than its mental state. So a nice way to check out optogenetics' potential for brain research is to examine the animal equivalent of Parkinson's disease, a disorder in which patients gradually lose their ability to control movement. About 1 million people in the United States, mostly over age 65, are affected, making Parkinson's the second-most common neurodegenerative disease after Alzheimer's.

While Parkinson's ultimate causes are unknown, the disease clearly involves the loss of a set of neurons located in a structure deep within the brain whose signals feed directly into two separate circuits crucial to controlling voluntary movement.

Recently, Deisseroth, UCSF's Kreitzer and their colleagues optogenetically unravelled the workings of those two nerve-cell circuits and proved that one of the two facilitates normal movement, while the other inhibits it. Using both the blue-light-responsive, nerve-revving opsin and the yellow-light-responsive, nerve-blocking one, the researchers showed that imbalances in these two circuits' function can produce Parkinson's-like symptoms in mice — and that optogenetic interventions can exacerbate or alleviate those symptoms. By stimulating one of the two opposing circuits, they could restore normal movement in mice even after destroying the upstream nervous circuit that normally drives this activity and whose loss is the hallmark of Parkinson's disease.

Those results were published last year in *Nature*. "That we could completely rescue motor behavior by stimulating this pathway using optogenetics was surprising," Kreitzer says. "This is the first time anyone's ever reversed Parkinsonian symptoms using activation of a specific neural circuit. These mice became indistinguishable from their pre-lesioned, healthy state."

The finding implies that Parkinson's patients' conditions could someday benefit from new drugs that might be able, unlike current treatments, to stimulate the circuit that facilitates movement but not the circuit that inhibits it.

With ingenuity, it's possible to explore, optogenetically, not only the control of movement but more subtle workings of the brain, such as those involved in addiction and depression. Deisseroth and his Stanford colleagues have mapped the circuitry of the brain's reward system, illuminating the biological basis of addiction and depression. In a study published last year in *Science*, they showed the importance of a class of neurons whose role in reward couldn't have been nailed down by less-specific approaches. They used a fairly standard experimental design employing two "rooms." A mouse entering one room gets cocaine; entering the other, it gets nothing. It soon starts to strongly prefer the former. But the scientists could induce the same degree of preference by using blue light to optogenetically stimulate a solitary circuit comprising only 1 percent of the neurons in a particular brain structure. Furthermore, the mice's cocaine-induced preference for one room over another was obliterated when, during cocaine administration, the researchers shut down that same circuit by shining yellow light on it, thus inhibiting its firing. Now these mice couldn't care less which room they wandered into.

Similar efforts are identifying key circuits' roles in sleep disorders, schizophrenia, epilepsy and autism. In schizophrenia, the neurons of interest are sparsely sprinkled throughout the brain, Deisseroth says. "They form a network that seems to fire in synchrony." Disrupting the network's natural firing rates by delivering optical pulses at different frequencies impairs information flow in the brain. Fine-tuning neuronal networks' firing frequencies at will is yet another example of optogenetics' superiority over earlier neuroscience methodologies.

Spreading it around

DEISSEROTH HAS SHIPPED his viral opsin-gene shuttles to 800 labs around the world. And thanks to Stanford's multidisciplinary research complex, Bio-X, directed by neurobiology and biology professor Carla Shatz, PhD, he's been able to set up a training lab inside Bio-X's main piece of turf, the Clark Center. Guest researchers jet in for three-day training sessions conducted by this lab's director, Maisie Lo, PhD.

"What is really neat is that this technique can be used for any cells in the body, not just nerve cells," says Shatz.

Optogenetics will probably reach far beyond neuroscience. It can be adapted to trigger cascades of biochemical events inside all kinds of cells, including those of the heart and pancreas. Deisseroth is busy expanding opsins' range of colors and effects. Combining two kinds of excitatory opsins that respond to different colors will let you see what happens when you switch from exciting one circuit to another, or stimulate both simultaneously. Bioengineered opsins that, after a single pulse of light, turn nervous impulses on or off for long periods will let animals "go wireless" — researchers deliver a pulse that sustains activity or inhibition, then set the animal free. Alternatively, fast-acting opsins capable of delivering hundreds of pulses per second will allow scientists to explore frequency-dependent brain-circuit effects in more depth than ever dreamed of before.

While direct therapeutic applications of optogenetics — such as restoring neuromuscular function in paraplegics, proof of principle for which was established in mice in a collaboration this year with bioengineering professor Scott Delp, PhD — can be imagined, they will have to await the successful introduction of gene therapy in humans, which is still a ways off. "There will always be a risk/benefit trade-off," Deisseroth says. "By far the biggest impact of optogenetics will be the new understanding it makes possible." **SM**

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WEB EXTRA VIDEO ON THE NEUROSCIENCE REVOLUTION: STANMED.STANFORD.EDU/2011SPRING

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if he or she is not truly informed," says Stanford's Scott. "That's an ethical problem. In this situation, we have individuals making choices based on who they've talked to and anecdotal information they have gathered. But on the other hand, when I talk to the people I know in this situation, I'm surprised to realize that they usually have a pretty good understanding of the science and the regulatory issues that impact their disease."

Regardless of how well-informed a patient is, clinicians and stem cell experts agree that there is really no way to stop someone from choosing to undergo an unproven treatment.

"I respect people's choices," says Loring, who has counseled several prospective patients. (Some have gone on against her advice to receive unproven treatments. Others have decided against it.) "The best I can do is to offer the information that people need in order to go into treatment with their eyes open. After that, other than physically restraining them, I can't stop them."

Loring's gone to greater lengths than most to get the information to people who need it. She's recorded a video for the California Institute for Regenerative Medicine warning against the use of unproven stem cell treatments, and she's offered to screen the composition of any sample of "stem cells" sent to her by a patient. No one has done so.

"One patient was going to, but he didn't because he was afraid he would be denied treatment by the clinic if he asked for a sample of the cells he was going to be injected with," says Loring. Patients are reluctant to put their hope under the microscope, even when their lives are on the line.

And so the argument rages on. Recent recalls have amply shown that successful clinical trials don't absolutely guarantee a drug will work as expected. Conversely, the fact that a particular treatment hasn't been thoroughly tested doesn't automatically mean that it won't benefit at least some patients.

"This is a new field," says Weissman. "We are learning what kinds of stem cells can regenerate which kinds of failing organs. But we always remember that our first goal is to do no harm. That's why we begin our tests in animals before moving into early phase clinical trials in humans, and at every stage we verify the solidity and reproducibility of the science and that the investigators have no potential commercial or personal conflicts of interest that could influence the outcome of the trials. Any attempt to commercialize unproven treatments in the absence of independent or regulatory oversight endangers not only the lives of those who receive the treatments, but also the entire field of regenerative medicine."

The precarious nature of a field balanced on the edge of a scientific frontier is illustrated by the fate of gene therapy. In the early '90s the technique, which relies on cells engineered to express genes that are missing or faulty, was viewed as a promising treatment for a variety of diseases. But the 1999 death of 18-year-old Jesse Gelsinger after his inclusion in a gene therapy trial led by the University of Pennsylvania set the field back immeasurably, says Weissman. *[See a Q&A with Gelsinger's father, page 14.]*

Without appropriate regulation and enforcement to stop the global marketing of unproven stem cell treatments, he and others fear a similar outcome for stem cell science. But it will take work to teach patients what's truly at stake. And in the meantime the clinics themselves perpetuate the confusion to their advantage with arguments that on the surface seem eminently reasonable.

'THEY ARE VERY LOGICAL. But they don't show evidence that their treatment works; they just say it should. It's hard to argue when there are no facts involved.'

"They are very logical," says Loring. "If it weren't for the fact that I'm a really educated scientist, it would all make sense to me. But they don't show evidence that their treatment works; they just say it should. It's really hard to argue when there are no facts involved."

"A plurality of anecdotes does not constitute evidence," says Sipp. "Just because people swear up and down that something works doesn't make it true." **SM**

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Although the idea might seem strange at first, there's a well-established precedent for antibiotics quieting inflammation. In the last decade, several groups of researchers have demonstrated that, for example, tetracycline's anti-inflammatory activity contributes to its effectiveness against rheumatoid arthritis, that macrolide antibiotics reduce inflammation in chronic airway disease, and that amoxicillin lowers bowel inflammation in ulcerative colitis.

If vancomycin is acting as an anti-inflammatory in PSC, says Kari Nadeau, MD, PhD, an assistant professor of pediatric immunology and allergy at Stanford, that suggests PSC is a disease of immune function run amok.

Scott Seki of Nadeau's group already has some enlightening preliminary data. Regulatory T cells, the immune cells that prevent autoimmune disease by tamping down the inflammatory response, exhibit interesting changes during vancomycin treatment, he has found.

Using blood samples drawn before and after vancomycin therapy, Seki showed that the drug doubles PSC patients' levels of regulatory T cells. Evidence from other autoimmune diseases suggests this change is big enough to cause therapeutically useful drops in inflammation — in other words, it may explain why vancomycin works. Two other experiments in Nadeau's lab also pointed to regulatory T cells as key players in the vancomycin response. However, this information is still drawn from observations of a very small group of patients, so the team is now working to expand and strengthen their data.

If the findings about the regulatory T cells do turn out to be the PSC linchpin, Nadeau says, "We might infer that some kind of inflammatory process is turned on early in the life of these children that we should move quickly to try to regulate."

And if the antibacterial effects of vancomycin are key, Relman says, the best approach would be to design a drug that gets rid of PSC-provoking bacteria but acts more selectively. Right now, vancomycin is probably killing beneficial bacteria that have nothing to do with PSC, he adds. "We'd rather not be using a sledgehammer if something more precise and elegant could be devised."

SURPRISE ENDING

In mid-November 2005, Ellery Woodward-Hartman's case was presented to the transplant selection committee at Packard Children's. Though medical records from her pre-vancomycin days clearly pointed toward transplant, the liver-function tests performed after her first 10 days on vancomycin looked promising. The committee decided to re-evaluate her case in December.

A few weeks later, after about a month on vancomycin, Ellery and her family saw their physicians again. "Dr. Safta and Dr. Cox couldn't believe how well she looked," Woodward recalls. Ellery's jaundice had cleared up. Her belly, previously swollen with fluids that accumulated when her liver function was at its worst, had returned to a healthy shape. She was still tiny in comparison with her twin but she was more energetic.

And by the time the transplant committee reconsidered her case, it was clear that the vancomycin was a success. Ellery didn't need a liver transplant.

"With the degree of disease she had, I was very surprised," says Safta, now an assistant professor of pediatric gastroenterology at the University of Maryland. Woodward and Hartman feel extremely grateful for the compassionate care Safta provided when Ellery was at her worst, and they still send periodic updates. "It's just amazing where Ellery has gotten to," Safta says. "She's probably the only one with such severity of cirrhosis that has turned the corner like this."

Now, after more than five years on vancomycin, Ellery is a thriving 7-year-old. Like other patients taking the drug for PSC, she continues to use it without side effects. Though her liver still bears the scars of cirrhosis, and there's a possibility she may need a transplant at a future date, her liver-function tests are now normal. Her growth has caught up to her brother's.

"I can't even calculate what Dr. Cox has been able to do for Ellery," Woodward says.

Cox sees Ellery's case as a gratifying success, and he's encouraged that emerging Stanford science supports the therapy he discovered by accident. This type of discovery is "one of the rewards of being an academic physician," he says. His collaborators agree. In a project like this, "the patients talk to you through their data," says Nadeau. "If they're getting better, that's what you take as real. That's what inspires you to go back to the lab and figure out what is happening."

But there's one last hurdle: Cox worries that too many patients like Ellery are never offered vancomycin. More than 6,000 people have received liver transplants because of PSC, he says. Though it sounds like a large number, the disease is rare enough that many gastroenterologists never see a case — and so they aren't reading the literature about new treatment advances. To try to bridge the gap, Cox has partnered with the Children's PSC Foundation in hopes of helping physicians and patients' families learn about the treatment.

At a recent foundation fundraiser, he got to meet a few children who had received the therapy from other doctors.

"Kids came up to say it had changed their lives," Cox says. "They were so thankful. That makes me think this is the right thing to be doing." **SM**

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practice clinical ethics. The debate over credentialing has come up repeatedly, says Magnus, and the lack of resolution has prompted a few outside, for-profit groups to express interest in setting up a clinical ethics certification process.

That outside interest, in part, has spurred the American Society for Bioethics and Humanities to update the core competencies for clinical bioethics that were established in 1998, setting forth the skill set required for hospitals that offer clinical ethics consultations. For instance, the skills would include the ability to distinguish the ethical dimension of a particular problem from the legal and medical dimensions, as well as being able to research peer-reviewed ethics publications for precedents. "In some hospitals, there may not be an individual who possesses the full skill set, but there should be a committee or group that collectively has all of the skills," Magnus says.

The revised core competencies will be published in the coming months, he says, although the requirements would not initially be binding. But he holds out hope that hospitals and other health-care organizations will play a stronger role in requiring that their clinical ethicists meet the core-competency requirements. "It's embarrassing, in some ways, how poor the quality of clinical ethics is at many institutions," Magnus says.

One organization that could influence the certification debate is staying on the sidelines for now. The Joint Commission, which accredits all hospitals, currently requires that hospitals have the ability to provide clinical ethics consultations, but hasn't stipulated the level of expertise needed for those providing the services. Paul Schyve, MD, senior vice president of the Joint Commission, says it "is not contemplating requiring certification of clinical ethicists" at this time, adding that it is up to each health-care organization to determine the competence of the people providing clinic ethics services.

Fox believes some sort of license or certificate would help assure that those practicing clinical ethics have the requisite knowledge for effectively interacting with patients and health-care professionals.

But Jonsen and others, while noting that a certification process would be helpful, wonder if the field is big enough to support the needed infrastructure. "Certification in medicine itself is a very complex and expensive business," Jonsen says. "I think the world of bioethics may be too small to support that at the present time. And given the diversity of theoretical and practical approaches, it's hard to figure out how to give a standard examination."

FOR TWO WEEKS,
the unconscious man remains at Stanford Hospital.

It's clear that he has end-stage liver disease and, given his host of other complications, he is not a candidate for a liver transplant. After consulting with the physicians and social workers, his family agrees to shift his treatment to comfort care only. He dies a few days later.

Being part of the decision to withdraw life-sustaining measures from a patient is one that bioethicists don't take lightly.

While the field debates accreditation and data-driven decisions, bioethicists know that the heart of their profession is aiding people as they confront the most difficult of dilemmas — both in the hospital room and in the lab. **SM**

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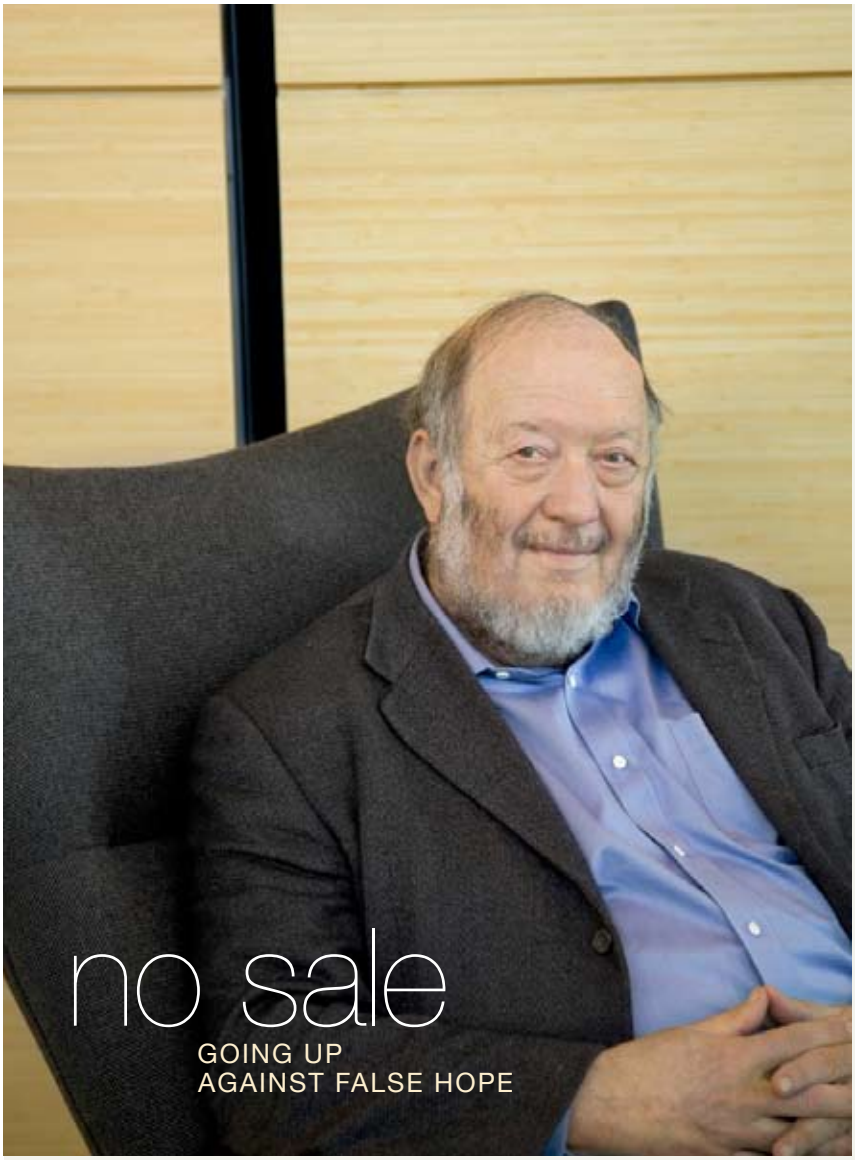

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GOING UP AGAINST FALSE HOPE

AS PRESIDENT of one of the world's pre-eminent stem-cell-research organizations last year, Irving Weissman, MD, paved the way for more research using the amazing self-renewing cells. But he didn't stop there. He also used his tenure to mount a defense against bogus stem cell treatments offered around the world.

This project, resulting in an online resource for patients, makes sense because Weissman believes that proliferating false stem cell treatments jeopardizes the development of real ones. And he had another, more deep-seated, motivation. • The story begins more than 50 years ago when Weissman was a high school student in Montana and a volunteer in the laboratory of pathologist Ernst Eichwald, MD, at the Montana Deaconess Hospital in Great Falls. • "I started as an animal caretaker and research assistant to the technician," says Weissman, now director of Stanford's Institute for Stem Cell Biology and Regenerative Medicine. "But I was soon reading scientific papers and puzzling out what they meant." Eichwald had him compile a bibliography of research articles for a paper he was writing; among the articles he recalls was an American Cancer Society publication detailing a plethora of phony cancer treatments. • "I remember there was one that involved a radon 'health mine' in Texas," says Weissman. "They were total quackery. But what struck me the most was that the American Cancer Society had taken on the responsibility of reporting not only treatments that had been proven to be effective, but also they published what was not proven." • Weissman had a more than academic interest. A few years earlier, a young friend had been diagnosed with leukemia. At the time there was no cure. But her parents wouldn't give up. • "They took her to a fake clinic in Mexico, and had her seeing a chiropractor," says Weissman.

The girl died of the blood cell cancer. That first year in the Montana lab another child with leukemia was in an experimental trial with cortisone, which ultimately also failed. These deaths spurred Weissman to begin asking the questions that led (decades later) to his isolation of the first blood-forming stem cell in humans. But his friend's desperate trip to Mexico also sensitized him to the exquisite vulnerability of families with a terminally ill loved one.

In 2009, when Weissman assumed presidency of the International Society for Stem Cell Research, he made it a priority for the organization to take a stand against marketing unproven treatments and to provide a tool to educate patients about stem cell science. The resulting website (closerlookatstemcells.org) teaches patients and caregivers how to spot clinics that offer unproven therapies, and it allows the public to submit the names of clinics offering such treatments to the ISSCR. *[See the story* Peddling hope*, page 16.]*

But there's always work to be done. In May 2010, Weissman gave a public talk in Great Falls about the latest clinical and scientific stem cell advances. "After the talk," says Weissman, "two separate people came up to say they had received unproven stem cell treatments overseas. Now, these 'treatments' cost tens of thousands of dollars. And I realized that, if Montana farmers are doing this, it's still just a huge problem. These people are going into the hands of predators, and we need to make it stop." — KRISTA CONGER

LESLIE WILLIAMSON

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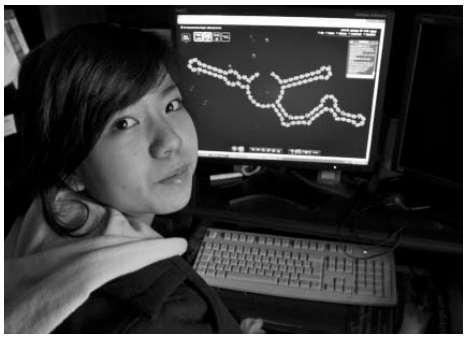
The EteRNA challenge

AN ONLINE GAME TURNS PLAYERS' DESIGNS FOR RNA INTO THE REAL THING

JACKIE GU'S MOM THOUGHT HER DAUGHTER WAS JUST GOOFING OFF, and told her to knock it off already with the online video game she spent so much time playing last summer. Little did she know that her 14-year-old was actually advancing the progress of science. • The game, called EteRNA, taps gamers' skills to accelerate biochemists' understanding of DNA's once-unsung chemical cousin, RNA. Gamers — no experience is necessary — design molecules composed of RNA, which is "the emerging superstar in the field of biochemistry," says Rhiju Das, PhD, assistant professor of biochemistry at Stanford. • Then comes EteRNA's unique kicker: Das' laboratory actually synthesizes the "winning" RNA sequences on a weekly basis, and figures out if they fold up as designed. The lab then feeds the experimental findings back to the players. "This way, there's a chance that thousands of non-expert enthusiasts will be able to collectively solve biochemical challenges that experts can't," says Das. "If the molecule folds as the players think, they win — and so do we."



HIGH SCHOOL STUDENT JACKIE GU and the RNA-folding video game she helped perfect.

Das and two Carnegie Mellon computer scientists launched the game they developed together in January. How many people have signed up?

"More than I imagined," says Das. So far 20,000 players have logged 8,000 hours. As a result, Das' lab is synthesizing eight designs a week.

Those hours Gu spent playing last summer, to her mother's initial chagrin, were her work for Das as an intern. When she first started, Das gave her an online link to the game. She went on to help shape the rules guiding the player interface.

Now she's back in school, with all the work that implies. But she still gets some time — maybe a half-hour a week or so — to play EteRNA. "It's really easy," she says. "The rules are definitely not as complicated as other games'. But it's fun to make these RNAs fold the way you want them to." — BRUCE GOLDMAN

PLAY ETERNA AT ETERNA.CMU.EDU

STEVE FISCH