

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

Spring 2010



girls' day out

TEENS WITH CANCER PAINT THE TOWN PINK

Destinee File was wondering. "Should I get my hair done? Maybe a facial? What about a makeup session?" • These were some of the tough decisions Destinee and 11 other girls had to make when they rolled into the San Francisco Institute of Esthetics and Cosmetology for a Girls' Day Out last October. The teens, all oncology patients who've been treated at Lucile Packard Children's Hospital, were benefiting from an unusual program, which allows kids at various stages of illness to meet, have fun and forge new friendships. • Bonding through shared experience is an important but sometimes overlooked therapy, say hospital social workers. "A teenage girl with cancer faces not just the impact of diagnosis, but also the effects on her appearance," says Tovah LeWinter, oncology social worker. "Some have lost hair and had feeding tubes and wheelchairs. We



IN THE LIMO HEADING TO SAN FRANCISCO, WITH SPARKLING CIDER AND NEW FRIENDS ON TAP.

felt a girls' day out would provide an opportunity to be with others who understand these challenges while sharing a day of beauty and fun."

Destinee was psyched. "I thought it would be cool to meet new friends and share what we've been through," says the 17-year-old from Watsonville, Calif. Diagnosed with acute myelogenous leukemia in 2008, Destinee spent five months in treatment. With her cancer in remission, visiting the beauty institute offered not just big-time pampering, but even some future direction. "This would give me a chance to discover more about cosmetology or fashion as a possible career," she says.

"We knew it would be a day they'd never forget," says Vanessa Ya Lopez, child life and recreation therapy specialist at Packard Children's.

No kidding. The girls journeyed to San Francisco in a sweet-riding, 34-foot, pink Hummer limo with "Girls Rock" on the windows. Inside? Sparkling cider and flowers. "Everyone laughed as people in cars driving by stared and took pictures," says Lopez, who notes the girls broke through their initial shyness with tales about treatments.

The institute donated the beauty services. "Regardless of what stage of treatment these girls were in," says Robyn Parrish, placement leader at the institute, "our goal was to help them all feel beautiful." For Destinee, she decided on a facial and hair styling. "I absolutely loved it," says Destinee, "and it made me feel great."

The event was part of the CHEERS program (Children Having Exceptional Educational and Recreational Support), which was created in 1986 by two Stanford students. Past events include kayaking, concerts and even a Boys' Day Out to see the U.S. Navy's Blue Angels in action. The girls' event was sponsored by the 19 for Life Foundation and coordinated by the hospital's child life and recreation therapy team.

After their glamour treatments, the girls hit the Cheesecake Factory for lunch and took photos at the Golden Gate Bridge. "Throughout the day, the girls became more familiar and enthusiastic with each other, especially after their beauty sessions," says Lopez. "They even began discussing central lines and comparing scars."

Eventually, the girls climbed into the limo for the trip back to Palo Alto, but not before giving Lopez plenty of let's-do-it-again feedback. "Everyone was asking, 'So, when's the next trip?'" Lopez says she doesn't have dates yet, but planning is under way. "When the girls come into the hospital or have clinic visits, they still talk about the limo, the makeovers and how much fun they had," says Lopez. "We saw a transformation take place on this day, and it was a wonderful experience for all of us." — ROBERT DICKS

WEB EXTRA: SEE THE VIDEO AT [HTTP://TINY.CC/GIRLSDAYOUT](http://tiny.cc/girlsdayout)

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

Special report

TAKING KIDS SERIOUSLY
Innovating to improve children's health

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Illustration by Greg Clarke

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Mark Blinder, see story, page 28

letter to our readers

Welcome to this issue of *Stanford Medicine*, a special report with Lucile Packard Children's Hospital at Stanford on pediatric care and research.

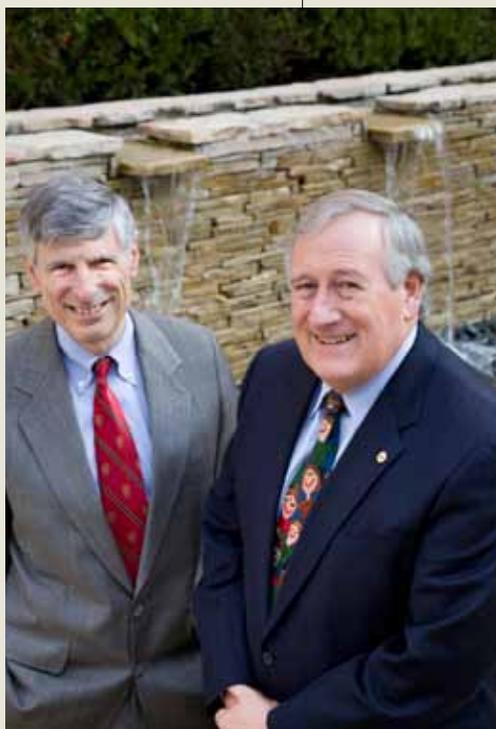
It's an exciting time in the relatively short history of pediatrics — a new specialty in the ancient profession of medicine. About 200 years ago, the thinking was that children were simply small adults, and pediatrics didn't even exist. A few decades later, when the first children's hospitals came along, they were places for sick children whose families could not afford a private physician. Through the 19th century, both pediatric and adult patients received only general supportive care. Curing them was largely out of the question.

Thanks to the advances in science and medicine, today's children's hospitals are light years beyond their early incarnations. Many children with complicated illnesses who walk into a pediatric hospital today have substantial chances for progress and recovery. Leukemia and many other childhood cancers can be cured. Faulty hearts are replaced. Pediatric researchers and clinicians increasingly focus on softening the medical experience and making it easier, faster and more beneficial for children and families.

Aided in large part by genetics research and technology-assisted surgery, pediatric medicine promises to continue advancing by leaps and bounds. The attempt to grow heart valves from stem cells, described in these pages, illustrates the potential. The goal is to create valves that will hold up for a lifetime in the turbulent environment of the heart, so children with heart defects won't need repeated surgeries to replace worn-out implants as they grow up.

The growth in genetic knowledge will bring sweeping change to how pediatricians practice medicine. Within just a few years, it will be possible to inexpensively sequence an individual's genome — the full set of genetic instructions. This capability will allow physicians to personalize prevention and treatment as never before. By referring to a child's genome, we'll know if he or she is predisposed, for instance, to adverse reactions to particular drugs or, conversely, to especially positive outcomes. The potential to provide comprehensive advice will grow exponentially, and will require careful monitoring to ensure that emerging ethical conundrums are handled thoughtfully and appropriately — another reason for a child- and family-focused approach.

Our researchers and clinicians are working together to positively transform the lives of patients and families. We hope you'll come away from this issue appreciating what pediatrics has accomplished, and inspired by what the future holds for children's health.



PHILIP PIZZO (LEFT)
AND CHRISTOPHER
DAWES

Sincerely,

CHRISTOPHER G. DAWES
President and Chief Executive Officer,
Lucile Packard Children's Hospital

PHILIP A. PIZZO, MD
Dean, Stanford University School
of Medicine

upfront

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

Sugar time

SCIENTISTS HAVE LONG STRUGGLED TO UNDERSTAND the body's biological clock. Its ticktock wakes us up, reminds us to eat and tells us when to go to bed. But what sets that circadian rhythm?

New research now shows that daily fluctuations in powerful hormones called glucocorticoids directly synchronize the biological clock by regulating "clock genes" that go on to play an important role in controlling blood sugar levels.

"The most surprising part of our findings is that our internal biologic rhythms are embedded directly into another pathway, one that is essential to regulate metabolism," says the study's senior author, Brian Feldman, MD, PhD, assistant professor of pediatric endocrinology at the medical school. Feldman also practices at Lucile Packard Children's Hospital.

The findings give the first in vivo evidence of a direct link between glucocorticoid hormones and genes that regulate our biological clock.



The study was published online Oct. 5, 2009, in *Proceedings of the National Academy of Sciences*.

Feldman's team applied a synthetic glucocorticoid to dishes of mouse and human stem cells to see which genes responded. To the team's surprise, three genes known to control the biological clock changed their activity in a direct response to the hormone.

Next, the researchers tested how the hormone's effect on the biological clock is linked with its other functions. The scientists gave the synthetic glucocorticoid to genetically engineered mice lacking a specific gene involved in regulating biologic rhythms. As the team expected, genetically normal control mice responded with blood glucose changes associated with increased diabetes risk. In contrast, the genetically engineered mice were protected from harmful effects on blood sugar levels.

The result shows that blood sugar regulation and the biological clock are entwined.

TIMING'S EVERYTHING

The close link between daily cycles of glucocorticoids, the body's daily rhythms and blood sugar fluctuations should prompt doctors to examine how they use glucocorticoid drugs, Feldman

says. For instance, prednisone is a powerful immune-suppressing glucocorticoid used to treat everything from severe asthma to cancer. Unfortunately, its side effects include poor regulation of blood sugar, weight gain and diabetes.

"Some very simple modifications in how we use glucocorticoids may change whether these drugs cause diabetes," he says. Giving prednisone in a daily pattern that matches the body's natural glucocorticoid cycle — with a peak in the early morning — might help solve the problem, he said. And because prednisone is already approved for human use, clinical trials of this idea would be fast and simple.

— ERIN DIGITALE

The research was funded by a grant from the National Institutes of Health.

Early cancer warning?

IMAGINE WAVING A MAGIC WAND over a region of a person's body to determine if he has early signs of cancer. Researchers at the School of Medicine have shown in a laboratory study that ultrasound energy delivered to specific body regions can trigger the release of biochemical disease markers

from tissues, making those markers more detectable as well as helping to pinpoint their source.

UPPING THE SIGNAL

Cancer cells produce substances not normally made by healthy cells and release those telltale biomarkers into the blood. In principle, this should allow relatively noninvasive early detection of tumors by monitoring patients' blood for various cancer biomarkers. But only a handful of them are used in clinical practice.

Circulating levels of some biomarkers are ordinarily too small for reliable detection, but there's a way around this. The cells that produce them carry multiple copies of these substances on their membranes — and at the right frequencies, ultrasound perturbs the membranes, spilling larger amounts of biomarkers into the bloodstream.

"Tumors are often not detected until they become sizable enough to cause recognizable symptoms or to be observed themselves as masses on an X-ray or CT scan," says Gary Glazer, MD, professor and chair of radiology. "By then, the prognosis is much poorer than it might have been had the detection occurred earlier."

In a study published online Sept. 21, 2009, in *Proceed-*

ings of the National Academy of Sciences, Glazer's team reported that they applied ultrasound to cultured colon cancer cells, causing the cells to release large amounts of a biomarker known as CEA into the surrounding culture medium. Then they optimized the ultrasonic energy level to trigger substantial CEA release from the cells without killing large numbers of them. (An important ultimate clinical objective is to be able to find a patient's tumor without killing adjacent healthy tissue during the search.)

The researchers then implanted CEA-producing tumor cells into mice with impaired immune systems. Once the cells had engrafted to form tumors, ultrasound beams were directed at both tumor-bearing and, for comparison, tumor-free sites. Ultrasound energy aimed at tumors significantly increased the mice's blood levels of CEA compared with the levels observed either before tumor cells had been implanted or when the beam was applied to non-cancerous sites.

— BRUCE GOLDMAN

The study was funded by grants from the Lucas Brothers Foundation, National Institutes of Health, National Cancer Institute, Canary Foundation and Stanford's Department of Radiology.

Ultrasound energy delivered to specific body regions can trigger the release of biochemical disease markers from tissues, making those markers more detectable as well as helping to pinpoint their source.



Kidney punch

FOR OLDER RESIDENTS OF U.S. NURSING HOMES, starting dialysis may do more harm than good, heralding a decline in their ability to perform daily tasks such as feeding themselves, getting dressed or brushing their teeth, say researchers at the medical school.

Within the United States, 400,000 patients receive dialysis — a method of removing waste products from the blood when the kidneys fail. The treatment can be particularly burdensome for frail elderly people because

they must travel to and from the dialysis centers, typically three times a week for three to four hours per treatment.

Americans over the age of 80 are the fastest-growing segment of the dialysis population, an increase not explained simply by population growth or an increase in diseases that cause kidney failure. This appears to be because physicians are much more willing to provide dialysis therapy to the very elderly, says Manjula Kurella Tamura, MD, assistant professor of nephrology. At least a third of these patients suffer from

multiple chronic illnesses, such as heart disease and diabetes, in addition to kidney failure.

“The findings are sobering,” says Kurella Tamura, who conducted the study with colleagues at Stanford and UC-San Francisco. “One of the rationales for starting dialysis in patients with limited life expectancy due to diseases other than kidney failure is that, even if dialysis doesn’t extend life, it will improve the quality of life by alleviating symptoms of kidney failure or improving the ability of patients to care for themselves.”

Depending on a patient’s other medical problems, this may not be true, according to the study by Kurella Tamura and her colleagues in the Oct. 15, 2009, *New England Journal of Medicine*.

The study identified 3,702 nursing home patients from national registries who started dialysis between June 1998 and October 2000 and who had at least one measurement of their functional status available before they started the treatment. Functional status was measured by assessing the degree of dependence in seven activities of daily living.

Researchers then compared the patients’ functional status over the year prior to dialysis with the status over the year following treatment. Results showed that 12 months after starting dialysis, 58 percent of the patients had died, and only 13 percent had maintained the functional level they had before starting dialysis.

“We have tended to overestimate the benefits and ignore or downplay the negative aspects of dialysis when we counsel patients about their treatment options,” Kurella Tamura says.

— TRACIE WHITE

The research was supported by the National Institute on Aging and grants from the National Center for Research Resources and the National Institute of Diabetes and Digestive and Kidney Diseases.

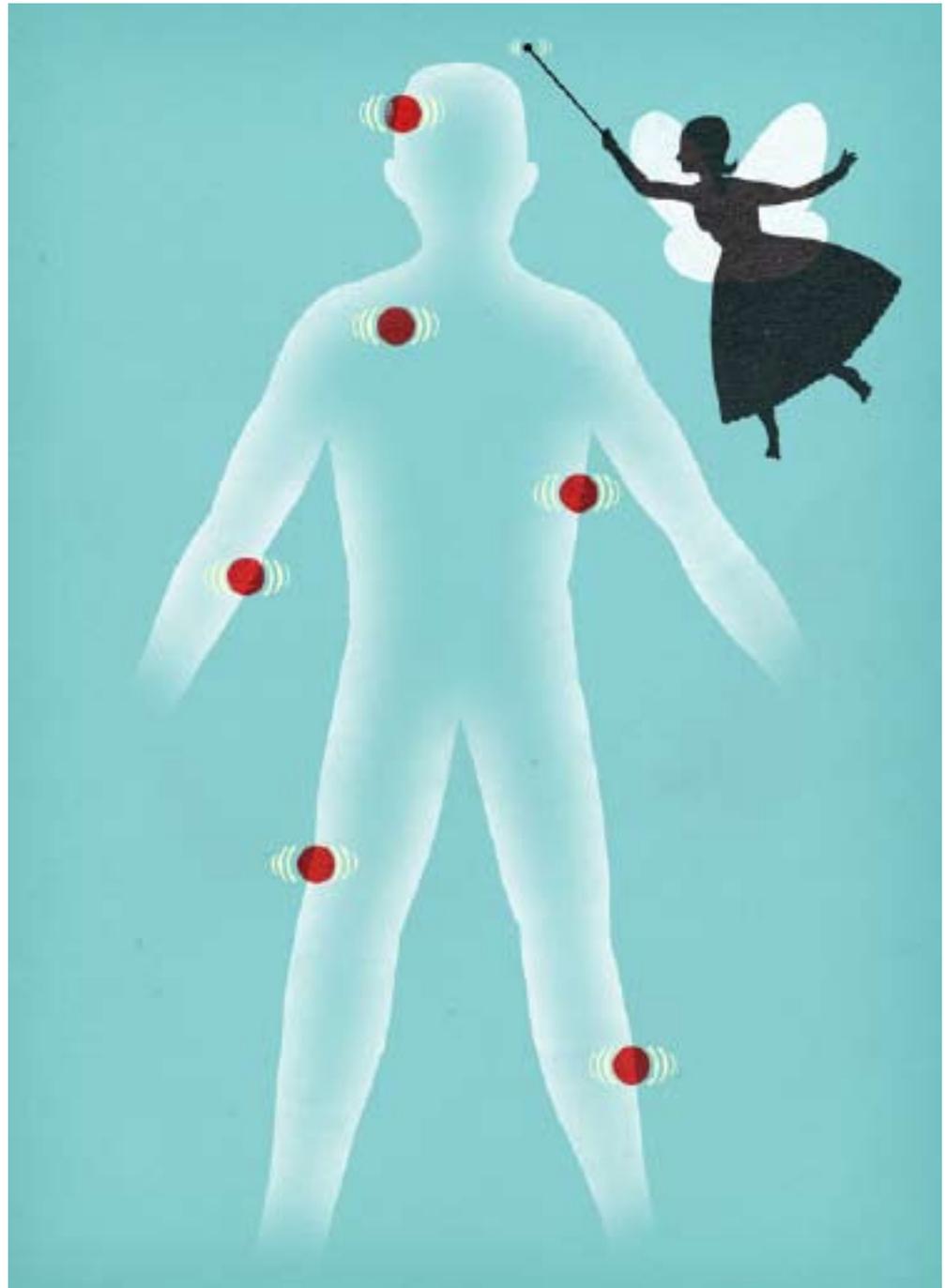
Rejecting rejection

The first doctors she consulted told Rachel Amato that the odds were vastly against her ever having a successful kidney transplant.

Then the 29-year-old mother of four from Turlock, Calif., traveled to Stanford Hospital & Clinics. "They were really honest with me," she recalls. "They said, 'We have seen proof that this new treatment works. We just don't know how many doses it's going to take.'"

In August 2008, Amato had her first four-hour infusion of a "desensitization" drug, intravenous immunoglobulin, or IVIG, designed to lower the number of organ-rejecting antibodies in patients who are highly "sensitized." That means they have weapons-grade antibodies — acquired in blood transfusions, pregnancies or during a previous transplant — that seek out and destroy invading antigens, particularly the human leukocyte antigens, or HLA, on the surface of a foreign organ. These patients' immune systems would reject a donor kidney.

Amato had one monthly infusion for four months, and in January 2009 she had a dose of an additional drug, Rituxan, which knocks out



many of the immune-system cells that produce antibodies. "Boom! My antibodies dropped," she says. "I got my transplant two weeks later."

The desensitization program, as well as improvements in minimally invasive surgery

and the promise of an experimental "tolerance induction" protocol, have placed Stanford at the forefront of kidney transplant programs. It was the only one among 240 kidney transplant centers nationwide that exceeded expected

results in both patient and graft (transplant kidney) survival at one year and at three years after transplantation, according to the independent Scientific Registry of Transplant Recipients. The registry also shows that Stanford was

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the top program in one-year transplant kidney survival rates for four years running, from July 2000 to June 2004.

“It’s not just a fluke,” says Stephan Busque, MD, surgical director of the adult kidney and pancreas transplant program. “Even though we’re treating patients at higher risk, we perform better than expected because we have a very good team and our patients get very attentive, individualized care.”

Busque and the other members of the program have been pursuing new tests, treatments and technologies to address the plight of people who, like Amato, need transplants but can’t qualify for them because they are highly sensitized.

The new protocol involves giving these patients a high dose of IVIG. The infusions, which may be repeated over several months, lower the patient’s number of organ-rejecting antibodies.

MANY COULD BENEFIT

Dolly Tyan, PhD, director of the program’s histocompatibility lab, estimates that 30 percent of the 80,000 people on the national waiting list are HLA sensitized and might benefit from being desensitized. The treatment is available at only a handful of medical centers, including Cedars-Sinai, Johns Hopkins, the Mayo Clinic and the University of Toronto.

Tyan and her colleagues have also developed a new assay system that “allows us to see very specifically what antibodies a person has, and exactly which ones are going to go away.”

In the meantime, Amato is grateful that she had the opportunity to get a kidney. While she still takes medication to ensure against her body rejecting the organ, her life is almost back to normal. “Stanford was my saving grace because they did not give up on me,” she says.

— DIANE ROGERS

Sperm from scratch

SCIENTISTS HAVE A PROMISING NEW TOOL for understanding infertility: cells derived from unused embryos created for in vitro fertilization.

Stanford researchers have devised a way to efficiently coax stem cells derived from embryos to become germ cells, which are the precursors of egg and sperm cells. And unlike previous methods, which yielded primarily immature germ cells, the cells made with the new approach generated nearly mature sperm.

“This is the first evidence that you can create functional human germ cells in a laboratory,” says senior author Renee Reijo Pera, PhD, director of Stanford’s Center for Human Embryonic Stem Cell Research and Education.

“Ten to 15 percent of cou-

ples are infertile,” says Reijo Pera. “About half of these cases are due to an inability to make eggs or sperm. And yet deleting or increasing the expression of genes in the womb to understand why is unethical. Figuring out the genetic ‘recipe’ needed to develop human germ cells in the laboratory will give us the tools we need to trace what’s going wrong for these people.” The study was published online by *Nature* on Oct. 28, 2009.

Previous efforts to study infertility have been hampered by the fact that the human reproductive cycle cannot be adequately studied in animal models. And because germ cells begin to form very early in embryonic development (by eight to 10 weeks), there’s been a dearth of human material to work with.

Her team first isolated stem cells from the unused embryos, treated them with proteins that stimulate germ cell formation and isolated those that began to express germ-cell-specific genes — about 5 percent of the total.

They then used a technique called RNA silencing to examine how blocking the expression of each of three genes known to be involved in male infertility affected germ cell development. Conversely, they also investigated what happened when these

genes were overexpressed.

They found that one of the genes functions very early in germ cell development, while two others stimulate the then-mature germ cells to form immature gametes, the next step toward becoming sperm and eggs. Overexpressing the three proteins together allowed the researchers to generate cells expressing proteins found in mature sperm.

After 14 days of this treatment, about 2 percent of the differentiated human embryonic stem cells had only one copy of each chromosome — indicating they were on their way to becoming sperm. (Most other human cells, including normal, untreated embryonic stem cells, have two copies of each.)

The researchers plan to use a similar strategy to optimize the production of eggs from embryonic stem cells, as well as investigating whether reprogrammed adult cells called induced pluripotent cells can also be used to create germ cells. By charting the germ cells’ development, they hope to identify problems that lead to infertility, miscarriage and birth defects.

— KRISTA CONGER

The research was funded by the National Institute of Health, the California Institute for Regenerative Medicine and the Tobacco-Related Disease Research Program.

TAKING
KIDS
SERIOUSLY

LITTLE PATIENTS, BIG

GETTING SERIOUS ABOUT HELPING WITHOUT HURTING

MEDICINE

In a small dressing room at Lucile Packard Children's Hospital, 13-year-old Aria Chimalamarri is following a familiar routine. She changes from her jeans and sweater to a hospital gown, then carefully removes the jewelry she made herself: delicate beaded earrings and a brightly colored bracelet, one of many she has designed to hold the MedicAlert tag that warns about her epilepsy. Her wire-rimmed glasses come off last. Aria is headed for the hospital's magnetic resonance imaging scanner, where she'll spend the next hour lying motionless in a noisy, claustrophobic tube so a radiologist can peer into her brain.

By Erin Digitale

ILLUSTRATION BY GREG CLARKE



BC

“My biggest worry is, what if I have a seizure in the scanner?” Aria says.

Aria’s regular journeys to the radiology department — she’s had 15 to 20 MRI scans since her 2001 epilepsy diagnosis — are emblematic of the paradoxes of pediatric medicine. Kids like Aria now receive better health care than ever before, yet this care still entails discomforts and dangers that would tax even a mature individual.

Today’s pediatric physician-scientists, at Packard Children’s and elsewhere, are working to unravel this conundrum. No longer content to jerry-rig adult treatments and medical devices for small patients, they’re turning to collaborators in disciplines from stem cell research to electrical engineering to devise treatments tailor-made for children. Drawing on disparate branches of science is allowing them to invent new ways around the collateral damage that complicates pediatric care. It’s a renaissance of the core concept of medical ethics: First, do no harm.

So pediatric hospitals and physicians are looking at game changers for young patients. In a research push that has been gradually gaining steam since the early days of pediatric laparoscopic surgery in the mid-1990s, pediatricians are asking how to keep children safer and more comfortable. Their efforts focus on every stage of treatment from the hours a patient spends in the hospital for a test or an operation to the years he lives with a surgical scar or transplanted organ.

MAKING MRIs LESS SCARY

Before every MRI procedure, the radiology nurses reassure Aria that if she feels a seizure coming on, she should call out to them — despite the noisy bangs of the machine, they can hear her, stop the scanner and get her out. Aria has decided to accept this reassurance and adopts relaxation techniques like listening to music in the scanner. (Rhianna is a favorite.)

It’s not an ideal solution, but the alternative seems worse. Many children in Aria’s shoes undergo general anesthesia before each MRI.

“About 50 percent of our cases are being done under anesthesia,” says Packard Children’s pediatric radiologist Shreyas Vasanawala, MD, PhD. “That takes a procedure that’s otherwise very safe and turns it into a big deal.” While MRI is radiation-free and completely non-invasive, the general anesthetic lowers heart rate, breathing rate and blood pressure, and carries risks of more serious complications.

To circumvent these risks, Vasanawala is studying ways

to shorten MRI scans for kids so children will be exposed to less anesthetic — or maybe none at all. The innovation is urgently needed. Many young children simply can’t hold still for an hour or more, Vasanawala explains: Three to five minutes of concentration per year of age is a realistic expectation. (Aria is unusual — even as a 5-year-old, she chose to go through 90-minute scans unanesthetized. “She has always been on the courageous side,” says her mom, Devi.)

So Vasanawala’s team is taking an approach that seems counterintuitive: Instead of collecting more data with each scan, they’re collecting less. The strategy uses the same concepts that allow a digital camera to collapse photo files down to a manageable size, but with a twist, Vasanawala explains.

A camera records over-detailed images, then throws out data in a way our eyes can’t detect. Similarly, MRI scanners collect thousands of tiny magnetic signals that are sent out by the body’s water molecules in response to the scanner’s strong magnetic field. A computer assembles the data into a 3-D image of the patient’s soft tissue. But instead of collecting and discarding extra MRI data, Vasanawala’s team is systematically gathering less information in the first place. The scientists have halved scan times, and are now investigating whether scan quality holds up in varied tissues and diagnoses.

“Right off the bat, we tried to push this technology very hard,” Vasanawala says. When he began clinical testing of the new method in 2007, he hoped to get good images from one-tenth the standard amount of data, but the scans were hopelessly compromised. “We backed off some — increased the percentage — and then it started working really well,” Vasanawala says.

But he’s still not content to stop at a 50 percent improvement in scan times. Because collecting less data won’t get him all the way to his goal, Vasanawala is studying two more approaches to speed up MRIs.

One plan calls for scaling down MRI equipment for children. Grown-ups’ scanners make it impossible for physicians to zoom in on kids’ smaller body parts, increasing the time needed to get detailed images.

“It’s a chicken-and-egg problem,” Vasanawala says. “You don’t have that many requests for MRI for kids because there’s such a high barrier imposed by the need for anesthesia.” Manufacturers don’t perceive a market for kid-specific equipment and don’t put much research effort toward child-sized technology.

To break this barrier, the Packard researchers are collaborating with engineers in Stanford’s Department of Electrical Engineering and at General Electric to redesign the inner circuitry of MRI scanners. They’re making child-sized radiofrequency coils, the parts of the MRI machine that receive

the electromagnetic signals. Smaller coils will improve the scanners' resolution and speed them up.

Another tactic, now in early development, aims to improve mathematical corrections that account for movement during scans. Even when a patient lies still, her internal structures still move: Blood flows through arteries and veins, for instance. Movement blurs magnetic resonance images, just as a photo of a moving car will blur if the camera's shutter speed is too slow. A better method of correcting for these small movements would cut the total time children spend in the scanner.

Vasanawala is excited by the progress. "When these techniques are combined, we expect they'll act synergistically," he says. "We still haven't fully exploited the ways of speeding things up for kids."

Aria is excited, too. "Faster would be better, definitely," she says. So far, she's been fortunate enough never to have a seizure in the scanner, and she knows faster scans would help keep it that way.

BYPASSING BRAIN DAMAGE

In one sense, Aria and her family have been lucky. They could choose to avoid the dangers of anesthesia for each of her many MRI scans.

But other medical procedures are a different story. For instance, pediatric cardiac anesthesiologist Chandra Ramamoorthy, MD, monitors young patients during one of the riskiest scenarios they can face: open-heart surgery. For these children, often infants undergoing lifesaving repair of congenital heart defects, few aspects of treatment are optional. The only way to keep them safer is for physicians to innovate past the risks.

Ramamoorthy's challenge is that, to let surgeons cut and sew, her team must stop the heart while making sure enough oxygen reaches the vital organs. Open-heart surgery requires several hours on a heart-lung bypass machine, raising the patient's chance of brain injury from low blood oxygen or prolonged exposure to anesthesia. Fortunately, there's one surefire method for slowing the brain's oxygen use.

"Keeping a cool head is one of the most protective strategies for the brain," Ramamoorthy says.

She's not speaking figuratively. Ramamoorthy uses controlled hypothermia — cooling the patient's blood as it passes through the bypass machine — to dampen brain metabolism. Chilling the patient's body by nine to 16 degrees Fahrenheit effectively heads off dips in blood oxygen.

However, new research shows that what goes down must be brought back up carefully. In a 2009 study of neonatal

heart valves from stem cells

GROWING LONG-LASTING

REPLACEMENT PARTS

Repeated open-heart surgeries are risky. Yet for infants born with severe heart defects, multiple surgeries may be the only shot at life.

Heart surgeon Frank Hanley, MD, is working to change that. Hanley, Packard Children's chief of pediatric cardiothoracic surgery and co-director of the hospital's Children's Heart Center, has spent years perfecting a technique that condenses the usual two or three surgeries for mis-plumbed hearts into one long operation. So far, he's saved more than 500 children from extra trips to the OR.

But lately, Hanley has hit a roadblock: Patients born with missing heart valves must receive prosthetic valves, which don't last forever.

"Little Johnny outgrows his T-shirts and shoes — kids also outgrow the valves we use, or the valves wear out," Hanley says. "The patients have to come back and get their valves replaced."

So Hanley is partnering with colleagues in regenerative medicine to learn how to make fully functional heart valves that grow and repair themselves. The scientists are now studying what goes on inside normal valves, the paper-thin leaves of tissue that prevent blood from backwashing on its trip through the heart.

"The heart contracts 40 million times a year," says senior research scientist Kirk Riemer, PhD, who leads the lab work. "The valves are very busy pieces of tissue. They flap like flags in a continuous windstorm."

That continuous turbulence wears out prosthetic valves in a few years, but doesn't cause

problems for natural valve tissue until old age, if then. "The tissue must be a master at repairing itself," Riemer says. Understanding self-repair is essential to build effective replacement valves, he adds.

But first the researchers needed a way to study valves in action. Plopping a valve in a dish wouldn't expose the tissue to the fluid forces thought to prompt self-repair. So Riemer spent a year rigging a "bioreactor" that pumps body-temperature fluid through rat heart valves at just the right speed and pressure.

Now, the team is ready to examine how individual cells within the valve signal damage and initiate repairs.

"We think if the valve starts to lose cells, a small breach can bring about a series of reactions that materialize as a big problem, like the tiles on the space shuttle," Riemer says. To catch the earliest hints of a problem, the team will have to detect minuscule changes in chemical signals sent out by valve cells — and figure out how such signals work in an environment as turbulent as a washing machine.

Ultimately, the researchers hope to program a patient's own stem cells to fashion functioning heart valves that last a lifetime.

"If we could form a heart valve with a patient's own tissue that would grow and heal itself, that would be a huge advance," Hanley says. "Then, we could operate on little Johnny at 1 year and say, 'He's cured.'"

pigs, Ramamoorthy and surgical colleagues demonstrated the brain was protected only if it was warmed up slowly and evenly after an operation.

“We found that, in our enthusiasm to come off the heart-lung machine, we might be rewarming too quickly,” she says. Temperature probes placed at two locations in the pigs’ brains showed that core brain temperatures often exceeded those at other sites in the body during rapid reheating. Hotter parts of the brain gobbled more oxygen, leaving them more prone to damage. The most vulnerable brain structures were those deep in the midbrain, positioned to get direct hits of warm blood from major arteries. The hippocampus, a midbrain structure that helps form new memories, was one of the brain parts at risk.

The cardiac team at Packard Children’s has changed its rewarming plan as a result of the pig study. Today, instead of quickly returning bypass patients to a normal body temperature of 98.6 degrees Fahrenheit, Ramamoorthy gradually rewarms them to 95 degrees, then monitors as their bodies bring themselves back to normal. If body temperature goes above 98.6 in the recovery room, the team cools patients off a bit. They can cool the blood passing through the heart-lung machine, or use cooling blankets and a lower room temperature to slow rewarming.

Even with these advances, anesthesia is still not an exact science. “Giving anesthetic isn’t like baking a cake,” Ramamoorthy says. Bakers can taste whether their creation turned out, she explains. “It’s very hard to measure how good an anesthetic was.” But despite the challenges, Ramamoorthy and her colleagues continue striving to attain the essential goals of anesthesia — blocking pain and memory of surgery — while reducing harm to the developing brain.

BIG SURGERIES, TINY SCARS

While skillful administration of anesthesia leaves no traces, pediatric general surgeon Sanjeev Dutta’s results are plain as day: The tumor is gone, the hernia is fixed or the malfunctioning body part works.

Dutta, MD, can also easily observe the unwanted after-effects of his handiwork, including pain, hospital stays and scars. While many surgeons want to reduce pain and hospital time, “they seem not to care much about scarring,” Dutta says. “They tend to say, ‘Suck it up, it had to happen.’ That’s the Calvinistic culture of surgery.”

But scars matter to young patients. Research shows children with prominent scars struggle with school performance,

socialization and self-esteem. That knowledge drives Dutta’s operating-room innovations. “My goal in life is to eliminate scarring,” he says. Rather than follow the old model of surgery, in which big incision equals big surgeon, Dutta and his Packard Children’s colleagues are pioneering another way. “We can do these big operations on the inside now, so we’re still performing a maximal operation, but with minimal collateral damage.”

The transition isn’t trivial. Tiny laparoscopic incisions radically change the surgeon’s view of the operation and require mastering new tools and techniques.

“People say that looking through a laparoscopic instrument is like looking through a straw,” Dutta says. But that’s not quite accurate. Laparoscopic tools magnify the surgeon’s view by a factor of 10. On small patients, the laparoscopic view is often clearer, once the surgeon gets used to it. “You need to understand and identify anatomy from this new vantage point,” Dutta says.

Once they’ve got the technique down, though, surgeons can begin substituting small, hidden cuts for big scars.

One child who benefited from this strategy was an 8-year-old who came to Packard Children’s with torticollis, an unnatural tightening of his neck muscles. The boy was forced to hold his head tilted awkwardly toward one shoulder, which could lead to permanent disfigurement. “The brain wants to see the world level, so the skull gradually reshapes itself to compensate, leaving the patient with a crooked head,” Dutta says.

Traditional surgery to cut the problem muscles would have left a prominent neck scar, trading one deformity for another. Dutta took a different route, making three tiny incisions in the child’s armpit and tunneling under the skin to reach his neck. “Not too many people will come up and stare at your armpit,” Dutta points out. An “after” photo shows the excited boy in Dutta’s office, grinning proudly as he holds his head straight.

The next step, after hiding scars, is eliminating them completely. One approach is to put a scar inside a scar. In a first-of-its-kind 2008 surgery, Dutta removed the spleen of a 9-year-old named Ryan using only an incision in the boy’s belly button. Ryan’s mom, Elaine, guessed her son might receive a laparoscopic procedure but was surprised the surgeons could use his belly button. “I thought, Wow, that seems even better, since there are no scars at all,” she says. Elaine herself has a large scar from her own splenectomy, necessitated by the same hereditary red blood cell disorder that led to Ryan’s surgery.

“These parents don’t want the same for their kids,” Dutta says.

Dutta’s next step is figuring out how to access surgical sites via natural body orifices such as the mouth. To that end, he’s

collaborating with engineers from SRI International (formerly the Stanford Research Institute) to build new tools for fixing esophageal atresia, a congenital gap in the esophagus that prevents infants from eating normally.

Figuring out how to perform a complete surgical repair of the esophagus through an infant's mouth will take 10 to 15 years, Dutta says. But he's optimistic the approach will eventually succeed. "We want to figure out how we can safely and reasonably use natural orifices for surgery in children."

A CRYSTAL BALL FOR TRANSPLANT REJECTION

Some forms of collateral medical damage don't occur until months or years after treatment. Packard Children's pediatric nephrologist Minnie Sarwal, MD, PhD, is working to lessen one such problem: damage inflicted by a cumbersome method used to monitor transplanted kidneys.

Children with kidney transplants face pressing danger that their immune systems will reject the organs — about one-quarter of pediatric patients have a bout of acute rejection in the year after surgery. Sarwal, who is also a professor of pediatrics at the School of Medicine, leads a team that has developed the first-ever method for detecting acute rejection before damage sets in.

"We're figuring out how to get transplanted organs to last longer and how to help patients live more safely with them," Sarwal says.

The new, non-invasive test gives doctors time to stop acute rejection in its tracks. Instead of an invasive biopsy, a blood sample is tested to measure activity of five genes that switch on when a patient's immune system starts rejecting a transplanted organ. Doctors can then respond to early signs of rejection with a prompt, moderate increase in immune-suppressing drugs, bringing the immune system under control before the transplanted kidney gets hurt. Urine samples may hold similar gene-activity clues to transplant rejection, so Sarwal's team is studying urine now.

Sarwal hopes the method will eventually replace the current system for assessing transplant health, which can't spot rejection until the kidney begins to malfunction. At that point, doctors use a biopsy to confirm the problem, then give big doses of immune-suppressing drugs. The drugs usually stop rejection, but not before the kidney sustains permanent damage.

In addition to predicting rejection, the new test will also show which patients could safely lower their doses of anti-

rejection medication to reduce infection risk and other side effects. Until now, clinicians have had no way to tailor immune suppression to individual patients.

Not only does the biopsy method do a poor job of spotting early signs of rejection, it strains patients and their families. Carla Combi, mom to 11-year-old kidney recipient Cole, knows the burden well: Her son received his first transplant at age 1, and got another kidney last March after the original transplant failed. Cole has had at least one biopsy a year throughout his childhood. Every procedure requires a long day at the hospital, general anesthesia and a week of bed rest afterward.

"It disrupts his life," Carla says. Her son, a very social fifth-grader who loves basketball and his family's two golden retrievers, struggles with the feeling that he's different. A week alone in bed certainly doesn't help.

"Telling Cole he can't be with his friends, he can't do what they're doing — that's the hardest thing," Carla says. The possibility of a more normal life for Cole, an easier balance between his medical needs and his desire to be ordinary, is tantalizing.

LETTING KIDS BE KIDS

In the end, inventing better pediatric medicine goes beyond developing technological firepower or physiologic knowledge. It's also about a search for ways to help sick children feel normal.

"This is really a culture change," says surgeon Dutta. "It's a difference in how we look at our patients." Instead of expecting patients to tough it out, he says, more physicians are moving beyond a narrow focus on immediate medical problems to treat the child as a whole.

For patients and their families, the change is welcome. Describing her son's lifetime of medical scrutiny, Carla Combi says, "He's OK with being in the hospital. Needles don't scare him, all that stuff does not scare him." She's effusive in her praise for the care Cole has received.

Yet she also acknowledges, a bit wistfully, that Cole's life-saving treatments can leave him feeling isolated, "different."

That's why parents like Combi appreciate the advances that allow pediatric medicine to surge ahead without leaving trouble in its wake. Yes, they care about the measureable benefits of innovating for children's health. But they're also excited about the intangible satisfaction of seeing their young ones be regular kids — the best possible side effect of safer, more comfortable treatments for seriously ill children. **SM**

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hand-me-down blues

ENDING

DEPRESSION'S

LEGACY

PEGGY FINISHED HER LAST FINAL OF HER FIRST COLLEGE SEMESTER, walked off the UC-Berkeley campus, headed down Telegraph Avenue and bought a bottle of sleeping pills from the nearest pharmacy. • “I was going to go home,” says Peggy, “wait until my grandmother went out shopping, take the pills with a bottle of whiskey that she kept hidden in the linen closet. I couldn’t see any other way out.” • Flirting with depression from the age of 5, Peggy’s first year of college had sent her into her blackest downward spiral yet. At 19, she felt helpless and utterly drained. “I thought, ‘Oh God, I’ve flunked everything.’” She’d never had any therapy, never had any help from home, had few friends and had finally just lost hope. Suicide seemed like her only option. • Thirty-six years later, Peggy, who asked that her real name not be used, is a mother of two living in Danville, Calif., and, along with her 15-year-old daughter, is a participant in one of a wave of scientific studies that could help prevent depression in adolescents. It’s an intriguing concept gaining ground within the research community: Identify the adolescents most at risk for depression, and pre-empt it.

By Tracie White

ILLUSTRATION BY MATT BANDSUCH



“We know rates of depression go up in adolescence. If we want to prevent depression, it makes sense to start early,” says Judy Garber, PhD, professor of psychology and human development at Vanderbilt University. “It seems like a much better way to go,” says Garber, who is testing interventions.

To attack the problem of how, first, to identify these kids, then second, to get them help, scientists are examining brain scans, measuring stress hormone levels, testing prevention programs. The hope is that by better understanding the interplay between human biology and environmental stressors, which together increase vulnerability for depression, researchers can better define those most at risk.

“For most kids, time does heal all,” says Manpreet Singh, MD, a child psychiatrist and associate director of the pediatric bipolar disorders clinic at Lucile Packard Children’s Hospital at Stanford who treats adolescent mood disorders.

“What we want to know is, why do some kids bounce back from stressful life events while some don’t?” says Singh. “What’s

different about that subset of kids who don’t do well?”

Much progress has been made over the past 50 years in developing a profile of adolescents who might have a vulnerability to mood disorders, Singh says. What is now known is that depression often first strikes in adolescence, that females are twice as susceptible as males and that children of depressed parents are at a 40 percent increased risk.

“The whole battle between nature and nurture is pretty much over,” explains Victor Carrion, MD, director of the Stanford Early Life Stress Research Program at Packard Children’s Hospital. “We know it’s the interaction between the two. What we now need to figure out is just how environmental factors stimulate certain genes to cause a mood disorder.”

Depressing facts

ALL PEOPLE AT TIMES FEEL SOME DEGREE of sadness in their lives, but clinical depression is something else entirely. It destroys the ability to feel pleasure. It exhausts, both mentally and physically. It makes it impossible to get out of bed, and

a community crisis

TEEN SUICIDES IN PALO ALTO

Twice an hour, red warning lights flash at the East Meadow Drive train crossing in Palo Alto. The gates lower to stop cars, a train whistle blares and the giant, silver commuter train blasts past. Sitting off to the side of the tracks in a folding chair is a city-hired security guard. In the afternoon, when streams of kids cross the tracks on the way home from school, nobody talks to him but everybody knows he’s there. Posted on a small sign next to him is a suicide hotline number. He’s there as a deterrent.

Since May of last year, five Palo Alto teens have killed themselves near this spot in a quiet, residential neighborhood by stepping in front of a moving train. In November 2009, spurred by a group of parents who began patrolling the tracks as part of a community-wide, coordinated effort to stop suicides, the city hired a private security firm to help.

“At first people thought we were crazy, but it just seemed to be common sense,” says Caroline Camhy, a Palo Alto mother who helped start Track Watch in October by recruiting volunteers to stand guard, particularly late at night when most of the suicides took place. “If suicide wasn’t so easy to do, it seemed like fewer people would do it.”

One suicide has occurred on the tracks

since the patrolling began. On the evening of Jan. 23, 350 yards north of a security guard who was stationed at the East Meadow Drive crossing, a 19-year-old died. But the patrolling continues.

The effort to prevent suicides is continuing on multiple fronts. Following months of collaboration between mental health experts and city and school personnel, a plan is in place to conduct routine screening of students at risk for mental health disorders, maintain a database of mental health services and conduct a psychological review of the victims and the circumstances surrounding the deaths, looking for trends and possible causes. And to continue patrolling the crossing, as well as others nearby.

“It’s important to know this is not completely out of our control,” says Shashank Joshi, MD, a pediatric psychiatrist at Lucile Packard Children’s Hospital and director

of the hospital’s school mental health team, which provides support to the Palo Alto Unified School District. “We’re trying hard to look for at-risk kids we might miss. We’re helping kids and families by teaching coping skills and resiliency,” adds Joshi, who is also an assistant professor in Stanford’s Department of Psychiatry.

“Ninety percent of people who die by suicide are suffering a psychiatric illness such as depression,” says Frances Wren, MD, assistant professor in the departments of psychiatry and pediatrics, who directs the Child and Adolescent Depression Clinic at Packard Children’s and who was instrumental in organizing an alliance of mental health, medical and educational professionals that began meeting over the summer.

“Effective treatments are available. The key is getting treatment to the kids who need it, quickly,” Wren says.

“I had a growing fixation with ending my own life.”

impossible to fall back asleep. It takes away appetite or causes overeating. It creates obsessive guilt and overwhelming grief. It affects 20 million Americans.

Debate continues over whether rates of adolescent depression are actually rising or whether better awareness has led to increased reporting. According to statistics from the U.S. Surgeon General, clinical depression among children ages 9 to 17 is estimated at 5 percent, making it the most common of psychological ailments.

“Whether it’s rising or not, the rates are really high and nobody is arguing that,” says Jane Gillham, PhD, a research associate in psychology at the University of Pennsylvania and associate professor at Swarthmore University.

Young people who have experienced a major depressive episode are at a greater risk of cycling through depression sometime again within the next five years and are at a higher risk of suicide and other mental health problems.

About 4,400 Americans between the ages of 10 and 24 commit suicide each year, making it the third most common cause of death in that age group, according to the Centers for Disease Control and Prevention. About 60 to 70 percent of this group has had a history of a mental health disorder, most commonly depression, which has typically been present for at least a year prior to their death.

Stanford mental health experts, in particular, have been focusing on the need for early and effective treatments of mood disorders during adolescence in the wake of the suicides of five teenagers in Palo Alto since May last year — a pattern that has stunned the community. *[See story at left.]*

“I had a growing fixation with ending my own life,” is the way an anonymous Stanford University freshman describes his experience with depression. “I had this feeling of being a thousand leagues under the sea — stationary, drowned, crushed by the stillness and pressure, trapped in the dark.”

During adolescence, symptoms of serious depression can be even more confusing and destructive than in adulthood. Irritability, anger, low motivation and boredom are more common in teen depression. Grades can drop, thoughts of suicide occur, substance abuse appears. Diagnosis is often difficult because of our society’s expectations for teens to be

moody, irritable and unpredictable.

“It’s hard for us to imagine or fathom that kids can get sad and do something devastating or catastrophic,” Singh says.

And even when teens are diagnosed, only 30 percent receive treatment, such as antidepressants or talk therapy or a combination of the two.

New research is also exploring the possibility that mood disorders such as depression leave a trail of damage in the brain, interfering with its normal growth, Carrion says.

“The environment can have a detrimental effect on brain development,” Carrion says. “But I also believe very strongly that psychotherapeutic interventions can have a palliative effect on the brain. The more we look at the brain, the more we realize how plastic it is. And the earlier we intervene, the higher the chances for this to work.”

Feeling protective

“Anxiety and depression is something I’ve dealt with on and off for years,” says Sarah, 37, who lives in Dublin, Calif., and who also asked that her real name not be used. She knows that depression runs in families so she’s watching her teenage daughter closely. “I try to mask it but sometimes my daughter is a casualty of it. She’ll ask me, ‘Mom, are you OK?’ She’ll try to make me feel better. She’ll be really good. She’s a great kid, but I see more sadness than happiness in her. I feel a lot of guilt and worry.”

Singh sees talk therapy as one way to reach out to families with mood disorders who want to prevent similar problems from occurring in their children. She conducts family-focused therapy sessions in which she teaches the family about mood disorders and promotes improved communication between family members.

“The kids who don’t do well develop maladaptive coping strategies,” Singh says. “In these kids, stress actually begets more stress. It compounds itself. They’re not able to detach themselves from a particular stressor.”

Signs of impending gloom

PEGGY'S AND SARAH'S TEENAGE DAUGHTERS ARE among those participating in studies at the Stanford Mood and Anxiety Disorders Laboratory directed by investigator Ian Gotlib, PhD, professor of psychology. Halfway through a five-year grant from the National Institute of Mental Health, Gotlib and colleagues at the university and medical school are comparing the responses to stress of 100 young girls with depressed mothers with a control group of 100 girls whose mothers have not suffered from depression. These researchers are continuing to recruit mothers and daughters into their study, with the goal of finding better predictors of which teens will get hit with the deep blues.

At the lab, the girls undergo tests that can detect high levels of the stress hormone cortisol, reduced hippocampus size (the brain structure that stores and retrieves memories) and susceptibility to negative moods — all of which have been linked to depression. Every 18 months, the girls come back for another round of these and other tests.

Measuring hormone levels and hippocampus size is straightforward enough, but how does one pin a number on negative mood? In Gotlib's lab, each of the daughters takes turns sitting with a researcher in a small room in Jordan Hall, the psychology building just off the main quad. They watch 10-minute clips of sad movies (including the death of Bambi's mother, and the part in *Dead Poets Society* where the best friend commits suicide), answer a series of difficult math questions and discuss problems they're having at home or in school or with friends. The tests are intended to cause a sad mood or a stressful response. During the tests, researchers take saliva samples at 15-minute intervals to measure cortisol levels.

Another test quantifies the girls' susceptibility to negativity by measuring how quickly they recognize a sad face versus a happy face on a computer screen.

The results have been surprising, Gotlib says. Initially researchers thought they'd have to wait for the at-risk girls, that is, the daughters of depressed mothers, to become depressed themselves before they saw physiological or psychological differences between the groups. But it turns out that even before ever experiencing depression, the at-risk girls are generally more reactive to stress than are the control girls. They already have higher levels of cortisol, they're perceiv-

ing more stress day to day and they have smaller hippocampi than the control group.

Gotlib has published a series of studies to support these findings. One paper currently in press at the *Archives of General Psychiatry* shows a decreased hippocampus volume in healthy girls at risk for depression. Another study, published in 2007 in the *Journal of Abnormal Psychology*, finds that girls at risk for depression are already primed to see negative aspects of their environment. And a 2008 study in the journal *Biological Psychiatry* reports that girls with a particular serotonin-transporter gene linked with depression produced higher and more prolonged levels of cortisol in response to stress.

A simple way of looking at the results is that when many of the at-risk girls watch a sad movie, it takes them longer to feel better. These girls have a higher physiological, neural and endocrine response to stressful experiences than do the girls without depressed mothers. Gotlib believes that this provides evidence that a certain response to stress may push these girls over the edge into depression.

"Reducing reactivity to stress, therefore, should be a critical target for prevention efforts," Gotlib says. "We could assess stress reactivity within a sample of children at risk for depression (for example, by virtue of having a depressed parent) and offer prevention programs to those with the highest levels of reactivity."

By simply measuring heart rate changes in response to stressors or even using self-reported reactivity to stress — rather than quantifying cortisol or conducting expensive brain scans — "at-risk" teens could be targeted for prevention programs.

"We have clues now about who and what to target," Gotlib says.

Heading off depression

IN THEORY THEN, STRESS REDUCTION PROGRAMS such as yoga, meditation, self-hypnosis or exercise could help prevent depression in adolescents. That's what researchers like Vanderbilt's Garber are exploring. She published a study last summer in the *Journal of the American Medical Association* showing that relatively modest intervention — fewer than a dozen group sessions — goes a long way to prevent episodes of depression in high-risk teens.

The study, published June 3, 2009, focused on teens whose parents had a history of depression. All 316 of the teens had experienced some symptoms of depression themselves. Half were randomly assigned to attend eight weekly group sessions

"It teaches kids to be more realistic, not to be so hard on themselves."

of a cognitive behavioral intervention. After nine months, teens who attended the sessions were less likely to have had an episode of depression than teens who didn't. Less than 12 percent of those who got the therapy suffered a depressive episode — while of those in the non-therapy group, 21 percent had one.

"Basically, you're trying to teach kids to evaluate the way they view the world," says Garber, whose colleague, Frances Lyndh, PhD, is now conducting a cost analysis of the program. "For example, when something bad happens, like you lose your job, a person at risk for depression might think: 'My God, my life is over. I'm never going to get another job. It's all my fault I lost the job.' Someone else might see this as an opportunity to try something new."

Research into similar prevention programs has exploded in the past few years, says Gillham, co-director of the Penn Resiliency Project at the University of Pennsylvania. Programs designed to prevent depression in young people such as Gillham's and Garber's are popping up across the country — from an interpersonal psychotherapy-based program at Rutgers University in New Jersey to a family-based model at the Children's Hospital of Philadelphia.

"When I did a review of the literature 10 years ago, there wasn't much out there," Gillham says. "Now I'm finding that it's hard to keep up with all the literature. There are two or three papers out just this month," she says in the December 2009 interview. "That's huge in this field."

Gillham's school-based program trains teachers and counselors to teach coping skills during 12 two-hour lessons either during or after school. Originally designed in the 1990s to prevent depression in adolescents, it has since branched out to include children between the ages of 10 and 14.

In a meta-analysis of 19 controlled studies co-authored by Gillham and published in December in the *Journal of Consulting and Clinical Psychology*, the program was found to successfully reduce and prevent symptoms of depression in adolescents.

"It teaches kids to be more realistic, and not to be so hard on themselves, and to cope with problems more effectively and more assertively," Gillham says. "It teaches life skills that are helpful to most kids."

Breaking the cycle

FOR PEOPLE WITH CHRONIC DEPRESSION, like Peggy, preventing depression in young people before it has the chance to spiral out of control makes the most sense. She's hoping for any tips that would help her own children avoid the periods of depression that she's cycled through most of her life.

"I know I'm going to be dealing with depression on and off," Peggy says. "I have gotten better. I think what helps me the most is to have somebody to talk to, whether it's a good friend or somebody you pay \$80 an hour."

Peggy never took those sleeping pills when she was a freshman at Berkeley. She went on to graduate. She worked many years as a magazine editor, and now is successfully raising a family. And she remains vigilant in watching for signs of depression in her own kids.

About six years ago, she was driving in the family car with her seventh-grade son when he confided in her. He was going through a tough time. He has a mild form of autism, and the social stresses of junior high had become overwhelming.

"Sometimes I think about killing myself," he told his mom.

"I just about fell out of the car," Peggy says. "I immediately just started talking. 'If you're that sad, we're here to help you. I know this is an emotionally sensitive time for you. This is not the answer.'" She took him seriously, got him the therapy he needed. Today her son is an 18-year-old freshman at the University of California, and she can't help but be nervous. She remembers her freshman year of college all too clearly.

"It's hard for kids," she says. "All they think is, 'I want my pain to stop. I'm miserable,' and sometimes they don't see any way out. They don't realize that life does get better." **SM**

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paging
mom
and **dad**

THE
FUTURE OF
CHILDREN'S
HOSPITALS

Jackie Seki celebrated her first birthday with a seldom-combined intestinal and liver transplant at Lucile Packard Children's Hospital. Jackie had been born with a bowel disorder called long-segment Hirschsprung's disease, in which certain intestinal nerve cells don't develop fully during pregnancy. The procedure was a total success and, after a six-month stay at Packard, Jackie was free to go home. As any doctor knows, that's often when the trouble begins — infection and other complications can follow a procedure, and without health-care providers on hand, these can worsen quickly.

Jackie hadn't been home long when her temperature started to rise. It was a subtle change — she didn't sweat profusely or change colors — but her mother, Liann, phoned their nurse at Packard Children's instantly. The call might have saved her daughter's life. Jackie's procedure had left her at risk for a dangerous obstruction, one whose initial symptoms present mildly but require immediate attention. As Karen Wayman, Packard's director of family-centered care, put it, "the average parent might have wavered in making the call to the hospital, a little unsure of what to do, waiting to see whether the temperature rose further." Liann and her husband were average parents, too — but before and after the transplant, Liann had spent months at Packard, participating in something extraordinary: a new program that's changing the very essence of care at Packard and children's hospitals across the country.

The rise of family-centered care in pediatric hospitals in the United States and other Western, developed countries represents a fundamental shift in how they operate. It's a change that started 30 years ago, with the

BY CHRIS COLIN

ILLUSTRATION BY CHRISTOPHER SILAS NEAL



increasing awareness of the importance of meeting children’s psychosocial and developmental needs — and the importance of the family’s role in accomplishing that. Family-centered care has continued to gain ground and is supported by research and leading organizations such as the U.S. Institute of Medicine, the American Academy of Pediatrics and the American Hospital Association.

Rather than bystanders to their child’s care, parents are increasingly regarded as essential partners in the process, no less vital to recovery than the doctor or nurse. From consulting them on their child’s treatment to inviting them to serve on family advisory councils, hospitals are reinventing their relationship to the people historically asked to wait in the hallway for news. This might sound like compassion, or perhaps a dollop of good PR. Not at all. Hospitals have found it’s simply good medicine.

It certainly was in Jackie’s case. Instead of attempting to memorize a complex care regimen hours before her daughter left the hospital, Liann

had been learning the ropes from the day she checked in — including the subtle signs and dire consequences of a fever.

“In the past, the nurse would have come in, hung the drip bags, asked, ‘How are you doing?’ said, ‘Here’s the plan for the day’ and left,” Wayman says. But in Jackie’s case, “every time the nurse came in to do a procedure, or give medication, she’d explain to the mother, ‘This is why I’m doing it, this is exactly what I’m looking for.’ On top of that, the mother was included in medical rounds, so she got to hear directly from the doctor every day.”

Not only was Jackie’s life likely saved, but her care providers’ jobs were made easier, too. Indeed, the pediatric community is increasingly recognizing the mutual benefits of involving the family in a patient’s care. Just 25 years ago, the predominant philosophy was, “We know what’s best for your child, leave him with us, come back for him on Sunday,” says Bruce Komiske, author of *Designing the World’s Best: Children’s Hospitals*, and chief of new hospital design and construction at the soon-to-open Ann & Robert H. Lurie Children’s Hospital of Chicago.

“That’s been blown up now,” he adds. “There’s been a lot of research showing that kids actually do better when the parents are there, and engaged. That’s leading to a lot of changes.”

CUE THE ARCHIVAL FOOTAGE. To appreciate where the country’s 250-plus children’s hospitals are heading, it’s impossible not to marvel at where they’ve been. Nobody who’s glimpsed the grim images of those bleak, early-20th-century sanatoriums forgets them, or the haunting inkling of what it was like to be a child in the era of incurable illness. (Inkling distilled: not so great.) But those first hospitals also had something right. By 1885, 10 children’s hospitals had opened in the United States and Canada, and their doctors had put their fingers on the cornerstone of pediatric medicine: Children aren’t just little adults. With their differently functioning organs and immune systems and metabolisms, they’re more akin to their own species.

In the years ahead, children’s hospitals granted children a medical space — but it was one that didn’t always leave a place for families in the equation. Enter Bev Johnson. As president

and CEO of the influential Institute for Family-Centered Care, a national organization based in the D.C. area, she works to establish that a patient’s family is essential to a cost-efficient, safe, high-quality health-care system. From having nurses do change-of-shift reports alongside families, to forming a rapid-response team that parents can call, Johnson’s organization is leading the push to open up children’s hospitals.

“The system has sometimes been very paternalistic. We’ve done things to and for patients, rather than with patients,” she says. “Now we know, especially with the increase in chronic conditions, that patients have to be involved in their own care. For a child with diabetes, very little time managing the diabetes actually happens in the hospital. So we have to work with patients and families so they see they’re a key player in their own health care.”

So how does that happen, exactly? To be sure, involving parents doesn’t mean having mom roll up her sleeves to re-set a broken arm. The thrust of the movement tends to come down to shifts in communication styles and decision-making processes. If that sounds like a somewhat nebulous undertaking, Johnson says it’s happening through formalized processes at a growing number of hospitals — having parents serve on patient safety committees, for example, or training medical students and residents about communicating effectively with families.

At Packard Children’s, Wayman and her department deploy a multilevel approach to delivering family-centered care — but a key part of the program is staff education. New nurses get a two-hour introduction to family-centered care, and later participate in trainings and simulations. In addition, Wayman’s team works with various medical services, such as liver transplant and neonatology, to determine more in-depth changes that could be made.

Then there’s Wayman’s health-care provider champion program. Rather than spread the good word entirely by herself, she realized family-centered care could be preached more effectively by enthusiasts already working throughout the hospital. So she assembled a cast of advocates, from physicians to nursing directors to patient safety staff. Now numbering about 140, the team’s members meet with her periodically — in groups or individually — discuss improvements that can be made in their departments, then fan out to bring the message to their direct colleagues. They might deliver presentations on what family-centered care is, or how it’s being implemented elsewhere. In other cases, they consult on

"It's about listening to kids more."

more intimate levels — a nurse, for example, explaining how a specific bedside conversation might have been improved with some family-centered care techniques.

Meanwhile, at Packard Children's and elsewhere, families are invited to participate in a growing portion of physician rounds, thereby opening up the conversation that happens at the bedside. As Johnson puts it, the parents are the people who know the patient best, and increasingly practitioners are seeing the value in that.

"Let's say the child has asthma. The doctor may say we think he should be on a certain medication, and the parent may say, 'That's hard with his schedule — he wants to be on swim team, which is also healthy for him — could we try X?' So there's a negotiation now, where in the past that wouldn't happen," Johnson says.

Among the more prominent changes spurred by the international family-centered care movement: the single-patient room. Long considered a luxury, this increasingly standard feature has gradually revealed itself to be the healthiest, and most cost-effective, way to provide care, resulting in lower infection rates and higher patient satisfaction. Packard Children's has some single-patient rooms, but the expansion planned to be completed by 2016 features them exclusively.

"There was talk long ago that we can't afford private rooms," says George Tingwald, MD, director of medical planning for the Packard Children's expansion. "But what's been proven is that the cost of operations is actually lower than the cost of operations for a multipatient room. In a relatively short time they pay for themselves."

As a principal at Array Healthcare Facilities Solution, a Pennsylvania-based design firm behind several high-profile children's hospital expansions and renovations, Patricia

Malick has seen the family-centered care philosophy make sense down to the level of room design.

"It's about listening to kids more. So people are more cognizant of how scary it is for them to hear a child two doors down screaming in pain," she says. "There's growing interest in treating the room as a safe haven, and having exam space out on the floor so it doesn't happen in the room."

The family-centered care movement isn't just a literal inclusion of mom and dad in the care process. It's part of a larger effort to better understand how a child is best nurtured, and to better incorporate the components of his or her daily life. This starts with loved ones and runs all the way to decor. Just 15 years ago, Disneyesque cartoons were de rigueur in patient rooms: a compensation, perhaps, for a previous era's dreary aesthetic. But Tingwald says Mickey and Goofy often came no closer to what kids actually craved.

"A lot of the decor in these hospitals was very frenetic, very bright colors. A lot of activity rather than calming influences," he says. "It was what adults would think kids want."

With his MD degree and AIA designation as a professional architect, Tingwald personifies the growing interest in "evidence-based design" — a movement intent on using research to shape the way hospitals are built. Recently he was discussing Packard's expansion project with Elizabeth Chaney, director of real estate planning and development.

"It turns out what kids respond to best are everyday things: being able to see the sun, nature, birds," Chaney says. "Kids are smart. You can't distract them from the fact that they're in a hospital. What they want in there is as much of their normal life as possible."

Parents aren't just beneficiaries of this more family-friendly environment. At many hospitals across the country, they're instrumental in creating it, as with Packard's family partners program, a group of 20 trained parents with children who received care at the hospital, and who now advise on policy issues pertaining to a family's experience at the hospital. The hospital often includes well-trained parents as members of ongoing hospital committees.

These parents are available each month to any staff member as an instant focus group, providing the family perspective on hand hygiene, IV line insertion, medication list accuracy, as well as the new pediatric hospital under construction.

“We have parents working with the board-level patient safety committee,” Wayman says. “Other parents give their input to the architects of the new hospital regarding the patient experience: What is the experience as you enter the lobby, when you move to the new gardens, when you are discharged home. The decisions made at the operations level of care have a downstream effect at the bedside.” And indeed the Packard expansion will have separate entrances for women coming to give birth, and for sick children — something that parents say will ease anxiety among women in labor.

On a more granular level, Wayman adds, it’s proven beneficial to involve parents on communication efforts, such as spreading the virtues of good hand-washing habits within the hospital. “We helped bring down the infection rate in one of our units, and part of the reason was our campaign urging parents of inpatients to wash their hands,” she says.

Hospitals are constantly evolving on a variety of levels — new technology, new surgery techniques and new administrative policies, spread out over multiple subspecialties. But to assess how care will be administered in the years ahead, the shift toward families would seem to have the broadest and deepest implications. And while family-centered care began as a movement within pediatrics, it has spread to adult services as well, especially in the care of the elderly. The institutions leading this movement aren’t just reshaping policies across the board — they’re reappraising basic assumptions about how a hospital works best.

TRACE THE EVOLUTION of the children’s hospital and you’ll trace the evolution of how society sees children, too. Debra Monzack’s job at Packard is a testament to this.

“When I started, I was the ‘play lady.’ The thinking was, let’s just keep the kids busy and distracted,” says Monzack, a child-life specialist for 34 years. “Now the focus is really on the psychological preparation for a child’s visit and supporting the child’s continued development. The whole thing is looked at very differently.”

Packard Children’s child-life program is one of many across the country helping families — patients, parents and, increasingly, siblings — negotiate the strains of hospitalization. At times this means preparing kids for a fright-

ening procedure; just as often, it means preparing parents, and helping them nurture their child as they would outside the hospital.

“The idea is to bring the outside world into the hospital with long-term-care patients. Otherwise you take away the joyful part of everyday life. And the benefits are clear. We see kids cope better, and recover faster, and many times they’re not as fearful about coming to the hospital again in the future,” Monzack says.

WITH SO MANY VIRTUES, does anyone oppose family-centered care? Direct opposition doesn’t materialize as often as something more nebulous — that paternalism Bev Johnson describes.

“It’s a cultural shift away from the expert model, and sometimes there are people who feel a little uncomfortable about it,” Wayman says. “At first blush, it’s like, ‘What do you mean a parent’s going to tell me what to do?’ But soon they realize it’s a partnership. And in fact shared decision-making is something many doctors and nurses already do.”

Taken individually, many family-centered care improvements are easily accomplished. For example, Wayman says at Packard Children’s parents will soon receive a printout of what’s happening with their child in the neonatal intensive care unit every day. And she anticipates that when the hospital’s expansion is complete, rooms will include computers so family members can easily keep in touch with friends and relatives. Being able to read an update or conveniently communicate with a loved one might not seem like much, but such improvements provide a sense of control during an unfamiliar and frightening experience. Few assets could be more valuable for parents of ill children, and as a result, the parents are better prepared to provide the support their kids need.

Wayman sees family-centered care as a new approach, to be sure, but also a return to a forgotten mode. The era of house calls and small-town medicine didn’t offer much in the way of medical sophistication, but she says it sometimes had one thing going for it: more dialogue.

“Children’s hospitals have become such an incredibly high-tech environment, such a fast-paced environment. Now we’re starting to foster family/health-care provider conversations again, and with a higher quality of exchange,” Wayman says. “After all, it’s a scary thing when your child arrives at the hospital. You don’t know the routine, the medication, what you do when you get home. It’s in everybody’s interest to change that.” **SM**

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MOTHER COURAGE

Mia Farrow's calling

ON HER BLOG, Mia Farrow writes about the plight of children in war-torn regions around the world. A tone of urgency, a feeling of passion and a sense of disgust leap off the page. “We live in a world of sorrow,” says the 65-year-old activist actress. “We have inflicted immeasurable suffering upon each other, and it is the world’s most vulnerable who suffer most. It seems we have learned nothing since we first declared ‘never again.’”

The pictures on her blog, miafarrow.org, illustrate the tragedy she has seen in Darfur, Congo, Gaza, Somalia and Haiti as a UNICEF goodwill ambassador. There, amid murder, mutilation and brutality, she is far from the sound stages of her movie career and her fabled childhood as the daughter of Hollywood royalty. Farrow was born in posh Beverly Hills, the daughter of Oscar-winning screenwriter James Farrow and actress Maureen O’Sullivan.

Perhaps it was contracting polio at age 9 that fueled her enormous empathy for the vulnerabilities of children. She is somewhat of a magnet to children in crisis. The mother of 14 — 10 adopted, four biological — says that one day she might give up acting altogether and start an aid organization in Africa.



Mia Farrow and refugee child in Haiti in 2008 after storms and flooding left hundreds of thousands homeless.

At the end of a December phone conversation from Farrow’s home in Connecticut, medical school executive communications director Paul Costello asked if, when traveling to some of the most desperate places on Earth, she was ever fearful. “I have normal fear, but it doesn’t stop me. I’ll dive to safety with the best of them, but it doesn’t stop me.” They spoke again shortly after the devastating earthquake in Haiti on Jan. 12.

COSTELLO: What have we learned from Haiti?

FARROW: There's a need for a response corps — an international response corps backed with contingency planning for sites known to be at risk of natural disaster. There's a need to set up a coherent game plan capable of putting rescue teams on the ground in any country with the same level of organization that we use when we have a military objective, because no matter how good an ad hoc response is, it will never be quick enough to stabilize in those first chaotic days of a catastrophe.

COSTELLO: What's the long-term outlook?

FARROW: A possible silver lining is that now with this focus there will be a serious attempt to help Haitians build an infrastructure that is self-sustainable, finally. Hopefully we will stay with them until something better is in place, better even than they had.

What the Haitian people have going for them is their own spirit. They have an amazing and deep faith. You've seen people being pulled from the rubble after five and even six days, bursting into hymns, praising God. This sense of readiness to celebrate life, however it presents itself, is an astonishing attribute of the Haitian people. And, the children have this.

COSTELLO: Is your passion to help children living in desperate conditions all-consuming?

FARROW: Pretty much. I have to say that what I'm trying to do now has eclipsed everything in my life except my children. I don't want to act anymore. This is what I care about. I'll do what I can, and then maybe, God willing, I would like to move there at some point. To Congo, eastern Chad or central Africa, and start my own aid organization.

Right now, I am archiving the traditional cultures of the tribes targeted for extinction by the Sudanese government. The Fur, the Masalit and the Zaghawa tribes' children's stories, the dances, songs, the traditional ceremonies. I've got approximately 40 hours of songs, dances and tribal culture, oral history, and I want this for a museum when peace comes some day — God willing, please God — to Darfur. I would put a museum in the middle of Darfur for the children, a place where they can go to reclaim what is theirs.

COSTELLO: You seem to have developed a sense of fearlessness while in these dangerous places. Is that right?

FARROW: Maybe. I was afraid of becoming a patient, because I think everybody is afraid of that. But I did find that I'm not afraid of knives and bullets. You know, I have the normal fear of that, but it doesn't stop me. I'll dive to safety with the best of them, but it doesn't stop me.

I wish I had a medical degree. I could be more use to the children and to people. When I see a child torn apart by a land mine or unexploded ordnance, slashed by knives or shot

by a bullet, or suffering from cholera, malaria, I wish I had the expertise to treat such children. I wish I had a doctor with me who would know what to do.

COSTELLO: What are the conditions under which the children of Darfur are living today?

FARROW: It is a struggle to convey through words. Here you have children driven from their homes and homelands under the worst sorts of circumstances. The children describe morning skies filling with gunships dropping bombs upon homes and families as they sleep, as they're cooking breakfast, as they're saying their prayers, as they're going out to their fields, as they're going to school. And then these aerial attacks were followed by ground attacks, by tribes that have come to be known as Janjaweed or "devils on horseback," that come on horseback, on camels and more recently in vehicles stolen from aid workers. They come shooting people as they run, as they're trying to gather their children.

Countless women have told me that they were raped, children were torn from their arms and bayoneted before their eyes. They describe the older people covering the children's mouths at night so they can't make a sound while Janjaweed hunt for those who survive.

And then, when they finally make it into the camps, there's humiliation and deprivation as the years pass. On food distribution day, they wonder: Will there be soap this month? Will there be salt this month? Will there be the usual ration of sorghum — which is barely sufficient to keep human beings alive? The water, even, in the camps is muddy. You wouldn't dare drink it. And now people, as six years have passed, are dying more of disease and hunger and despair in the camps.

COSTELLO: The psychological problems for these children must be just astronomical.

FARROW: Yes. The psychological problems from the circumstances I described, and from the fact that the camps themselves are not safe. They're continually invaded by all sorts. Janjaweed invade for the food, to prey upon the women, the children, to kidnap. Also, government forces invade the camp. And then, there are marauders and rebel forces recruiting children from the camp. So, there is never a point that the children are feeling safe.

COSTELLO: Why do you think it has taken the world so long to recognize the severity of the problem and take action? Why have we been so acquiescent?

FARROW: Well, because we don't care. We don't care enough. After the Holocaust, Elie Wiesel wrote: "The victims [of the Holocaust] perished, not only because of the killers, but also because of the apathy of the bystanders. What astonished us after the torment, after the tempest, was not that so many killers killed so many victims, but that so few

A starving 9-year-old boy is carried in to a feeding center in Congo. Far right: Darfuri women requesting a well for clean water in a refugee camp.



had been on the run — they’d moved six, seven, 10 times — and they all had a dream. And every woman, every mother, is hoping for a better tomorrow. So I come back from those places that seem to be most hopeless, filled with hope.

And I have a screensaver of a little girl whose parents had been killed. I don’t know if she’s still alive. She was surrounded by her attackers — and I’m looking at her right now — but her face is so full of hope that I don’t allow myself the luxury of feeling hopeless.

COSTELLO: What can ordinary people do to help?

FARROW: I would say to people who are listening, that



cared about us at all.” And I think that sort of says it.

Are we not defined by our action or inaction? If we are permitted one final lucid moment, can we say to ourselves, “I lived my life in the best way I could”? And does that include helping those who are the most vulnerable? Are we doing it to the maximum of our ability? And if we’re not, you know, when? If not in the face of a genocide, when is it time?

I mean, to me, I’d say it’s past time.

COSTELLO: Last spring you went to the length of depriving yourself of food to bring attention to the problems of Darfur. Why did you choose this dramatic action?

FARROW: I felt there was nothing left to be done. I only lasted 13 days because my blood sugar dropped. You don’t know how your body is going to let you down, and for me it was my blood sugar, and I would have gone into convulsions and then a coma. I promised my children I wouldn’t go to death. And then, all these people stepped in, and an organization had formed around my hunger strike, and I think it’s continuing to this day. Members of the U.S. Congress and businessmen and all sorts of people took over the fast, doing one day each.

COSTELLO: So, it did culminate in a positive outcome.

FARROW: Well, culminate is too big a word. I did feel, when the Congressional Black Caucus invited me to come to Washington, D.C., and declared that they wanted to fast, that on that day, that the people of Darfur’s voices were being heard in the nation’s capital, and I thought how they would have been pleased. But you know, in fact nothing has changed for them.

COSTELLO: Where do you get your inspiration daily?

FARROW: It’s the children. Every child that I look at, there’s hope in their face. In Congo I spoke to children who

we have a voice as long as we live in a democracy. The late Sen. Paul Simon put it best, saying of the Rwandan genocide that, if just 100 people from every district had phoned in or contacted their leadership, then we would have taken action.

So there is a number, 1-800-GENOCIDE, that people can call at no cost. Take a couple of minutes. You can be plugged into your local leadership or to the White House. You don’t have to be an expert, but you can say, “Look, it’s unacceptable to me that 3 million people are in these camps now for six years in Darfur and still they’re not safe. I want our government to do more.”

COSTELLO: What do you hope that physicians and professionals in the pediatric medical community take away from hearing you talk about the plight of children worldwide?

FARROW: I wish that in the most forgotten places, doctors could donate a little bit of their time at some point in their lives, if not every year. And right now, as we struggle for health care for 40 million uninsured people, I wish they would also do it right here in America.

This interview was condensed and edited
by Rosanne Spector

wishbone

saving mark's arm

BY ERIN DIGITALE
ILLUSTRATION BY BRYAN CHRISTIE

When 3-year-old Mark Blinder was diagnosed with a rare bone cancer, doctors gave his parents three agonizing options: Amputate the affected arm at the shoulder, irradiate the tumor and risk a second malignancy, or try a limb-preserving surgery that had never been attempted on a toddler.

Sitting in a procession of doctor's offices at Lucile Packard Children's Hospital, Alla Ostrovskaya and Gene Blinder tried to concentrate in spite of their shock. Their son's arm pain had been diagnosed months earlier as a bone infection, curable with antibiotics. "No one in our family had ever had childhood cancer," Ostrovskaya says. But new tests showed a tumor growing through Mark's entire right humerus, the long bone in the upper arm. Now that it was clear antibiotics weren't the answer, the couple heard the pros and cons of each possible treatment.

Amputation was simple and would vanquish the tumor, explained orthopedic surgeon Lawrence Rinsky, MD. "But you can't go back," Rinsky told them. Radiation



After a few rounds of chemotherapy, this tumor seemed to calm down. Mark stopped crying through the night with pain. He fell in love with his oncology nurses, calling out "Nurse, nurse!" in his most winning voice when he wanted an extra bit of attention.

would preserve Mark's hand but kill the growth plates in the affected bone, said pediatric oncologist Neyssa Marina, MD, leaving Mark's upper right arm small and fragile. Radiation might also make the malignancy return, a particular concern because Mark's diagnosis, Ewing's sarcoma, recurs more often than most childhood cancers.

The third choice sounded simultaneously best and worst: Rinsky offered to try replacing Mark's diseased bone with a titanium implant that could be expanded as Mark grew. The cancer would come out, and the arm would be saved, but Blinder and Ostrovskaya would have to put their 3-year-old through an untried surgery with a long, painful recovery. And the artificial bone would have to be designed from scratch.

Ostrovskaya was heading into her last year of medical school when Mark was diagnosed in July 2008, and in some ways that complicated the decision she and her husband faced. For 12 years — first in Russia and then in the United States — she had devoted herself to learning the rhythms of medicine, learning that medical innovation progresses in cautious baby steps.

Except when it doesn't. Except when someone sits you down and says, please let us do something radical to your youngest child. If you say no, we may have to cut off his arm.

In the past, it was considered nearly impossible to treat a small child's humerus tumor without amputating. Scientists have struggled to devise cancer treatments that will save a limb and accommodate several inches of future growth in the upper arm, so many doctors simply call for amputation.

"Amputation was our last resort," Ostrovskaya says. "We said, 'We are not going to amputate if there is a chance to save his arm, because he is so little.'" Mark loved swimming, kicking a soccer ball, climbing the jungle gym, playing mini-golf and chasing his big brother, 7-year-old Tony; it was painful to think about such an active child losing a limb. And he was right-handed, Blinder says, which made the prospect of amputation even more dismaying.

So Marina started Mark on chemotherapy, the logical first step to preserve his arm. Chemotherapy alone wouldn't vanquish the cancer,

but it would reduce the tumor's blood supply and give other treatments a head start.

"Most bone tumors are very vascular tumors — they're angry," Marina says. Bone tumors furiously spew out biological signals that spur growth of new blood vessels, bringing lots of nutrient-rich blood to feed the tumor's rampage. Surgeons who attempt to remove these tumors prior to chemotherapy often find a welter of pulsating blood vessels obscuring their target. "Chemo makes surgery a lot simpler," Marina says — kill the tumor, and the extra blood vessels shrink or disappear. Chemo was the logical first step before radiation, too.

After a few rounds of chemotherapy, this tumor appeared to calm down. Mark stopped crying through the night with pain. He fell in love with his oncology nurses, calling out, "Nurse, nurse!" in his most winning voice when he wanted an extra bit of attention. He began using his right arm again, freed from months of throbbing. On the oncology ward, Marina noticed him happily engrossed in computer games.

"It was hard because if we had just chosen radiation, not surgery, that would not have been as physically painful for him," Ostrovskaya says, recalling how they considered their options while watching the improvement in their son. The parents had several conversations with Marina and Rinsky, consulted with an oncologist who specialized in pediatric radiotherapy, read everything they could find in the medical literature and talked the decision through several times. In the end, though they hesitated to put Mark through more pain, the long-term drawbacks of radiation seemed worse. Blinder told his wife, "It's surgery and nothing else; if Dr. Rinsky said we can do surgery, he's going to have surgery." Yet even as they gave Rinsky the go-ahead, Blinder and Ostrovskaya still worried. The first-of-its-kind operation came with no guarantees.

Rinsky had mixed feelings about the surgery, too. When he first proposed the idea, he says, he remembers "sort of secretly hoping that there was some other way." Surgically, amputation would have been much easier, but, like Mark's parents, he wanted to save the little boy's hand and arm. With just the right replacement bone, maybe the surgical team would have a shot. "There's no pre-existing prosthesis for a child this small," Rinsky says.

MARK BLINDER TELLS HIS PARENTS, "I HAVE A SPECIAL ARM." HIS SURGEON REMOVED HIS RIGHT HUMERUS, CONTAINING A RARE BONE CANCER, AND REPLACED IT WITH AN IMPLANT THAT EXPANDS AS HE GROWS — A TREATMENT NEVER BEFORE ATTEMPTED IN A TODDLER.



LARA TOWLIN

The engineers went through several rounds of planning over a two-month period, sending Rinsky each iteration of the design. "They would show me something that I could not fit into the arm, and I would say, 'I have to close the incision!'" he says.

The prosthetic bone had to be small enough to fit in a 3-year-old's arm, strong enough to last a lifetime and expandable to allow for growth. Rinsky knew that balancing these demands would pose a big challenge for engineers, especially because of the need for moving parts that would allow him to expand the prosthesis in later surgeries. On top of that, because Mark's entire humerus had to be removed, the prosthesis could attach only to soft tissue — muscles, tendons and ligaments. Most bone prosthetics replace half of a bone and are cemented to healthy bone. Rinsky had to find another way to hook up this implant, while preserving as much function as possible in the shoulder and elbow joints.

He began collaborating with Indiana-based bone implant manufacturer Biomet Inc., sending engineer Aaron Smits X-rays of Mark's arm, a list of the characteristics he hoped for in the finished prosthetic and a deadline that coincided with a logical point to pause Mark's chemotherapy. Rinsky, who has no financial relationship with the company, had collaborated with Biomet before and knew its strong reputation for semi-custom prosthetic bones. He had confidence that they were right for this more complex job.

"The age and size of the patient presented an unusual challenge," Smits says. "And what Rinsky was trying to accomplish by performing partial joint replacements on both the shoulder and the elbow was kind of unorthodox." From an engineering standpoint, it would have been easier to replace Mark's entire elbow with a metal joint, Smits says, but that would have required removing parts of Mark's two lower arm bones, the radius and ulna, in addition to the humerus.

But Smits relished the challenge. He had come to prosthesis design almost by accident, when a college internship with Biomet made him realize he'd rather be building replacement body parts than engineering new cars. And he had already planned one-of-a-kind implants for other unusual patients: people with gene defects of bone formation, dwarfs with bony deformities and kids with rheumatoid arthritis.

Starting with designs for telescoping prostheses intended for larger patients, Smits and his co-workers began scaling down to produce a customized device for Mark. The boy's humerus was 17

cm long; based on measurements of his parents' arms, Rinsky estimated the prosthesis needed to expand an additional 10 cm.

The engineers considered the options for materials, choosing a smooth, low-wear cobalt-chrome surface for inside the elbow, where the implant would rub against Mark's ulna, and porous surfaces in other spots where they wanted Mark's soft tissues to knit themselves together with the implant.

They also took a hard look at the expansion mechanism for the prosthetic. In the past, they had made expandable thighbones that could be lengthened by inserting a screwdriver through a tiny incision in a patient's bent knee, allowing the physician to turn a screw that ran parallel to the length of the upper leg. But the shoulder and elbow joints have a different geometry than the knee, and inserting a screwdriver end-on into a humerus implant would require invasive surgery. Instead, the team tested designs for a worm gear that would allow Rinsky to lengthen the prosthesis with a small cut in the side of Mark's arm. (Worm gears shift the direction of rotation 90 degrees — so a screwdriver inserted and turned perpendicular to Mark's bone could be used to extend a prosthesis running the length of his arm.)

"Because of the patient's age, we wanted to give them a device that was as minimally traumatic as possible," Smits says.

The engineers went through several rounds of planning over a two-month period, sending Rinsky each iteration of the design. "They would show me something that I could not fit into the arm, and I would say, 'I have to close the incision!'" he says. It was hard to design a small implant strong enough to extend to the size of an adult humerus, Smits explains. Eventually, the collaborators settled on an implant with less lengthening capability than Rinsky had hoped for — instead of extending 10 cm, the final implant will "grow" 4 cm with Mark, leaving his right arm a bit shorter than the left.

Fortunately for the time-crunched team, the new implant didn't require FDA clearance because it was a custom device prescribed by a surgeon to meet Mark's specific needs.

Even when the design was finalized, Rinsky wasn't sure the prosthesis would fit inside Mark's arm. He ordered a back-up metal rod to have on hand during surgery, just in case.

Early on Dec. 4, 2008, the surgical team wheeled Mark to the operating room. His parents watched him go with trepidation. Not wanting to scare the little boy, they hadn't told him much about what to expect, but they were anxious. Ostrovskaya hadn't slept the previous night.

Rinsky was concerned, too. Conditions weren't ideal: He was hobbling around on a broken foot, the result of a fall at home. His team was adjusting to a new work environment, the new pediatric surgical suites at Packard Children's, which had opened just three days before. And, because of Mark's chemotherapy-weakened immune system, everyone on the team was encased in space-suit-like outfits to cut infection risk. The team members also had to talk more loudly than usual, to be heard over the whirl of the fans inside the suits.

Then there were the technical challenges of the procedure. "The surgery involved taking out the entire bone without touching it," Rinsky says. The bone had cancer cells on its surface, which could easily have spread to surrounding healthy tissue. "It was like carving out a peach pit without ever touching the pit, staying in the pulp." He removed the bone along with a thin, protective layer of soft tissue and muscle, working carefully to preserve nearby nerves and blood vessels.

Once the cancerous bone was out, Rinsky implanted the artificial bone. It was daunting at first — Mark's arm looked "like a banana peel with the banana removed," Rinsky says. "There was a little tiny bit of muscle, enough to work, and then the main pipes and wires and the skin."

The prosthesis had a piece of Dacron fabric at the top, which Rinsky sewed to soft tissue in Mark's shoulder. At the elbow, he saved Mark's ligaments and placed those around the prosthesis as best he could, snuggling the implant's smooth end into the pocket next to the other bones in Mark's elbow. Then he started sewing up Mark's arm. Luckily, the incision closed. The surgery had taken about five hours.

"Dr. Rinsky came out of the operating room and said, 'The prosthesis fit perfectly fine, he is doing great,'" remembers Blinder.

Soon, there was more good news: Mark's tumor was confined to the bone that had been removed, and its malignant cells were dead, a sign that his chemotherapy had worked properly. He spent a

month healing from surgery, then received more chemotherapy to reduce the chance the cancer would return. He'll have three to four minor surgeries over the next several years, in which Rinsky will lengthen the implant. After obtaining more follow-up data, Rinsky and his colleagues plan to write about the case for the scientific record.

Mark's parents knew he was truly feeling better when he began getting into mischief again. In June, just before his final round of chemotherapy, he was playing "strongman" and accidentally dropped a 2-pound dumbbell on his head. "It was pure 4-year-old," says Rinsky with a grin. (A CT scan showed the bump had caused no harm.) "He is a very spunky kid," says Marina.

At home in Palo Alto, Mark is gradually relearning to use his right hand and arm. He had switched from being right- to left-handed after the surgery, but is now shifting some tasks back to his right hand. He's moving his right wrist and fingers, can pick up small objects, and is receiving physiotherapy to rebuild strength and flexibility in his elbow and shoulder joints. Although Mark won't ever regain full function in those joints, he's using the arm more each day, Ostrovskaya says. He tells his parents, "I have a special arm."

And he's back to his active self. On a warm fall afternoon nearly a year after surgery, he chases big brother Tony enthusiastically around their neighborhood playground. The boys, now 4 and 8, kick a soccer ball back and forth with strong, practiced shots. The ball has helped strengthen Mark's right arm, too. "Hands out!" Tony calls, standing ready to toss it to his little brother, who catches it with both arms outstretched.

Later, Mark holds his orange plastic baseball bat high above his head — again, with both arms — then jumps off a low platform on the climbing frame, shouting "Tarzan!" with a wild gleam in his eye. Seeing his interest in the bat, Ostrovskaya tries to coax him to play baseball, but, like most 4-year-olds, he's much more pleased with his self-made entertainment than a grown-up game.

Again, he's up on the climbing frame, bat aloft, poised to jump.

Mark leaps into the air.

"TAAAR...ZAAAN!!!" **SM**

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Once the cancerous bone was out, Rinsky implanted the artificial bone. It was daunting at first — Mark's arm looked "like a banana peel with the banana removed," Rinsky says. "There was a little tiny bit of muscle, enough to work, and then the main pipes and wires and the skin."

THE INNER CHILD

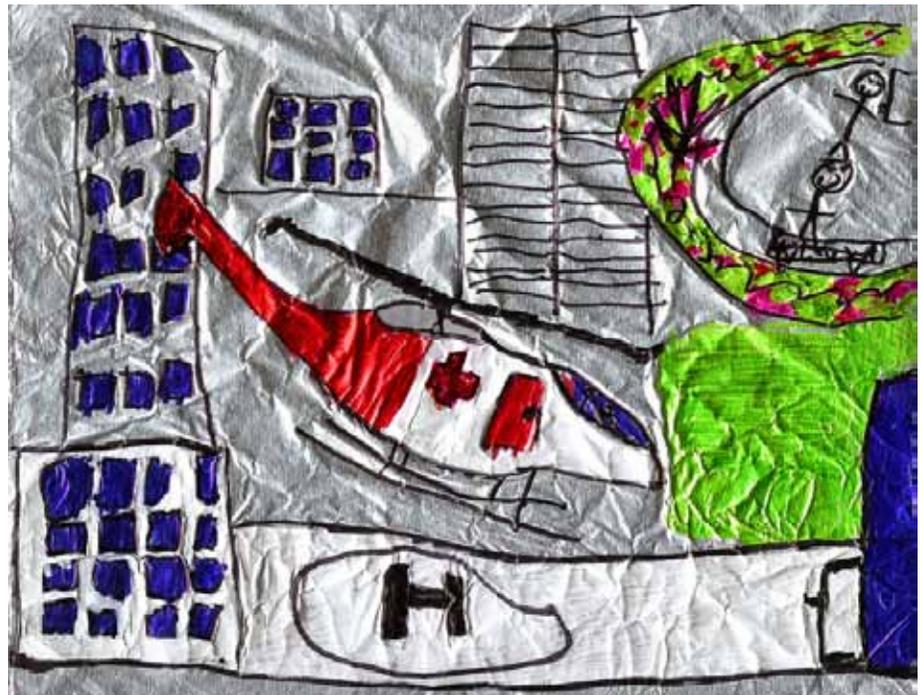
Art offers an opening

SOMETIMES A LITTLE ART is just what the doctor ordered. If you give children at Lucile Packard Children's Hospital a pad of paper and a box of crayons, their creations will likely go far beyond their family's refrigerator door. Caregivers know that because art is fun and non-threatening, it can help patients get into the groove of hospital life.

Kevin Danie, a teacher at Packard Children's in-house school, says that he and the other teachers and volunteers regularly use art projects to help reticent newcomers ease into the classroom environment.

Jo Wallace uses the kids' art to learn what they're thinking and feeling. As a board-certified art therapist, she helps children who need extra support or alternative ways to express themselves as they tap into fears or concerns. She sees the art as stepping-stones to further conversations.

For example, she asked a 5-year-old to draw a picture of herself in the hospi-



tal. The result was a sad little girl, alone and vulnerable during a blood draw. *[See Blood Draw, right.]* When Wallace asked her to describe the drawing, the girl said it showed her crying because she'd done something wrong and was being punished. Wallace gently assured the young patient that she hadn't done anything wrong, and saw to it that her medical situation was explained to her in terms she could understand. With the girl's permission, Wallace shared the drawing — tangible evidence of her angst — with the girl's medical team. Armed with insight, they were able to treat her more effectively. — M.A. MALONE

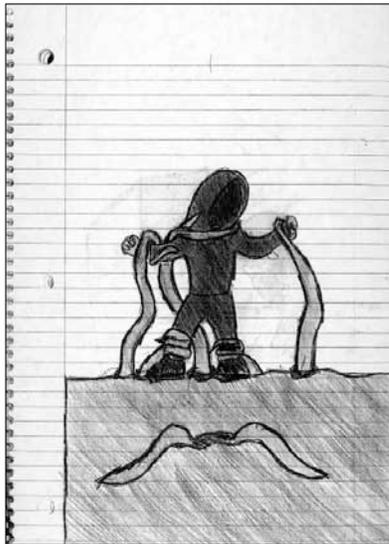
HELI
Andrew Cyrus, 8

Artwork by patients
at Lucile Packard Children's Hospital

RECOVERY IS POSSIBLE
Emily Ho, 14



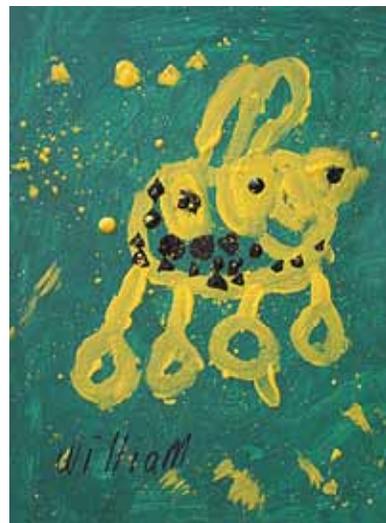
PAIN
Shon Habar, 13



BLOOD DRAW
Anonymous, 5



HOSPITAL ROOM
Coral Martinez, 15



BUG
William Tjeersdema, 10



Anna Penn, MD, PhD,
in her lab, where research
focuses on the placenta.

a most mysterious

Looking

for answers

about

the fetus's

lifeline

Organ

It's the black sheep of human organs — the one we can't wait to get rid of. Most often, it's tossed in a bucket for easy disposal. But Lucile Packard Children's Hospital neonatologist Anna Penn, MD, PhD, and Stanford neuroscientist Theo Palmer, PhD, and their colleagues are keen to get their hands on as many as possible.

“What we don't know about the placenta is astonishing,” says Penn. “At the end of a pregnancy, there it is. But what does it do in the meantime?”

The placenta used to be thought of as just a glorified housekeeper — delivering nutrients and oxygen, removing fetal waste and generally chaperoning biochemical interactions between mother and child. Because it's conveniently delivered into the waiting hands of the attending physicians or midwives soon after birth, we know a lot about what it looks like after its job is done. However, it's been tough to catch it in the act of supporting a growing fetus.

“We've really described the structure of the placenta in extraordinary detail,” says Penn. “But its molecular biology is exceptionally poorly studied.”

That needs to change. Recent research suggests that hormones produced by the placenta orchestrate how the fetal brain is organized. Missteps in production or delivery of these molecules during pregnancy can have effects

TAKING

KIDS

SERIOUSLY

By Krista Conger

PHOTOGRAPHS BY LESLIE WILLIAMSON

that spin out over years or decades, either in subtle learning difficulties like attention deficit hyperactivity disorder or in more dramatic problems like autism and schizophrenia.

Despite our increasing recognition of the placenta's critical role in the long-term health of the baby, only a few institutions in the world have dedicated multidisciplinary placental research teams. The placenta doesn't attract the funding many other organs do, in part because of its transience — it doesn't develop chronic diseases. Few researchers or physicians spend much time thinking about the placenta. Neuroscientists-turned-placentophiles like Penn and Palmer are swimming against the tide, hoping to substantially increase what's known about the placenta's contribution to the later health and behavior of the child.

"The placenta has always been credited with supporting the baby," says Palmer, "but the link between placental anomalies and later cognitive deficiencies is really strong. Much stronger than we had anticipated."

Premature babies, deprived of this molecular hormone factory too early, bear the brunt of our ignorance. Recent research has shown that important portions of their brains remain abnormally small for years. Neonatologists like Penn can sustain them with breast milk, and perform basic life support techniques, such as helping their lungs to breathe or their hearts to function better, without knowing what they're not getting from the now-discarded placenta. And yet the key to helping these children live successful, normal lives may very well be recreating as closely as possible the conditions they left behind in the womb.

"It used to be that the big focus was on keeping these kids alive," says Penn, who recently received a \$1.5 million New Innovator Grant from the National Institutes of Health to investigate how placental hormones affect fetal brain development. "It's not that that's no longer a problem, but now we're better-equipped. We can start to think about their long-term

In this close-up, the umbilical cord lies looped over the placenta. The cord carries enriched blood to the fetus.



status. But we don't know what they are missing physiologically, and how we can give that back." At least not yet.

As part of her research, Penn's working to establish a "bank" of full-term, premature and damaged placental samples to use for future studies. The unique bank, which the researchers hope to eventually share with physicians and researchers nationwide, will contain a wide variety of samples,

from tissue to genetic material, and will link to information about the long-term health of the mother and baby. Unfortunately, federal funding for tissue collection can be hard to come by. Also, because placentas quite literally straddle the nebulous boundary between obstetrics and pediatrics, many different doctors are needed to coordinate such an effort. But the researchers have forged ahead, and will begin gathering placental samples this spring. Their expectations are high.

"Lucile Packard Children's Hospital has over 5,000 births per year," says Penn. "If we can capture placentas from even half of these, we'd have enough tissue for even large-scale studies." She, Palmer and their colleagues — placental pathologist Amy McKenney, MD, geneticist Julie Baker, PhD, and developmental biologist Gill Bejerano, PhD — envision linking the structure and gene and protein levels in the placenta samples with the mother's medical history and the developmental outcome of the babies months and years later. Their tongue-in-check name for the effort?

The Bucket Brigade.

Dressed in a black top and pants and wearing a colorful, chunky necklace, Penn is happy to discuss her work. Her tiny, tidy office is brightened by pictures of her two children on one wall and a beautifully serene Asian floral scroll given to her by the parents of a patient — a boy born four months too early. Although she spends about 75 percent of her time in the lab, she treasures the days she spends caring for infants in Packard Children's intensive care unit for newborns and its nursery, keeping kids alive hour after painstaking hour.

Liam Sikes was one of those kids. Born more than three months early at Dominican Hospital in Santa Cruz, Calif., in December 2005, Liam was quickly transferred to Packard Children's for advanced care. Penn threw her medical arsenal at the 1-pound, 9-ounce baby as he struggled with kidney failure, severe infection and later a common but severe eye condition known as retinopathy of prematurity. Many times she wondered if he would survive. But the tiny baby beat the odds.

"When he was discharged, we were completely blessed and amazed," Liam's mother, Paris Trudeau-Sikes remembers. "We were coming home with our son thinking, 'Thank you. This is all we asked for.'" But then the waiting began — because they knew Liam might still have a huge struggle ahead.

"Premature male babies are more at risk than equally premature girls for just about everything, including death, lung and vision problems and long-term neurodevelopmental delays," says Penn. "But we don't really know why." This isn't to say that premature girls face no risk, merely that for boys it's higher. Specifically, girls have about a one-week ad-

vantage over boys. That is, a girl born at 24 weeks and a boy born at 25 weeks will fare about the same statistically. She believes that some of this gender difference lies in the sudden loss of protective sex hormones provided by the placenta — hormones that baby girls can make for themselves, at least a little, and boys cannot.

“We spent the first couple of years wondering about Liam’s neurological outcome,” says his mother. “And now, even though his MRI before discharge looked normal, it’s apparent that he does have a neurological injury.” Now 4 years old, Liam has cognitive difficulties, and problems with his vision and motor skills. Because he also doesn’t like to chew solid food, he’s fed mainly through a tube.

If Liam had been a girl — or if physicians understood how to give back the placental hormones he would have had in utero — he might not have these challenges. “In an ideal world,” says Penn, “we’d take blood or spinal fluid from these babies, assess the levels of the hormones that we know are important for brain development, and give back as medications those that are missing.”

But first we have to figure out what they are.

For such an important organ, the placenta is pretty ugly. At full term it is an approximately 1-pound, flattish and roundish mass resembling a deflated soccer ball or an unleavened loaf of bread. (In fact, the word “placenta” originates from the Latin word for cake.) It has a maternal side that faces the uterine lining and a fetal side facing the inside of the uterus. And, of course, it’s very, very bloody.

That’s because it’s chockfull of arteries and vessels to deliver oxygen and nutrients from mother to child. The two blood supplies don’t mix freely, however. A thin layer of cells called the placental barrier separates the network of vessels on the maternal side of the organ from those on the fetal side. Some molecules such as oxygen, carbon dioxide and certain medications and hormones either diffuse or are actively transported across the intervening tissue. Other circulating factors, like most cells, are blocked to protect the fetus from harm and attack by the mother’s immune system.

Penn became interested in the placenta gradually. As a graduate student in the laboratory of Stanford neurobiologist Carla Shatz, PhD, she studied early spontaneous activity and organization in the developing neural system. When she joined the laboratory of Stanford developmental pathologist Matthew Scott, PhD, as a postdoctoral scholar, she investigated factors that control cerebral activity. She describes herself as a developmental neurobiologist.

“This is the next step,” she says of her current line of re-

search. “I wanted to explore what the extrinsic organizing signals are, and what happens when they are suddenly lost. What stops, and what keeps going? Are there big things that are missing when we take away the placenta?”

Penn quickly learned that the placenta is more than just a molecular transit station orchestrating the trafficking of maternal and fetal factors. It also makes its own hormones to support the developing pregnancy. Some we know about, including the sex hormones progesterone and estrogen, which thicken the uterine lining and support the first steps of egg development in female fetuses. Progesterone and estrogen are also involved in brain development, and may be responsible for the varying survival statistics between premature boys and girls. But many more placental factors remain mysterious.

“We have a little list of candidates,” says Penn with a grin. “About 100.” She studied microarray data generated by Baker, another placenta enthusiast, to identify hormone-related genes expressed in the mouse placenta at various times during gestation. To earn a spot on the list, the hormones had to be shared between mice — the study animal used by the researchers — and humans; to be secreted from the placenta; and to — theoretically at least, based on their DNA sequence — cross the blood/brain barrier in the fetus to influence the development of the growing brain.

“We’re also interested in the many small peptides that appear to be secreted from the placenta,” says Penn. “They increase during the course of the pregnancy and there is some evidence that they get to the fetus. But nobody knows what they are doing.”

Obviously, one problem with studying the placenta is its relative inaccessibility during gestation. It’s been difficult to come up with a way to block or amp up the expression of genes in the placenta in mice without also changing their levels in the mother or fetus. But Penn and her colleagues have done it.

She and postdoctoral scholar Danielle Leuenberger, PhD, took advantage of the fact that the placenta develops from the outer cells of the blastocyst — the ball of cells that develops from a fertilized egg. (Cells inside the ball become the fetus.) They used a virus to infect only these outer cells with the DNA of candidate genes coupled to on and off switches called promoters that allow them to be expressed or shushed at specific points during gestation. They also used DNA that reduces the natural expression of these genes. They then implanted the developing embryos into female mice. They hope that by toggling the individual gene candidates on and off, they will be able to identify those molecules that play a vital role in brain development.

In addition to identifying new placental hormones, Penn is working to figure out why boys are more at risk than girls for neurodevelopmental problems. She’s found that exposing



NO LONGER

Electroconvulsive therapy is a lifesaver

By Ruthann Richter

ILLUSTRATION BY MATT BANDSUCH

TO THIS DAY, HE DOES NOT KNOW WHAT DROVE HIM TO THE RAILING OF THE GOLDEN GATE BRIDGE. He had just exhausted all hope and energy to continue. He left a goodbye note for his family, saying that he was sorry. • He was, by all external measures, a man in the fullness of life. He had his thriving medical practice in the Bay Area, a loving wife and three wonderful kids. He enjoyed economic security, abundant friends and a vibrant social life. But by some weird twist in his brain chemistry, he had become trapped in a prison of despair. • “I was sailing along, and literally one day this world that looked great was black as midnight. Everything just shut down,” says Henry, an ophthalmologist in his late 50s who asked that his real name not be used. “I was so shocked by the impact. It was as if someone had turned a switch, and it just got worse from there.” • He had a strong family history of depression — his mother had suffered from the condition — but he had only the barest hint of the disease earlier in his life. While an undergraduate at Stanford, he had suffered an “identity crisis,” a feeling of temporarily being lost. But nothing like this darkness. • “It’s a sensation as if you’re already dead,” he says. “There is no color. It’s absolutely inconceivable that you’ll ever get better again. You have no reason to be alive.” • So he stood at the edge of the bridge, contemplating his demise. He saw a police car approach. • “I remember that moment well. The officer came and stopped 5 feet away. He said, ‘I think I know why you’re here.’ It was disarming. He said, ‘Why don’t you get in the car.’” • Though it seemed too painful for life to go on, Henry said he realized it would have been a terrible thing to do to his children if he ended it there. “That was the battle going on. I think I would have jumped immediately if it weren’t for them,” he said. He was taken first to Marin General Hospital, then transferred by ambulance to Stanford Hospital, as he had longstanding ties to Stanford. There, he incessantly paced the courtyard of the locked psychiatric ward. It was the fall of 2008. In his troubled mind, he would never practice medicine again or return to anything that resembled a normal life.

S H O C K I N G

PALE GREEN CURTAINS SEPARATED PATIENTS IN THE THIRD-FLOOR AMBULATORY CARE CENTER AT STANFORD, where four people lay calmly, awaiting a treatment that they desperately hoped would lift them out of the shadows. Each had a history of profound depression; some had attempted suicide more than once. One had been admitted to the hospital a month before in a catatonic state, mute and completely unresponsive.

Their treatment, known as electroconvulsive therapy, or simply ECT, uses a device that outwardly resembles an ordinary stereo receiver. Henry, hospitalized by now for a month, was among the group of patients prepared for the treatment. He had small pads on his temples to deliver an electric current and recording patches attached to his head to track the resulting seizure. He received anesthesia through an IV, enough to put him to sleep for five or 10 minutes. Then he was given a drug, succinylcholine, that left him temporarily paralyzed.

The anesthesiologist placed a black rubber bite block in his mouth to prevent him from biting his tongue or cracking a tooth and then positioned a clear plastic dome over his nose and mouth, providing oxygen to his brain as he slumbered. Then psychiatrist Brent Solvason, MD, PhD, pressed a pre-programmed button on the box. Henry's arms clenched a bit as a blood pressure cuff on his arm kept the succinylcholine from paralyzing it. This allowed doctors to monitor the seizure by following the movement in the arm as well. Within 20 to 60 seconds, it was all over.

Henry's brain had just been jolted by an electrical current less than that used to power a light bulb. It produced an organized firing of brain cells, thought to affect structures deep within the brain. The ECT seizure is unlike an epileptic seizure, which is confused and disorganized across the entire brain, Solvason says.

Within 10 minutes, Henry was awake, though still foggy from the procedure. He remembered being wheeled into the outpatient center, the nurse starting the IV, even what Solvason was wearing that day. After that, his recollection fades. He was taken back to his hospital room with the hope that this somewhat daunting treatment somehow would release him from his anguish.

SOLVASON ADMITS THAT ECT, COMMONLY KNOWN AS ELECTROSHOCK THERAPY, seemed like a strange procedure when he first observed it as a fellow in 1998. "But after I began to treat people, I was stunned at how effective it was," says Solvason, an associate professor of psychiatry and behavioral sciences who directs the Psychiatric Neuromodulation Service at Stanford. The program is part of the Stanford Mood Disorders Center, one of 15 centers in a national depression treatment network.

Since then, he has treated many hundreds of patients with

"There's still a stigma associated with it that

the technique, with results that he says can't be matched by any other form of treatment. All patients who receive ECT at Stanford have failed many rounds of medication treatments and therapy, says Solvason. These patients suffer a sadness so profound that they find themselves struggling on a minute-to-minute basis with a desire to die and are so disabled by depression that they can no longer care for themselves, he says.

With ECT, "People get better faster, and more of them improve than with any other treatment, which is gratifying to see," he says.

About 100,000 patients undergo the treatment every year in the United States, where ECT is enjoying a quiet renaissance of sorts. Typically these are patients with major depressive disorder, or with bipolar depression, which is characterized by manic highs and depressive lows, or with psychotic depression, in which patients also lose touch with reality. ECT is widely recognized as the most effective, acute therapy for these serious mood disorders.

Though the therapy remains imperfect, with some disquieting effects on memory and cognition, it has improved dramatically from its early days and incorporates strong safeguards for patients. Still, it remains dogged by a tortuous history.

"There's still a stigma associated with it that can dissuade psychiatrists and psychologists from recommending this treatment," Solvason says. Because of that stigma, millions of patients who don't respond to medication and could benefit from ECT don't receive the treatment, says Sarah Lisanby, MD, professor of clinical psychiatry at Columbia University and an expert in the field.

ECT originated in the 1930s after scientists observed that people with mental illness who suffered convulsions made surprising recoveries from their mental disabilities. Ugo Cerletti, a renowned Italian neurologist, was the first to test it in a patient, a delusional engineer from Milan found wandering the city's train station. Using a crude shock device invented by fellow physician Lucio Bini, Cerletti delivered 100 volts of electricity to the head of the schizophrenic man, jolting him back into reality and into a normal state of mind.

The results ignited excitement in the psychiatric community, for it was the first treatment that was found to help in managing psychiatric illness. The practice soon spread throughout the world and for the next three decades, it would dominate psychiatric treatment as the preferred method of therapy.

In the early days, however, patients were not anesthetized while being treated, and some reported the experience as a kind of torture. Nor were muscle relaxants used, resulting in cracked vertebrae and fractured limbs, as patients flailed wildly during seizure. The procedure also suffered from

can dissuade psychiatrists and psychologists from recommending this treatment."

abuses, as institutionalized patients were sometimes coerced into treatment against their will.

These inglorious practices were immortalized in the 1975 Academy Award-winning film, *One Flew Over the Cuckoo's Nest*, in which institutionalized patients thrash violently about after being herded into shock therapy by Nurse Ratched, who resembles a sadistic prison guard.

ECT's popularity was further eroded with the introduction of the first antidepressant medications, the so-called tricyclic drugs, in the late 1950s and early 1960s. These were followed by even safer drugs, the SSRIs (selective serotonin reuptake inhibitors), such as Prozac, Zoloft and Lexapro. Soon we were a nation on medication, and ECT seemed altogether less attractive than popping a pill.

But there are an estimated 14 million adults in this country with major depression, and only about a third respond to medication, Lisanby notes. As the drawbacks of medication became apparent over time, psychiatrists slowly turned their attention back to ECT, primarily as a last-resort option for patients who were otherwise beyond help.

HENRY LANGUISHED IN THE LOCKED PSYCHIATRIC WARD after his brush with suicide, still out of reach. He had tried multiple drugs — Prozac, Elavil, Zyprexa — but he never ceased to despair. He went on suicide watch. His suffering was so acute that Solvason says he was deeply concerned for his safety. Henry's doctors suggested ECT.

Henry was terrified of the treatment but at the same time relieved to have an option, because he could see no other way out. "There was nothing in my life that I felt needed working out in psychotherapy, where I could say, 'Let's talk this out.' And I was afraid I would just get worse," he says.

Friends and colleagues did not respond well to the idea of shock therapy. "There was a lot of negative reaction," Henry says.

It is not known how ECT works, though it is believed to mobilize a number of different systems in the brain, says Alan Schatzberg, MD, professor and chair of psychiatry and a depression expert. It is likely to cause release of neurotransmitters, mood stabilizers such as serotonin, he says. It also is thought to help regulate cortisol, a stress-related hormone, and stabilize the so-called stress axis — the link between the hypothalamus, pituitary and adrenal glands — which can affect mood and brain function.

"It's hard to know which is the key, but it is causing a really profound effect," Schatzberg says.

Henry sees it as a method for resuscitating a failed organ.

"There are some people whose brains and psychological makeup just fail them," he says. "Some systems go haywire. It's analogous to the kidney shutting down. I think the drugs available are good at helping people who are very sad, but they may not help people with comprehensive failure of the chemical system in the brain. It's like having to take your computer and reboot it."

Initially, Henry was treated three times a week with ECT over a month, the typical course of therapy. He would suffer the usual side effects: nausea, headache, muscle aches and confusion, but these soon disappeared. What did linger was a profound loss of memory. He read voraciously while in the hospital, about a book a day, but to this day he does not remember a single word of what lay between those pages. His knowledge of medicine — the decades spent in training and practice — seemed to evaporate from his mind overnight.

"It was pretty frightening not to be able to think or remember," he says.

He went home Christmas Eve, stable but not recovered. He would go to parties with his wife and have her secretly whisper people's names or give him other clues about who they were. One day he set off to go to the neighborhood bookstore, one of his favorite haunts, but couldn't remember where it was or how to get there. He had always been an organized person, a man with a long to-do list, so to lose this organizational capacity was devastating, he says.

Cognitive difficulties, including memory loss, may occur with ECT, with these problems sometimes persisting six months after treatment, according to a 2006 study led by researchers at Columbia University. These side effects vary from one treatment center to another, depending on different practices, such as the dosage and waveforms of electricity and the placement of electrodes.

"There is memory loss, but that risk has been significantly reduced by modifications in how the treatment is used," Lisanby, the Columbia professor, says. For instance, giving ECT with ultra-brief electrical pulses, just a few milliseconds each, can reduce side effects, as can placing the electrodes on one side of the head rather than both, she says. Physicians also are investigating the possibility of pretreating patients with certain drugs to minimize memory loss, Schatzberg says.

For Henry, the memory problems were unusually severe. If he were ever going to work again, he realized he would have to retrieve everything he had learned in his medical training — a daunting task. He decided to start by rereading the textbooks he had used 25 years before in his residency.

C O N T I N U E S O N P A G E 4 9

GROWING
MINI-INTESTINES
IN
A
DISH

gut BALLS

BY BRUCE GOLDMAN

ILLUSTRATION BY GREG CLARKE

Calvin Kuo's got a gut in a dish. He's introducing it to a lot of his fellow researchers at Stanford to help him get up to speed on what to do with it. "I'm a hematologist. My specialization is blood," says Kuo, who's been at Stanford since 2001. "The intestine is a little far afield for me."

About five years ago, Kuo, an MD/PhD and associate professor of hematology, tripped on the gut when he crossed paths with Akifumi Ootani, MD, PhD, a young researcher in Japan. Between them, they're making rapid strides in growing intestinal tissue in culture. Having succeeded at making mini-mouse intestines, they're moving on to re-creating human innards.

Scientists have cultivated other tissues — skin, prostate, lung, thyroid, liver, stomach and more. Being able to do this with intestines would bring big payoffs, says Ootani, who now works as a postdoctoral research scientist in Kuo's lab. For example, scientists could much more readily test drugs, study bowel cancer and learn more about the mechanisms of infectious diseases (many of whose causal pathogens access our innards via our entrails), he says. Kuo, Ootani and their collaborators are already using the mouse intestine cultures to study intestinal stem cells. In September, the Kuo lab received \$2.5 million from the National Institutes of Health to start a parallel effort with human intestinal tissue, with a lofty long-term ambition of engineering artificial intestines to replace injured or defective ones.

What's inside of those dishes Kuo and Ootani are holding looks like extremely



tiny gumballs — “gutballs,” you could call them — that have assembled themselves from bits of a mouse’s intestinal tissue embedded in a protein matrix, or gel. Under the right conditions, those fragments grow into round structures, which, aside from their spherical shape and petite proportions, mimic the intestine in both form and function.

“These cultures are little mini-organs, up to a quarter-inch big. They’re large enough that you can pick up the dish every couple of days and see them growing,” Kuo says.

“If you were to take a thin section of one of them and stain it and put it in front of a pathologist, they’d look at it and say, ‘Oh, that’s a section of an intestine,’” says Justin Sonnenburg, PhD, an assistant professor of microbiology and immunology,

one of several researchers who’ve begun putting the Kuo lab’s mouse intestine cultures through their paces.

They even contract, just like the real McCoy. The intestine is, in its essence, a tube surrounded by rings of smooth muscle that periodically undergo rhythmic, sequential contractions followed by relaxations. This squeezes food through the tube — a process called peristalsis. Along the way, the food gradually gets absorbed.

Getting anything even remotely similar to happen in a petri dish — or for that matter, just getting intestinal tissue to survive in culture for longer than a week or 10 days — hasn’t been easy. In fact, until just a few years ago it had never been done, although people have been trying for more than 30 years.

Until now, the only alternative to studying the intestine in a living organism was to study it in cultures generated from one or another intestinal cell type. But most of these single-cell cultures begin with cancer cells, which are by definition cells gone haywire. Anyway, cultures of a single intestinal cell type can't possibly mimic the environment the real intestine experiences.

It takes a village to make an intestine. Just to get the ball rolling, there are four different major cell types that collectively comprise the intestinal epithelium — the gut's surface lining, which does what most of us think of when we think about what an intestine does, and more. These four basic epithelial cell types absorb nutrients — in the small intestine, carbohydrates, amino acids (the constituents of protein) and fats; in the large intestine, chiefly water. They secrete mucus that lubricates the intestine, and hormones that regulate feeding behavior and peristalsis. And they promote immune functions including fighting off pathogens. On top of all that, the gut epithelium manages to play host to trillions of friendly bacteria, without which we'd be toast because they do everything from helping us digest our food to fending off incursions by nastier bugs.

All that crunching and punching and lurching, plus all that constant direct exposure to the toxins and villains of the outer world (the intestinal lumen is considered the outside, not the inside, of the body), take a toll on the intestine's hard-working components. The organ has evolved to accommodate the burnout rate by replacing its constituent cells very rapidly — most of them turn over every five to seven days. This calls for ship-shape, active-duty stem cells, and lots of them.

But intestinal stem cells don't grow on trees. To thrive, they need a support system composed of a network of numerous cell types that, together, provide just the right microenvironment, or "niche." Within that niche, stem cells benefit from a complicated cascade of largely uncharted biochemical signals that tell them to chill out, or proliferate, or start differentiating into one or another mature epithelial cell type.

Early attempts by numerous researchers to grow intestinal cells in culture using disaggregated cells typically ended in tears when the cells started to die within hours of being removed from their normal position in a living tissue. Being separated from neighboring cells, with which they must constantly interact, was not OK with them. Even with researchers' best efforts, they remained viable for less than two weeks. It's a vicious circle: Healthy stem cells are key to a healthy intestine, but for lack of a real intestine's three-dimensional architecture, stem cells couldn't do their job of replacing differentiated cells.

"THE FACT THAT THESE LITTLE SPHEROIDS CAN CONTRACT INDICATES THE PRESENCE OF WORKING MUSCLE CELLS AND NEURONS."

Recently, researchers in the Netherlands (with a lot of help from a postdoctoral researcher trained by Ootani in their native Japan some years ago) figured out how to grow an intestinal cell culture from a single stem cell, using a complex mix of exotic external growth factors. But this method is pricey and inefficient. Moreover, the intestinal stem cell can mature into only the four basic intestinal epithelial cell types, so it can't produce supporting tissues such as blood vessels, muscles and nerves.

The Kuo lab's tissue-culture methodology gets around all that by starting with bits of minced tissue that are large enough to retain the original intestinal architecture, including the stem-cell niche. "We have a lot of the supporting cells — not just the intestinal epithelium, but supporting cell types such as fibroblasts," Kuo says. "The fact that these little spheroids can contract indicates the presence of working muscle cells and neurons." Jay Pasricha, MD, chief of the division of adult gastroenterology and hepatology in the Department of Medicine, has now confirmed this presence.

Kuo gives all the credit to Ootani: "It was Akifumi who single-handedly came up with this intestinal culture technique and introduced us to its potential."

Chef Ootani's secret sauce

FIVE YEARS AGO, IN 2004, Kuo found himself in correspondence with a stranger from Saga, a city of close to 1 million on Japan's Kyushu Island. Akifumi Ootani had spent his life in Saga, gone to high school and college and finished medical school there. Now he was a PhD student in the school of medicine at Saga University, trying to figure out how to get intestinal cells to grow in culture in the laboratory of internal medicine professor Kazuma Fujimoto, MD, PhD. "My mentor asked me to develop a culture system for intestine. In Japan, when the boss asks me something I have to say yes." It was "a good challenge for me," he adds with some understatement.

From another mentor, pathology professor Hajime Sugihara, MD, PhD, he learned a new technique for culturing skin, cornea, thyroid, lung and fat tissue, which relied on preserving the stem-cell niche. "I imagined that this microenvironment would also be important for maintaining intestine in culture," Ootani says. In order to mimic it by preserving the stem-cell niche, he tried using fairly intact tissue fragments, not single cells, as starter materials.

That was the first key ingredient in Ootani's recipe. A second component was to encase those bits of minced tissue within a porous protein matrix, or gel, that preserves the

from lab to ab

TRYING TO GROW A HUMAN GUT

When you're on a roll, why stop with mice?

"We'd like to extend our examination of mouse intestinal culture system to human tissue," says Calvin Kuo, MD, PhD. "That will allow even more accurate recapitulation of different disease processes that affect people. We also see potential for one day being able to grow artificial human intestines that can be transplanted into patients," says Kuo, an associate professor of hematology. The long-term vision: replacement parts for people with Crohn's disease or other severe intestinal abnormalities.

Not that we're going to see a full-sized, full-fledged, flexible, fleshy tube rearing up from a petri dish like a cobra charmed by a flute anytime soon. Realistically, the first steps will be to simply get human intestinal fragments to grow in culture.

Trying to grow human intestine in culture comes with plenty of challenges. The mouse cultures grow best if you start with very young (neonatal) tissue. "You can't do that with humans," says Kuo. "We're trying to acquire tissue samples surgically removed from patients here at Stanford Hospital, and to use that as starting material."

So far, human cultures haven't lasted nearly as long as their murine counterparts, says research scientist Akifumi Ootani, MD, PhD. Kuo thinks human gut may prove tougher to grow in culture than mouse gut. "It's a bigger organ, with thicker walls composed of more-cohesive tissue that may be more difficult to disaggregate," he notes.

As their collaborator, Sarah Heilshorn, PhD, assistant professor of materials science in the School of Engineering, explains: "In living organisms, cells exist in a three-dimensional world, touching materials of one sort or another all around them. In the lab, we put them on flat petri dishes and expect them to behave

the same way. Sometimes they do, and sometimes they don't."

Kuo and Ootani use a commercial collagen gel for their intestine cultures. Heilshorn's lab spends a lot of time thinking about how to design materials that mimic the body. "Calvin and I wondered if maybe the gel composition and oxygen availability might need to be adjusted to make these human tissues feel more at home," she says.

Kuo has enlisted Heilshorn to develop a superior scaffolding material for human tissue and perhaps, down the road, a more fully developed organ. The scaffold would be composed of specially engineered proteins whose carefully spaced components can mimic growth factors identified by Kuo as critical to sustaining Ootani's cultures.

Is there any possibility of coaxing these spheroid intestinal cultures into going tubular? Heilshorn's lab is developing scaffolds to encourage tubular structures such as blood vessels and has already developed scaffolding for application and delivery of neural cells. "It's quite conceivable that you could encourage these intestinal cells to grow as tubes, too," she says.

"A complete, full-scale intestine would be the eventual dream goal," says Kuo.

unique three-dimensional gut architecture, sustaining the microenvironment in which stem cells grow best.

On top of the gel layer is air, while underneath is a nutrient-rich liquid medium. Air and liquids easily diffuse into the matrix and reach the cells directly. The idea is to reproduce what the cells lining a living intestine are seeing — which includes plenty of oxygen supplied by red blood cells. "When tissues are cultured, they don't get all that much oxygen, since they are not connected to the heart," says Kuo. The air layer above the porous gel makes oxygen freely available. Likewise, the liquid phase below puts all the cultured cells in contact with the nutrients they need.

By mid-2004, Ootani had figured out how to get intestinal fragments to grow in culture. This meant, by definition, that his little gutballs were providing the all-important biochemical signals their resident intestinal stem cells needed.

But he wondered whether externally supplied biochemical signals could spur the cells on to greater feats.

And externally supplied biochemical signals, or growth factors, happened to be a specialty of Kuo's. Earlier that year, Ootani had read a paper Kuo had published in *Proceedings of the National Academy of Sciences* describing intestinal cells' requirement for an external growth factor called Wnt. When such a growth factor binds to receptors on a cell's surface, it can ignite a furious pinball game of rapid-fire interactions among different molecules within the cell, causing it to proliferate.

Kuo's laboratory had stumbled on the intestine somewhat accidentally. "We had been studying blood-vessel and bone growth, and were evaluating a lot of growth factors and their inhibitors," Kuo says. "When we gave mice one of the proteins we were testing, an inhibitor of the Wnt pathway, we were very surprised to find they rapidly lost weight and

died within days with gastrointestinal symptoms.” Autopsies showed the guts of these mice had shriveled up.

Then a postdoctoral scholar in the Kuo lab, Frank Kuhnert, PhD, found that the Wnt-inhibiting protein caused stem cells in the mice’s intestines to disappear — pronto. Clearly, Wnt was critical to intestinal stem-cell health. Kuo’s group immediately spun their attention to intestinal stem cells and regeneration.

In October 2004, Ootani e-mailed Kuo and let him know he had an intestinal culture system up and running, and asked if they might benefit from one another’s expertise. The timing was propitious, as Kuo was scheduled to give a presentation in Tokyo in December. Ootani came up from Saga. They met, and exchanged observations in a restaurant. Each recognized their common interest. The sake didn’t hurt, either. Kuo offered Ootani a job on the spot.

Let the sun shine in

OOTANI SHOWED UP and started working at Stanford in August 2005. It was a good move. First of all, Ootani’s cultures felt right at home in dry, sunny California. “It’s much easier to grow these cultures without contamination here than in Japan,” says Ootani.

Second, the foreseen synergies between Ootani’s and Kuo’s work paid off. While Ootani’s cultures could expand on their own by providing themselves with growth factors, stimulating the Wnt pathway using a variety of techniques developed by Ootani and Kuo has dramatically increased the growth of Ootani’s cultures, which now can thrive for a year or longer — a huge leap from the mere minutes or hours intestinal tissue could survive in culture prior to the innovation.

“Many of the spheres start to rhythmically contract, just like live intestines do, within about 10 days or two weeks,” Ootani says. “Apparently they’re pretty comfortable here.”

Contraction of the spheres

JUST ASK MANUEL AMIEVA about that. Amieva, who went through Stanford’s MD/PhD program simultaneously with Kuo, is an assistant professor of pediatrics and of microbiology and immunology. Amieva’s research interest lies with pathogens that infect the intestine and cause diseases such as diarrhea, the biggest cause of infant death in the developing world. He is also a widely acclaimed microscopist.

Hoping to do some imaging of his intestine-in-a-dish cultures, Kuo asked Amieva if he could help.

“I said, ‘Oh, that sounds interesting, bring it over,’” Amieva recalls. When Ootani showed up, petri dish in hand, Amieva stuck it under a microscope and started focusing on one of the little spheroids, trying to get the best view for shooting

some video footage of it. As he was looking through the lens, the gutball impulsively perpetrated peristalsis.

“I jumped back! This thing was alive. It scared me. Usually, cells move at a sluggish pace,” says Amieva. But not this thing. “Now I was hooked, because I realized that we were dealing with this little Frankenstein monster living in a petri dish.”

Getting the word out

THIS NEW TECHNOLOGY PROMISES to diffuse rapidly — because it’s such a valuable research tool and because Kuo is reaching out to establish collaborations with key researchers.

“Our ability to grow mouse gut in culture helps us to study stem cells in a way not possible using any other methodology,” Kuo says. “Now we can begin to learn how intestine works by introducing target genes into cultured cells one at a time and seeing how each affects the tissue. No one’s been able to do this before using bona fide intestinal cells.” (Previous attempts had to rely on cancerous cells.) “We can study intestinal stem cells, as well as their relationship to, for instance, colon cancer initiation and proliferation. We can also test the effects of cancer therapeutics in the culture system, and perhaps even use it as a screening methodology.”

He’s already working with Amieva and Sonnenburg to study bacterial interactions with the intestine.

In one of Amieva’s projects, the spherical organoids allow him to follow the process of infection as it happens. With a microneedle, he injects pathogens into the hollow center of the spheres, which corresponds to the open tube inside an intestine; the mouse tissues have been bioengineered so their cells glow green, the bacteria have been designed to glow red.

“That way we can follow the infected cells under a microscope,” he says. “And we can start looking for exactly which bacterial factors and which interactions between the bugs and the intestinal cells are important for the bacteria to succeed in causing the infection.”

Amieva and Sonnenburg are also teaming up to pit good against evil inside the gutballs. Sonnenburg has been introducing friendly bacteria, one strain at a time, into germ-free mice so he can study their actions with the mouse’s gut and with one another. “We’re putting first Justin’s good bugs and then my bad bugs into these cultures, to see whether the good bugs can treat or prevent disease,” Amieva says.

“The rest of us are very lucky that it’s Calvin who’s developed this, because he’s so interested in having this model widely applied,” says Sonnenburg. “He understands that this system is powerful beyond any single person’s vision. So he’s trying to put it in the hands of as many people as possible.” No guts, no glory. **SM**

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FEATURE No longer shocking

CONTINUED FROM PAGE 43

Even the most basic aspects of ophthalmology seemed faint and distant at first, he says. He read journals, watched surgical videos and studied his own previous notes. He sat in on colleagues' surgeries and recorded his observations. Two months out of the hospital, he decided to try his hand again at surgery.

That day, "I awoke feeling like I did as an early resident, a sense of concern approaching dread at the possibility that I would fail to perform well," he recalls. He asked a colleague to assist him at every step.

He decided to leave a textbook open in his office at all times so he could quickly retrieve information that had been wiped from his brain. His first week back at work, he was visited by a patient with herpes zoster infection in the eye, a serious syndrome that can cause blindness. Henry recognized the problem but says he "had no clue what to do."

"It was so striking because I started reading in the textbook, and all of a sudden, the whole thing came back," he says. "The memory comes in these little pockets. Some of those pockets you may lose forever, and some are accessible."

Gradually, he returned to the surgeries he had done before — cataract operations, LASIK, intraocular lens implants and a wide range of laser procedures.

"Surgically, I believe I'm noticeably better than I was because I had to go back and rethink everything," he says. He is also a more empathic physician, he says, often taking extra time to talk to patients about their general health and personal lives.

"I had the sense that it reprogrammed my brain — the empathy center, the friendship center, the 'feeling hassled' center. I don't feel hassled anymore," he says.

While he was regaining his medical skills, his mood very gradually improved. Still, it would be months before he could look at a flower and appreciate its beauty. He returned to the hospital for periodic ECT treatments to make sure his recovery stayed on track.

That is important, Solvason says, because of the risk of relapse. If patients get no follow-up treatment at all, the relapse rate is 80 percent, Lisanby says. With maintenance ECT treatments or a combination of ECT

and medication, the likelihood a patient will remain healthy is about 50-50, she says. Recently, she launched a clinical trial in older patients to try to improve these odds.

"It's hard to keep people well," Solvason says. "You have to work very hard to keep the symptoms from creeping back. With depression, the brain is prone to disregulate even when there is nothing stressful happening in your life. So we do everything to help keep people well in the hope that the brain will be able to stay in a normal pattern of functioning that ECT has been able to re-establish."

Henry had his last ECT treatment in April 2008 and has been depression-free since, though he continues taking medication. "In that year and a half, I have not had a second of a worrisome mood," he says.

Recently, he's been preoccupied by a serious illness in the family and has had to work at keeping his equilibrium intact.

But, he notes, "There is some kind of inner strength that came out of this experience that is helping me," he says. Indeed, the procedure did far more than that, he and Solvason agree. It saved his life. **SM**

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FEATURE A most mysterious organ

CONTINUED FROM PAGE 39

newborn male mice to periods of low oxygen generates changes in their brains that mimic the effects of prematurity in humans. The brains of female mice also change, but the response is less pronounced. They plan to test whether giving the male pups sex hormones usually provided by the placenta can prevent or reverse the damage.

None of this is likely to make a big difference for Liam. "His injury is over, there is nothing we can do to fix that now," says his mother, Trudeau-Sikes. "My hope for Anna's research is that, in the future, it will be possible to develop medicines that will improve the outcomes for these kids."

Penn is hopeful, but realistic. "We finally have the money to start to look at human placenta and to develop the mouse models that may eventually lead to help for premature babies," she says. "There are almost too many different interesting questions to explore." **SM**

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down to the wire

A NEW WAY TO CLEAR CLOTS FROM LUNGS

WILLIAM KUO
WANTS
MORE PHYSICIANS
TO KNOW
ABOUT A NEW
WAY TO
OPEN BLOCKED
VESSELS.

William Kuo, MD, was the on-call interventional radiologist one Friday night three years ago when he received a call from the intensive care unit at Stanford Hospital & Clinics. He was asked to attend to a 62-year-old woman who had collapsed and was rushed to the emergency room with blood clots in her lungs. • “I get very emotional when I think about what happened,” says Kuo, assistant professor of radiology. “I could immediately see the patient was not doing well. The ICU team had notified the family that she was going to die very soon.” • What happened that night set Kuo on a three-year mission to investigate the safety and effectiveness of a new treatment — catheter-directed thrombolysis — for the patient’s condition, acute pulmonary embolism. • As in most cases of pulmonary embolism, blood clots had first formed in the patient’s legs, then traveled to her lungs, interfering with oxygenation and the heart’s ability to pump blood into the lungs. Because of the blood clots, she was quickly suffocating to death. The ICU staff had already done everything they could. • Kuo was initially consulted to perform a minor procedure — placement of a special filter in the major abdominal blood vessel to prevent more clots from traveling to the lungs, but he knew it would do little to save her. Then an idea came to him. • “I had been reading about experimental catheter-based treatments to remove these clots from the lungs,” Kuo says. “I told the staff, ‘We can do more than just insert a filter. We can go after these clots using

specially designed catheters.’ The ICU staff was at first skeptical, but I just kept insisting because I knew it might save her life. We obtained consent from the family and went ahead with it.”

He quickly made a small incision in the patient’s neck, inserted a catheter — a thin plastic tube — into the blood vessel. He then used real-time X-ray images (fluoroscopy) to guide the catheter, navigating through the heart and finally reaching the blood clots within the lungs. First, he injected clot-busting medicine through the catheter directly into the clots. Then, he used the catheter to mechanically break them up. Finally, he suctioned them out.

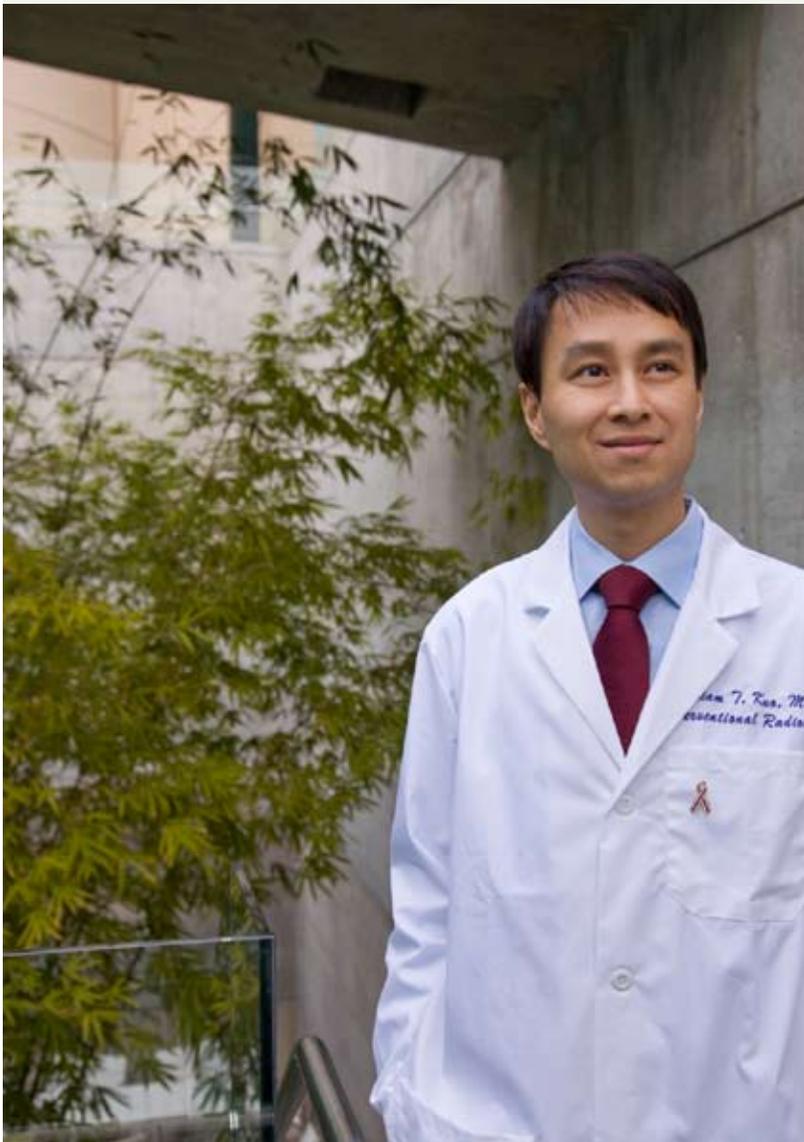
The results were immediate. The patient’s oxygenation improved, her blood pressure started to rise and she no longer required the blood-pressure drugs to keep her alive. The angiogram showed that blood was now able to flow into her lungs and the blood clots were much smaller.

“We just stood there,” Kuo says, “and we were amazed that the treatment had saved her life. She walked out of the hospital nine days later.”

But that was just the beginning for Kuo.

“At that moment three years ago, I recognized that this was a potentially life-saving procedure, but I also realized that few physicians were aware of it. The experience from that case really inspired me to begin my clinical research.”

Results from that research, a meta-analysis of scientific data from around the world, appeared in a report in the November issue of the *Journal of Vascular and Interventional Radiology*. The study shows that when catheter-directed therapy is used to treat dangerous blood clots, it saves lives. — TRACIE WHITE



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The TV diet

CUTTING HOURS WATCHED REDUCES WEIGHT GAINED

MOST PEOPLE CAN STAVE OFF WEIGHT gain by simply spending less time watching television. • A recent study reports that overweight adults who cut television time in half were more active, burning more calories as a result. • Even mellow activities including reading, writing and talking on the phone used more energy than TV watching. • “Really, almost any activity burns more calories than watching television, aside from sleep,” says Jennifer Otten, PhD, postdoctoral scholar at the Stanford Prevention Research Center and lead author of the study, which she conducted while earning her doctorate at the University of Vermont.

The study, published in the Dec. 14, 2009, *Archives of Internal Medicine*, determined how reduced television watching affected calories eaten, energy used, body weight, time spent sleeping and the balance between calorie ingestion and activity in obese and overweight adults.

On average, American adults watch five hours of television a day, the third most time-consuming activity in our lives — after sleep and work. And the more time adults spend in front of the television, the more likely they are to suffer from obesity, diabetes and cardiovascular disease, says Otten.



The study followed 36 adults, weighing in above the healthy range, who watched an average of five hours of television daily. After three observation weeks, half of the participants were limited to 50 percent less television for three additional weeks, using monitors that controlled their screen time. For the last week of each three-week period, participants wore activity-monitoring armbands, kept sleep logs and answered phone surveys about their diet.

The group instructed to halve their television did not change their calorie intake but burned 120 more calories a day on average, creating a trend of negative energy balance. “The energy burned is equivalent to walking more than a mile,” says Otten. “We don’t know if these short-term changes will translate, but the results may be similar in a longer term study and could prevent weight gain.”

The study was funded by grants from the U.S. Department of Agriculture’s Hatch Funds Act and the National Institutes of Health. — JENNIFER WELSH

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