special report

LIFE BEGINS

Inside the womb
The fetus as a patient

Genetic 411
Prenatal knowledge from a drop of mom’s blood

Marian Wright Edelman
The children’s defender

Not so fast
Caesarean births revisited

Way too high
Infant mortality in the United States

Too deeply attached
The epidemic of placenta accreta

plus

On the Rosebud Indian Reservation
Seeking hope at the end of the road
EGGS WAKE UP
A NEW TREATMENT FOR INFERTILITY?

Kazuhiro Kawamura, MD, PhD, an associate professor of obstetrics and gynecology at the St. Marianna University School of Medicine in Japan, doesn’t usually cry after performing a caesarean section. The operation itself is routine. But this birth was special. “I couldn’t sleep the night before the operation, but when I saw the healthy baby my anxiety turned to delight,” says Kawamura. “The couple and I hugged each other in tears.” Kawamura had just delivered the first baby conceived through an experimental infertility treatment developed in the Stanford laboratory of Aaron Hsueh, PhD, professor of obstetrics and gynecology. The birth was announced in September in a report in the Proceedings of the National Academy of Sciences. Kawamura led the clinical aspects of the study, with all patients receiving their treatment in Japan.

The technique, which the researchers refer to as “in vitro activation,” or IVA, requires an ovary (or a portion of an ovary) to be removed from the woman, treated and then re-implanted near one of her fallopian tubes. The woman is then treated with hormones to stimulate the growth of specialized structures in the ovaries called follicles in which eggs develop.

Twenty-seven women with a condition called primary ovarian insufficiency took part in the study. Normally they would have required an egg donor to become pregnant.

The researchers were able to collect mature eggs for in vitro fertilization from five women. One has had a healthy boy and another a miscarriage. Although the approach has not yet been tested in women with other causes of infertility, the researchers plan to investigate whether the technique can also help women with early menopause caused by cancer treatment as well as infertile women between the ages of 40 and 45.

“Women with primary ovarian insufficiency enter menopause quite early in life, before they turn 40,” says Hsueh. “Previous research has suggested that these women still have very tiny, primordial primary and secondary follicles, and that even though they are no longer having menstrual cycles they may still be treatable.”

Women are born with hundreds of thousands of primordial follicles, each containing one immature egg. Usually, only one follicle develops to maturity and releases an egg each month. About 1 percent of women of reproductive age in this country experience primary ovarian insufficiency, meaning that their ovaries don’t produce normal amounts of estrogen or release eggs regularly.

The successful birth stemmed from two treatments known to induce follicle growth. The researchers found that cutting the ovary into pieces disrupts a growth-arrest pathway called Hippo, which modulates the growth of many organs in the body. In the ovary, the Hippo pathway appears to help ensure that only a few follicles at a time are growing to better conserve a woman’s supply of eggs. Ovaries activated by cutting, or fragmenting, were then treated with a substance to modulate a second follicle-development pathway previously identified in Hsueh’s lab.

“When I first saw the data, my eyes lit up,” says Valerie Baker, MD, chief of Stanford’s division of reproductive endocrinology and infertility and the medical director of the Stanford Fertility and Reproductive Medicine Center. “These women and their partners come to me in tears. To suddenly learn at a young age that your childbearing potential is gone is very difficult. This technique could potentially help women who have lost their egg supply for any reason.” — KRISTA CONGER

WEB EXTRA More on video at http://youtu.be/6iLoaWvI_Tc
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The walls of the neonatal intensive care unit at Lucile Packard Children’s Hospital at Stanford are lined with tiny incubators.

The premature babies who lie inside, connected by tubes and wires to the most advanced medical technology, are a testament to modern medicine. Many of these babies, some born as early as 23 weeks’ gestational age, wouldn’t have survived only generations ago.

Yet for all this progress in raising the survival rate of increasingly premature babies, prematurity remains the leading cause of newborn death in the United States. One in eight babies born in the United States arrives early, a rate among the industrialized world that’s second only to Cyprus.

For nearly half the cases of premature birth, there is no clear cause. It’s a medical mystery. And although some factors are known to influence preterm birth — such as an expectant mother’s age or socioeconomic status — this knowledge has not led to a decrease in preterm births in this country. In fact, the premature birth rate in the United States has risen by 36 percent over the past 25 years. The babies in those tiny incubators, then, are also a testament to the limitations of modern medicine.

In 2011, with generous support from the March of Dimes, the Stanford University School of Medicine and Packard Children’s established the world’s largest multidisciplinary research center to study the causes of preterm birth, to move beyond the limitations of modern medicine.

At the March of Dimes Prematurity Research Center at Stanford, over 130 researchers from diverse fields in the life sciences, physical sciences and social sciences are searching for answers to the prematurity riddle. They are studying the interactive biologic and environmental factors that cannot be understood with singular studies from isolated disciplines. Among the initial Stanford research projects:

- Pediatrician/bioinformaticist Atul Butte, MD, PhD, is taking a “big data” approach, analyzing databases to identify genes and environmental factors that interact to raise the risk for premature birth.
- Richard Mahoney, PhD, director of robotics at SRI International, is using pattern-recognition software to pinpoint geographic regions at high risk for premature birth.
- Stanford microbiologist David Relman, MD, is exploring how disturbances in the balance of microbes in a pregnant woman’s body can lead to premature birth.

Here at Stanford, it is the limitations that motivate us. We are attracted to the most difficult and intractable problems, those that require innovative approaches where traditional methods have failed. This issue of Stanford Medicine magazine, produced with the support of Packard Children’s, explores how far modern medicine has come in advancing maternal and pediatric care, how far we have to go, and some of the ways we at Stanford Medicine are collaborating and innovating our way to better health for the youngest among us.

Sincerely,
Lloyd Minor, MD
Carl and Elizabeth Naumann Dean of the School of Medicine
Professor of Otolaryngology-Head & Neck Surgery
New Alzheimer’s suspect

THE PHARMACEUTICAL INDUSTRY has spent billions of dollars on futile clinical trials directed at treating Alzheimer’s disease by ridding brains of a substance called amyloid plaque. But new findings by School of Medicine researchers have identified another mechanism, involving an entirely different substance, that may lie at the root not only of Alzheimer’s but of many other neurodegenerative disorders — and, perhaps, even the more subtle decline that accompanies normal aging.

Ben Barres, MD, PhD, professor and chair of neurobiology, is the senior author of a study, published in the Journal of Neuroscience, revealing that a protein called C1q steadily accumulates in healthy brains of aging mice and people, possibly predisposing them to disorders including Alzheimer’s and Parkinson’s.

“No other protein has ever been shown to increase nearly so profoundly with normal brain aging,” says Barres. Examinations of mouse and human brain tissue showed as much as a 300-fold buildup of C1q with advancing age.

He found C1q deposits heavily concentrated at synapses, which are the contact points connecting nerve cells in the brain to one another. These deposits don’t necessarily cause much damage themselves, says Barres, but they may render synapses more prone to destruction by immune cells triggered by a brain injury, infection or other shock.

“The first regions of the brain to show a dramatic increase in C1q are places like the hippocampus and substantia nigra, the precise brain regions most vulnerable to neurodegenerative diseases like Alzheimer’s and Parkinson’s disease, respectively,” says Barres. — BRUCE GOLDMAN

Report card

MOST OF THE STUDENTS who chose to have their genome tested as part of a groundbreaking Stanford course on personalized medicine reported being pleased with their decision, according to a study by researchers at the School of Medicine.

While the sample size was small — 23 students in the class sent their saliva to a commercial genetics testing company; eight did not — 83 percent of those who chose to undergo testing said they were glad they did. Seventy percent said they had a better understanding of genetics as a result of having their own genomes tested.

The course, created in 2010, was one of the first in the country to give students the choice of personal genotyping as part of the curriculum. The study was published in PLOS ONE.

— TRACIE WHITE
Ear whacks

LONG-TERM HEARING LOSS from loud explosions, such as blasts from roadside bombs, may not be as irreversible as previously thought, according to a new study by researchers at the School of Medicine.

Using a mouse model, the study found that loud blasts actually cause hair-cell and nerve-cell damage, rather than structural damage, to the cochlea, which is the auditory portion of the inner ear. This could be good news for the millions of soldiers and civilians who, after surviving these often devastating bombs, suffer long-term hearing damage.

“It means we could potentially try to reduce this damage,” says John Oghalai, associate professor of otolaryngology and senior author of the study, published in PLOS ONE.

If the cochlea, an extremely delicate structure, had been ripped apart by a large blast, as earlier studies have asserted, the damage would be irreversible. “The most common issue we see veterans for is hearing loss,” says Oghalai.

The increasingly common use of improvised explosive devices around the world provided the impetus for the new study. Among veterans with service-connected disabilities, tinnitus — a constant ringing in the ears — is the most prevalent condition. Hearing loss is the second-most-prevalent condition. But the results of the study would prove true for anyone who is exposed to loud blasts from other sources, such as jet engines, car air bags or gunfire. — TRACIE WHITE

Stemmed cells

STANFORD RESEARCHER IRVING WEISSMAN, M.D. and his lab recently went searching for a kind of stem cell touted as an alternative to those derived from human embryos. The tiny cells, called very small embryonic-like, or VSEL, cells, were reported in 2006 as the only naturally occurring pluripotent cells in adult animals and humans. Since that time, the cells amassed some significant proponents, including the Vatican, which believes VSELs could provide all the benefits of embryonic stem cell research with none of the ethical controversy. A U.S.-based company called NeoStem plans to start a clinical trial to examine the cells’ potential to treat periodontal disease.

But there’s a problem: The cells don’t seem to exist.

Weissman published a study in Stem Cell Reports detailing efforts to identify the VSELs through a variety of procedures, including those described by the original researchers. Try as they might, his team was forced to conclude that the tiny “cells” are in fact a mixture of debris, and that the findings of pluripotency are wrong. Although some researchers disagree, it appears that these “very small embryonic-like” cells are nothing more than a cellular Bigfoot. — KRISTA CONGER

Nobel week

NOBEL LIGHTNING STRUCK TWICE this year at the medical school. On Oct. 7, Thomas Südhof, MD, professor of molecular and cellular physiology, won the 2013 Nobel Prize in Physiology or Medicine. A scant 48 hours later, Michael Levitt, PhD, professor of structural biology, won the Nobel Prize in Chemistry. Südhof shared the $1.2 million prize with James Rothman, PhD, a former Stanford professor of biochemistry, and Randy Schekman, PhD, who earned his doctorate at Stanford under the late Arthur Kornberg, MD, another laureate. Südhof and the others were awarded the prize “for their discoveries of machinery regulating vesicle traffic: a major transport system in our cells.”

Rothman is now a professor at Yale, and Schekman is a professor at UC-Berkeley.

Levitt, shared the chemistry prize with Martin Karplus, PhD, of Harvard and the University of Strasbourg in France, and Arieh Warshel, PhD, of USC, “for the development of multiscale models for complex chemical systems.” — ROSANNE SPECTOR
Rebuffing rape

IN THE SLUMS of Nairobi, Kenya, as many as one in four adolescent girls are raped each year. But a recent study shows that a short self-defense course can dramatically reduce the girls’ vulnerability to sexual assault. • “Self-defense training taught these young girls to say ‘no’ with confidence, and empowered them to escalate their own defense to a higher level, if necessary,” says senior author Neville Golden, MD, professor of pediatrics at Stanford and chief of adolescent medicine at Packard Children’s. • The study, published online in the Journal of Adolescent Health, looked at 402 girls who participated in a program developed by a Kenya-based nongovernmental organization that taught them verbal and physical self-defense techniques. The program was designed to combat a culture in which discussing sexual assault is taboo. • In the 10 months after receiving the training, more than half of these girls reported using what they had learned to fend off would-be attackers. The proportion who were raped fell from 24.6 percent in the year before training to 9.2 percent in the 10-month period after. • The self-defense classes were also cost-effective: Providing the training cost $1.75 per student, whereas immediate after-care for rape in Kenya costs $86, a figure that does not account for long-term costs such as new HIV infections or unwanted pregnancies. — ERIN DIGITALE
hello in there

SEEING THE FETUS AS A PATIENT

By Erin Digitale

ILLUSTRATION BY DANIEL HOGWITZ
As I type this sentence, someone small is kicking me. We haven’t been formally introduced, but I know him better than anyone else does. He likes human voices, chocolate and iced tea; startles when his big brother drops something on the floor; and can make his displeasure known if I try to rest my laptop on my growing belly. • This individual hasn’t been born yet. I’m 34 weeks pregnant.
• My knowledge about my family’s impending arrival — which includes his gender and key facts about his health — goes far beyond what any prior generation of pregnant women could have expected.
HE MORNING I WAS BORN, MY MOM HAD TO COUNT MY FINGERS AND TOES TO make sure there were 10 of each. In contrast, I’ve already counted the four chambers of my son’s heart. Pregnancy is a black box no longer. • The gestational process is yielding its secrets thanks to a revolution in prenatal care. Starting in the early 20th century, obstetricians honed a low-tech routine for prenatal visits that averts many common problems of pregnancy: They provided nutrition counseling, tracked the size of the mother’s abdomen, measured blood pressure and performed simple urine tests, for instance. Since the 1970s, that foundation has been bolstered by a series of technologic innovations that continue today, giving expectant couples and their physicians a wide array of ways to see inside the womb, detect fetal abnormalities and pregnancy complications, and act on these findings to care for both mom and baby.

“What is most dramatically changing is that we have an increasing view of the fetus as a patient,” says Yasser El-Sayed, MD, director of maternal-fetal medicine and obstetrics at Stanford University, obstetrician-in-chief at Lucile Packard Children’s Hospital, and co-director of the Johnson Center for Pregnancy and Newborn Services at Packard.

Obstetricians have always wanted the ability to diagnose and treat the fetus, but in the past they lacked the necessary tools, says El-Sayed, also a professor of obstetrics and gynecology at the School of Medicine, and an obstetrician for nearly 20 years. Today, he helps lead a world-class, multidisciplinary team at Stanford and Packard Children’s that is greatly expanding the power of prenatal and maternal-fetal care.

The change has benefited both expectant mothers like me whose prenatal care turns up no warning signs and the smaller number who find out they have an extreme need for medical help.

We’ve now learned how a variety of fetal problems typically develop, says Richard Barth, MD, radiologist-in-chief at Packard Children’s and a professor of radiology at the School of Medicine. Barth’s team often uses MRI scans to provide families with detailed information about fetal abnormalities initially diagnosed by ultrasound. “We can counsel the parents about the likely outcomes and management options,” he says. “Families can be much better informed prior to delivery.”

Good prenatal care has societal benefits as well, says Maurice Druzin, MD, professor of obstetrics and gynecology at the School of Medicine, and the director of the residency program. Druzin serves on the State of California’s Pregnancy-Associated Mortality Review, which reviews deaths among pregnant women or those who have recently delivered in California. Such deaths, though fortunately rare, represent the tip of the iceberg of medical complications in pregnancy, the panel has found. And fragmented or absent prenatal care is, sadly, a common contributor both to such complications and to potentially preventable maternal deaths.

“Women with low socioeconomic status and limited resources suffer the most,” Druzin says. “They may not have access to prenatal care because they lack insurance. They come in with complications of pregnancy that were preventable or avoidable.”

As of 2009, about 6 percent of pregnant women in the United States received either late prenatal care — starting after week 28 of the 40-week gestational period — or none at all. Very young mothers are least likely to be cared for during pregnancy: In 2010, 22 percent of expectant mothers under age 15 had late or no prenatal care, a figure that dropped to 10 percent for 15- to 19-year-olds and to 4 percent for women in their 30s.

The Healthy People 2020 initiative aims to lower these figures, at least in part by helping women find the prenatal care they’re entitled to receive. Low-income U.S. women can obtain prenatal care through Medicaid, which pays for 40 percent of births in the United States. It provides care during pregnancy and delivery, and for 60 days postpartum. In many states, women qualify if their families’ earnings are below 185 percent of the federal poverty line, though the threshold varies; the California cutoff is 200 percent. Once the Affordable Care Act takes effect next year, women with incomes below 400 percent of the poverty line will be eligible for financial assistance in purchasing insurance on state-run exchanges, and insurers will no longer be able to classify pregnancy as a pre-existing condition to deny coverage to pregnant women.

In California, women can receive publicly financed prenatal care even if they lack legal immigration status; one study of this practice from UC-Irvine, published in 2000, calculated that every dollar spent on prenatal care for California’s undocumented immigrants saved $3.33 in postnatal care for newborns and $4.64 in long-term costs.

“It’s a huge burden on society to have a child born with a preventable complication, when you consider that we could have done something about it and had a productive citizen who would have required less health care,” says Druzin.
Fortunately, most U.S. women — more than 70 percent — seek prenatal care in the early weeks of pregnancy. Almost immediately, these patients have the opportunity to start learning about the fetus, getting a window into the womb that can give clues to the health of the fetus and the well-being of the pregnancy.

The first obstetric check-up for my current pregnancy was a combination of sublimely exciting (hearing the fetal heartbeat for the first time) and dully routine (filling out forms about my medical history). Like most expectant women, my basic prenatal care began with doctor visits and screening tests geared toward problems that affect large swaths of the pregnant population. At the early prenatal visits, following a decades-old pattern, obstetricians assess their patients for everything from anemia to substance abuse to infectious diseases. They collect baseline information on weight, blood pressure and other vital signs; give advice on prenatal vitamins; and evaluate the safety of medications the pregnant woman is using. If red flags turn up — a patient wants help quitting smoking, has an HIV infection or needs a flu shot, for instance — her doctor can act quickly to minimize risks for the mother and baby.

In the first and second trimesters, which encompass the first 27 weeks, a series of newer tests also help expectant parents learn about the fetus’ health. For instance, parents can be screened for genes that cause such disorders as cystic fibrosis and sickle cell disease; if both are carriers, genetic counselors can help them decide what to do next. Depending on the circumstances, a woman might use the knowledge to prepare for the child’s treatment and care, or she might decide to end her pregnancy.

Another form of testing, called “integrated screening,” combines results from two maternal blood tests that measure proteins made by the placenta with findings from an early ultrasound scan to provide a noninvasive estimate of the risk of genetic defects such as Down syndrome. The noninvasive tests lack the miscarriage risk associated with older, invasive methods such as amniocentesis and chorionic villus sampling, which require physicians to remove fluid or tissue directly from the uterus. (The trade-off is that the integrated screening results are less accurate.) “We used to offer routine amniocenteses on all moms over age 35, but those days are gone,” says El-Sayed. Instead, women now use their integrated screening results to decide if they want a definitive — but invasive — genetic test.

The latest development in fetal genetic screening represents an even bigger advance: Stanford scientists have figured out how to use fetal DNA floating through the maternal bloodstream to find certain kinds of genetic defects. These noninvasive “cell-free” fetal DNA tests are just beginning to be offered in the clinic. [See our story about cell-free fetal DNA testing, page 30.]

Another possible addition to standard prenatal care is now under investigation: prenatal treatment for cytomegalovirus, which can cause permanent hearing damage, vision loss and mental disabilities among infants infected in utero. CMV is a virus that is transmitted in body fluids such as saliva and urine, often making the rounds of preschools and day care centers. It is generally harmless in children and adults, but the 1 to 4 percent of pregnant women who first contract the virus during pregnancy can pass it to their fetuses. A small fraction of these congenitally infected babies — about 5,000 infants per year in the United States — suffer lasting disability or die as a result. Routine CMV screening has never been included in prenatal care because there hasn’t been an effective treatment. But that may be changing. Stanford is one of 14 research sites now recruiting 800 women to evaluate a new treatment method in a clinical trial sponsored by the National Institutes of Health. Women in the randomized, controlled trial who become infected with CMV during pregnancy will receive intravenous doses of an antibody that researchers hope will stop the virus from passing to the fetus. The trial runs until 2018.

“If it proves to be effective, that will be a major, populationwide change,” El-Sayed says. “We would screen all pregnant women for CMV. It would have a large public health impact.”

As the second and third trimesters progress, obstetricians check fetal well-being — listening to the fetal heart rate and measuring mom’s expanding belly, for instance — and test their patients’ blood, urine and vital signs for evidence of common obstetric complications, such as gestational dia-
tes and pre-eclampsia. This screening, though low-tech, can be lifesaving. In the early 1900s in the United States, 10 to 30 percent of women who developed eclampsia, characterized by high blood pressure and seizures, died of the condition. Today, in the industrialized world most cases are found before the condition becomes life-threatening, says Druzin.

And, of course, there’s the prenatal visit that expectant parents anticipate most eagerly: the anatomic ultrasound near the halfway point of pregnancy. The detail provided by these scans — which show every part of the baby’s body, from brain to toes — would have been unimaginable not long ago.

“When I started as a resident, we had static ultrasound; it was like an X-ray, not a moving image,” Druzin says. Then, in 1975, during Druzin’s residency, a senior obstetrician at Denver’s Rose Hospital called him in to watch one of the first real-time prenatal ultrasound scans conducted in the United States. “The image was this fuzzy, grainy thing, but we could see the heart beating and the baby moving,” Druzin says. “It was a revelation.”

Real-time ultrasound, which has been standard since the early 1980s, solved many diagnostic challenges. For the first time, if a woman had first-trimester bleeding, doctors could easily look for the fetal heartbeat and determine if the patient had miscarried. Diagnosing ectopic pregnancy, in which the embryo implants in a fallopian tube instead of the uterus, also became much simpler. “Ruptured ectopics, in which the fallopian tube bursts, used to be one of the leading causes of death in pregnancy; the patient could quickly bleed to death,” Druzin says. Early diagnoses not only saved women’s lives but also their fertility; obstetricians could give drugs to end the ectopic pregnancy without damaging the fallopian tube.

Twins could also be diagnosed consistently. Before real-time ultrasound, 25 to 50 percent of twin pregnancies were thought to be singletons until delivery. (Hearing this during my interview with Druzin, I screech in alarm. In my gigantically pregnant state, I can’t fathom the idea of getting this particular news in the delivery room.) “We would deliver the baby and then, suddenly, there was another hand or foot,” Druzin says, chuckling a little at my reaction. When I later ask radiologist Barth, who also remembers the days before real-time ultrasound, about undiagnosed twins, he says drily, “Some parents want to be surprised about the gender, but nobody wants to be surprised about the number.”

Today, the view into the womb is clearer than ever before. Two-dimensional, real-time ultrasounds are standard and powerful: On each of my two sons’ 20-week anatomic scans, my husband and I could look at the wrinkles in their developing brains, count the chambers in their hearts, see their bones and eyeballs and fingers and toes. During one scan, the technician gleefully pointed out that we could watch the baby peeing. Another time, after our car was rear-ended with me in the front passenger seat, a physician used ultrasound to show me a reassuring close-up of my placenta, still fully attached to my uterus. And at a routine checkup a few weeks ago, when my obstetrician had trouble determining the baby’s position with a manual exam, an ultrasound instantly solved the mystery — the little acrobat had folded his feet in front of his face.

Many centers, including Packard Children’s, also offer some patients three-dimensional ultrasounds, which were developed about 10 years ago. “3D scans are really helpful at showing anatomic relationships, especially for facial abnormalities,” Barth says. “For things like clefts of the lip and palate, it gives parents a much better understanding of what the abnormality looks like than 2D grayscale.”

When ultrasounds turn up fetal abnormalities, magnetic resonance imaging scans of the fetus can offer a different, and helpful, view of the problem.

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“An MRI is like having a picture of an entire room, whereas with ultrasound, you have a flashlight,” says Diego Jaramillo, MD, who is radiologist-in-chief at The Children’s Hospital of Philadelphia and professor of radiology at the University of Pennsylvania. “With ultrasound, you can reconstruct the picture of, well, this is a couch — and you can get behind it or look underneath, getting angles you couldn’t get with an MRI — but you always have a limited view. You don’t get an overall picture of the fetus, the uterus and the placenta in a single image.” A comprehensive image is especially helpful for evaluating large structural defects, such as sacrococcygeal teratoma, a large tumor that can grow from the base of the fetal spine, Jaramillo says.

MRIs also show soft tissue contrast in much finer detail than ultrasound scans. If ultrasound detects too much fluid in the brain, an MRI can show whether brain development is on track. MRI is good for looking at lesions of the lung or diaphragm, and abnormalities of the kidneys, liver or genitourinary system. A few years ago, Barth’s team used MRI to determine that a fetus with an apparent bowel obstruction actually had a genetic disease affecting fluid absorption from
the intestine; this prenatal diagnosis allowed the medical team to start taking care of the disease right after delivery and prevented weeks or months of uncertainty that often precede identifying this rare condition after birth.

The next step in fetal MRI, performing scans with stronger magnets, holds the promise of even greater discoveries. For instance, mapping the brain’s fiber tracts, a mainstream procedure for child and adult patients, will also become an option for the fetus, leading to the tantalizing possibility that certain psychiatric and brain disorders could be predicted before birth. “It’s potentially very exciting,” Barth says.

Jaramillo’s team is now leading U.S. efforts to bring the stronger magnets on board. The higher-strength scans, which use a magnetic field strength of 3 Tesla instead of 1.5 Tesla, are already standard for children and adults. The stronger magnetic field allows for faster scans and better spatial resolution, but safety concerns and technical challenges — such as the fact that amniotic fluid creates more anomalies on higher-field scans — have slowed the use of the technology for fetal patients. But newer, safer magnets and technical innovations to reduce artifacts are eliminating these obstacles, Jaramillo says. And, because MRI does not require radiation, it is inherently safer than imaging methods such as CT scanning, which is avoided in pregnancy due to the relatively high radiation dose used.

“We’ll see some major diagnostic improvement with 3T magnets,” says Barth, adding that Packard Children’s will begin 3T fetal scans within the next year. “We’ll be able to get into functional imaging, where, for example, you could stimulate the fetus with an external stimulus such as an auditory pulse and image the fetal brain to see if there’s a normal auditory response.”

One effort in that direction was Packard Children’s 2009 opening of its Center for Fetal and Maternal Health. The center has now treated more than 1,100 expectant mothers, uniting all the specialists relevant to each patient’s pregnancy, delivery and the baby’s care to make joint decisions for her case. “We have a single point of entry and we can make sure that all of the pieces of the complex puzzle are put together for families and babies,” says Packard Children’s neonatologist Susan Hintz, MD, the center’s medical director. The doctors and other team members work to develop medical plans that include everything from deciding when and where delivery should be planned, to which caregivers should be in the delivery room, to anticipating what types of follow-up care the baby will need throughout infancy and childhood. For infants with severe congenital defects to their hearts, respiratory systems or other essential organs, this includes planning lifesaving surgeries for the first hours or days after birth.

Often, says Hintz, who is also professor of pediatrics at the School of Medicine, close interaction between the different specialists brings to light that a case is much more complicated than any one sub-group of people might have realized. “We’ve really come to a recognition that for the patients and families, the whole team is much more important together than the sum of the individual parts,” she says.

The next frontier is minimally invasive surgery on the fetus to correct certain anomalies before birth. Minimally invasive techniques, already known to speed healing, reduce infections and minimize pain for pediatric and adult patients, offer even bigger safety advantages for surgeries performed in utero. In open fetal surgeries, the large incision made in the uterus to access the fetus often triggers labor. “That’s the Achilles heel of open procedures,” El-Sayed says. “You may have done a surgery that benefits the fetus, but the benefit may be profoundly diluted by prematurity.” In contrast, he says, in minimally invasive procedures, which are performed through small incisions, “you carefully avoid any mass disruption of the fetal environment.”

Minimally invasive approaches also protect pregnant women from surgical complications and large uterine scars, which could endanger their future fertility. “You have to..."
If a pregnant woman rushes into a hospital with labor pains, one of the first questions she’s asked is how long she’s been pregnant. If the answer is much less than the usual nine months, then the normal course of action — wheeling the soon-to-be mother to a labor and delivery room — is set aside. Instead, doctors immediately begin giving her drugs to stop contractions that could deliver the baby too soon, then inject her with steroids that speed the development of the infant’s underdeveloped lungs. Finally, they alert the neonatal intensive care unit that there may be a premature baby on its way soon, one who needs extra attention.

“If we can delay labor by even a few days in a mom who comes in beginning preterm labor, it makes our job treating that newborn exponentially easier,” says pediatrics professor William Benitz, MD, who cares for babies in intensive care at Lucile Packard Children’s Hospital at Stanford. “Those few extra days matter so much because babies born too early are at the crux of the lamentable rate of infant mortality in the United States.”
This year in the United States, more than 25,000 babies will take their last breath after only hours, days or months of life. Twenty-five thousand tiny bodies, many hidden beneath bright lights, monitors and tangles of tubes as they die. Twenty-five thousand grieving families. This is what an infant mortality rate of six in 1,000 in a country of 4.3 million babies born per year means in real terms.

Considered from another perspective, for every six infants who die before their first birthday in this country, 994 will live. But those numbers — like flowers and cards — don’t lessen the losses. And compared with most of the developed world, the statistics aren’t something to brag about. According to a 2011 World Bank report, the United States ranks 46th when it comes to infant mortality, coming in behind the vast majority of Europe, behind Australia, New Zealand and Canada, behind Korea and Cuba. Every year twice the number of U.S. babies die on their first day alive than in all 27 European Union nations combined, although 1 million more are born there (4.3 million versus 5.3 million respectively). This is one of many disconcerting statistics in Save the Children’s State of the World’s Mothers report published this year.

It would be comforting to attribute the poor ranking to a quirk in how the deaths are calculated. After all, not all countries define birth the same way. For example, in the United States, arrivals of all living infants are counted as births, but a few European countries (the Czech Republic, France, Ireland, the Netherlands, Norway and Poland) have more restrictive definitions. For example, France and the Netherlands report live births only if the infant weighs at least 500 grams — a little more than a pound — or were born at 22 weeks’ gestation or later.

But these reporting differences cannot account for the full extent of the gap between countries, says Paul Wise, MD, a pediatrician at Packard Children’s and a health policy analyst at Stanford. “The reporting differences are a minor part of the story but not an excuse for why the U.S. has such a high mortality rate.”

Because even when researchers look only at births that meet the criteria for all European countries — 500-gram babies born at 22 weeks and later — the United States doesn’t fare any better. In 2009, Marian MacDorman, PhD, a statistician at the Centers for Disease Control and Prevention’s National Center for Health Statis-

ics drew up a new ranking list, comparing the United States with 20 European countries and excluding the deaths of all babies born before 22 weeks’ gestation. The United States still ranked below most European countries.

So the problem is real, which begs the questions: What’s going on? And what’s to be done about it?

THE ROOT CAUSE

Over most of the 20th century, infant mortality rates in the United States and other industrialized nations steadily declined thanks to improving medical knowledge and technology. Hospitals established neonatal intensive care units for infants born with health problems, women began taking folic acid supplements to decrease the occurrence of certain birth defects and pediatricians learned the best sleeping positions for babies to prevent sudden infant death syndrome. And compared with much of the world — African countries like Somalia and Mali with infant mortality rates around 10 percent and South American countries like Honduras and Ecuador with rates over 2 percent — the United States wasn’t faring poorly.

But by the end of the century, the declines had slowed, the United States lagged behind other developed countries, and it was becoming clear that a drastic socioeconomic divide existed even within the United States when it came to infant mortality. According to the CDC, African Americans had — and continue to have — almost double the rate of infant deaths as Caucasians, and babies born in Mississippi and Alabama are more than twice as likely to die in their first year of life as babies born in Massachusetts and Vermont. (The differences between states reflect, in part, differences in the racial and ethnic makeup of their populations.)

Five main causes of mortality play into the statistics for babies under a year old: birth defects, sudden infant death syndrome, maternal health complications, unintentional injuries and preterm-related causes of death. But when scientists, including Wise and MacDorman, have crunched the numbers on infant mortality, they find that one factor is the biggest difference maker between the United States and other industrialized countries: premature births.

The poor infant-survival rates in the United States are intrinsically linked to high rates of preterm births, those that occur when a woman is between 22 and 37 weeks pregnant, rather than full-term — 37 to 41 weeks. And the same socioeconomic divides seen in infant mortality rates are seen with
preterm birth rates — mothers who are African American, live in certain states or experience high levels of emotional stress during their pregnancy are more likely to give birth preterm. And although fertility treatments and teenage pregnancies both raise the risk of preterm births, neither explains the diversity in infant mortality rates — states with high infant mortality have no higher rates of either.

In fact, the analysis published in 2009 by MacDorman and her colleagues at the CDC found that if the United States had the same rate of preterm births as Sweden, our infant mortality rate would be 33 percent lower. Instead of six deaths per 1,000 births, it would be four, closer to Sweden’s rate of three per 1,000.

To save infants’ lives in this country, says David Stevenson, MD, Stanford professor of neonatal and developmental medicine, researchers must first understand the complex causes of preterm birth.

“Over the past 30 years, the rate of preterm births has remained an intractable problem,” says Stevenson. “I think that we now need to take a different kind of approach to solving it.” The approach that’s needed, he says, is one that integrates scientists from many disciplines. To understand the biology of preterm birth and the effects of stress and environmental exposures on that biology, and to develop ways that the U.S. health-care system can address the problem, clinicians can’t work alone. Instead, they need to collaborate with statisticians and mathematicians, with social scientists and ecologists.

The challenge in understanding preterm births isn’t making the link between preterm births and mortality rates; that much is already clear to anyone who has worked with premature infants. • “From a clinical standpoint, infectious diseases are going to adversely affect preterm births because these babies don’t yet have fully developed immune systems,” says Stevenson, who also directs the Johnson Center for Pregnancy and Newborn Services at Packard Children’s Hospital. “And they’re also more vulnerable to many other stressors due to their incredibly fragile bodies.”

At 22 weeks’ gestation, a fetus doesn’t yet have fully formed lungs, its nervous system and brain connections aren’t established, its senses are still maturing and its bones aren’t hardened. By 37 weeks, though, these organ systems are mature. Between these two time points, even a few extra days’ gestation can make a difference in which body systems are formed and in a baby’s likelihood of survival — there’s been found to be a 3 to 4 percent increase in survival odds per day in babies at the youngest end of that spectrum. A 2010 study led by Stanford pediatrician Henry Lee, MD, using data from the California Perinatal Quality Care Collaborative on more than 4,000 babies born between 22 and 25 weeks’ gestation found that mortality could be predicted by birth weight, sex and whether the baby was part of a set of twins or triplets. (Heavier babies and females have better survival rates; twins and triplets have worse rates.)

In the United States, almost one in eight babies is born between 22 and 37 weeks’ gestation. That’s nearly the highest rate in the industrialized world — second only to Cyprus. The U.S. prematurity rate is double that of Finland, Japan, Norway and Sweden, according to the 2013 report by Save the Children.

At any given gestational age, doctors in the United States are as good as doctors in other developed countries at keeping babies alive.

“If you look at a baby born at 25 weeks in the United States and any other developed country, we do really well,” says neonatologist Philip Sunshine, MD, who has cared for more than 30,000 premature babies during his career at Stanford and Packard Children’s. “We have the technology and we have the resources.”

Some causes and risk factors for preterm births are well-established: smoking cigarettes or drinking during pregnancy, infections, high blood pressure or diabetes. But even when studies take these risk factors into account, there are still unexplained differences in infant mortality between different populations. Women on Medicaid, for example, are more likely to deliver preterm, as are women in lower income brackets. And single women, those who induce labor, as well as women with a husband deployed with the military, are more likely to have a preterm baby.

In 2011, the March of Dimes, a nonprofit focused on improving maternal and child health, turned to Stanford researchers to help decrease the rate of preterm births in the United States. The organization promised $20 million — $2 million a year for 10 years — to create the March of Dimes Prematurity Research Center at Stanford University School of Medicine. The center, led by Stevenson; Wise; pediatrics researcher Gary Shaw, PhD; and Maurice Druzin, MD, a gynecologist and obstetrician, aims to bring together scientists...
A CONVERSATION WITH MARIAN WRIGHT EDELMAN

the children’s defender

Her name is synonymous with child advocacy. No one in the nation is more celebrated for being a champion for children than Marian Wright Edelman. Forty years ago, she founded the Children’s Defense Fund. Since then she and the organization have been at the forefront of overhauling public policy in child poverty, early childhood development, education and health. They’ve pushed to protect poor and minority children and those with special needs. They’ve worked to prevent gun deaths among children and teens for over two decades. Edelman calls the culture of violence in America “an obscenity.”

Her stature in the public policy arena is unparalleled. A graduate of Spelman College and Yale Law School, she was the first black woman admitted to the Mississippi Bar. Her awards and honors include the Albert Schweitzer Humanitarian Prize, a MacArthur “genius award” Fellowship, the Presidential Medal of Freedom, the Robert F. Kennedy Lifetime Achievement Award and more than 100 honorary degrees.

Paul Costello, Stanford Medicine’s executive editor, spoke with Edelman about the state of America’s children. She began the interview with a rapid roll of data detailing a state of peril for children. At the end, Costello asked her to describe the world she would conjure if she were to rewrite the iconic John Lennon song Imagine. Read on to see what she believes belongs in a museum.

Costello: Last spring in a commencement speech, you said that nowhere is the paralysis of public and private conscience more evident than in the neglect and abandonment of millions of our children whose futures will determine our nation’s ability to compete and lead in the new era. I found that to be a very provocative statement.

Edelman: Well, we have 7.9 million children in extreme poverty. Every 47 seconds, we stand by as children are abused and neglected. Every 82 seconds, a child is born to a teen mother. We could fill up the city of Atlanta with the children who are having children. While we’ve made some progress on health coverage, every 72 seconds a child is born without health insurance. And the figure that worries me the most is every three hours and 15 minutes a child or teen is killed by a gun.
We have lost more children to guns in the last 50 years than we have lost in American battle casualties in Vietnam, Afghanistan and Iraq. That’s disgraceful, and we’ve got to stop.

**Costello:** How do you reconcile all of the facts and figures you’ve just enunciated and remain optimistic about the future for kids? **Edelman:** The fact is, over the last 40 years I thought we’d be out of business by now, because I thought if we told people that here’s the right thing to do for children, and here’s the cost-effective things for us to do as taxpayers that they would do the right thing. They haven’t. On the other hand, I remain optimistic because I’ve seen change. I mean, when we started doing child gun-violence reports 22 years ago, there were 16 children dying every day from gunfire. Today, it’s seven and three-quarters. That’s still an obscenity, but it’s more than halved.

**Costello:** Nearly half of the states are opting out of Medicaid expansion under the Affordable Care Act. These states are, essentially, walking away from billions of dollars, and walking away from expanding health care to the poor. The impact for children’s health? **Edelman:** It’s a dumb investment policy. These Medicaid expansion refusals are a real disservice to the people of those states. It’s going to cost them more and is going to spill over into many other things. This is an education issue, not just a health issue. Children who can’t see or hear the teacher are not going to learn well. Children whose attention-deficit disorders are not diagnosed are not going to do well. It is very unfortunate, and we need to be monitoring and raising a ruckus.

**Costello:** There are some who believe that philanthropy can fill in the gap left by cuts in government social programs. **Edelman:** There’s not enough charitable dollars that can make up for the food stamp cuts and the cuts in other nutrition programs. Charity will not educate all those children who were cut from classrooms in the summers and, during the school year, the teachers that are lost. In a fair system, there needs to be just provision for those who cannot make it for themselves, and there ought to be just opportunities to work: just opportunities for every child to be able to come onto this Earth with a level playing field and succeed according to their abilities. We don’t have that.

**Costello:** One in three black and one in six Latino boys born in 2001 is going to end up in prison in their lifetimes. You describe this as the cradle-to-prison pipeline of mass incarceration, as America’s new apartheid. Those are jarring words. **Edelman:** The combination of poverty, race and illiteracy is overwhelming. Many of them are being shuttled off into the prison pipeline. This is exacerbated by school discipline policies that now are applied disproportionately against children of color — particularly on the black and Latino males.

They’re criminalizing our schools. They’re criminalizing children at younger and younger ages. I never thought I’d see the day when we’d be arresting and expelling 5-year-olds and 6-year-olds, and handcuffing them, and sending them off to the juvenile justice system for things that used to be handled in the principal’s office.

**Costello:** What worries you about pop culture today? **Edelman:** Its triviality, its mindlessness. I think we really threw out the spiritual baby in the bathwater of American materialism. The question is, how do we find a way of redefining the measure of what we mean by success in America, because I think we’ve gone astray. Our children are lost. I may be old-fashioned but certain enduring values don’t change: the basic concept of justice, the basic concept of mutual respect. As we celebrate the 50th anniversary of Dr. King’s “I Have a Dream” speech, I hope we will pay attention to the first part about the uncashed promissory note for millions of children and people of color and people with special needs who have not been able to find total inclusion in our society.

**Costello:** Shortly after the school shootings in Newtown, Conn., in your online column you quoted David Wheeler, the father of a 6-year-old who was killed there, as saying, “This time around, I promise there will be change.” But a bipartisan effort to expand background checks on gun sales failed in the U.S. Senate last spring. What would you tell Mr. Wheeler about why his promise hasn’t been fulfilled? **Edelman:** Change is very hard in Washington, and it seldom happens on the first time or the second time. You have an incredibly powerful opposition — even if it does not reflect the professsed majority sentiment of this country. The NRA never gives up, and the gun manufacturers never give up, and they’re well-funded. But I’m not unhopeful when I look at what has happened in Connecticut and Colorado and New York State [all of which passed gun-control laws after the Newtown shootings, in December 2012]. The momentum hasn’t died. We’ve just gone back to regroup. I’m still more optimistic since Newtown than I’ve ever been. The organizing is going to continue. The parents are absolutely determined their children will not have died in vain.

**Costello:** If you would write your own lyrics to Imagine, John Lennon’s song about a better world, what would they be? **Edelman:** I’d like to imagine a world where every child is healthy, where every child is educated and has a good early start. Where every child is safe in their home, walking down their street and being who they are. That every child can dream. I did a piece for The Huffington Post on my friend Nobel Peace Prize winner Muhammad Yunus, who envisions a world where poverty would be visited in a museum and we wouldn’t see it anymore in our lives. That’s what I would imagine.

*This interview was condensed and edited by Rosanne Spector.*

**WEB EXTRA** Hear the conversation at http://stan.md/19KNxSw
Before her third son was born in 2010, Maya Adam had to face a possibility modern medicine has made almost obsolete: She could bleed to death before or during delivery. A rare defect in her placenta left both Adam and her fetus vulnerable to sudden, fatal hemorrhage. • “We made a video for our two older boys in case they needed it as their final memory,” Adam says, recalling the compilation of family photos and video that she and her husband, Lawrence Seeff, assembled for sons Kiran, then 5, and Misha, then 2, near the end of her pregnancy. The family lives in Menlo Park, Calif., where Seeff invests in startup companies and Adam, a physician by training, teaches child health and nutrition at Stanford. Months earlier, when they decided to have a third child, Adam and Seeff never considered that Kiran and Misha might be left without a mother. “We had plenty of love and resources to give,” Adam says. “You just don’t think that you’re playing roulette with the stability of the older children’s lives.” • Adam’s situation, unusual as it is, reflects a growing problem in obstetric medicine. She had placenta accreta, in which the placenta, the organ that connects the pregnant woman to her fetus,

By Erin Digitale

PHOTOGRAPHY BY LESLIE WILLIAMSON

MAYA ADAM AND MILAN AT HOME

When they decided to have a third child, Adam and her husband never considered that the older boys might be left without a mother.
attaches with dangerous tenacity to the uterus. Sometimes — as in Adam’s case — it grows through the uterine wall and invades other organs. Once vanishingly rare, with only one in 30,000 pregnancies affected in the 1950s, placenta accreta now hits around one in 500 pregnancies. Up to 7 percent of placenta accreta patients die of the disease. Scientists have linked the increase in cases to rising caesarean rates, but the exact mechanism of the disease — a conversation gone awry between the placenta and the uterus — remains profoundly mysterious.

Treatment is daunting: Doctors often must remove the entwined placenta and uterus immediately after delivery, a procedure that is both technically challenging for surgeons and potentially devastating for women who want other children. Such a surgery, a combined caesarean-hysterectomy, is difficult because the interior of the pelvis looks different just after birth than it usually does — the enlarged uterus has pushed other tissues out of their typical locations. Add to that a welter of blood vessels growing from the abnormal placenta, and the result is that, in spite of recent advances in the technology used to diagnose placenta accreta, the surgery remains unpredictable and challenging.

“Even though we have better imaging than we’ve ever had before, it’s still difficult to assess how bad the actual bleeding will be,” says Edward Riley, MD, professor of anesthesia at the School of Medicine. Before delivery, surgeons treating a placenta accreta patient typically have a sense of where the abnormal blood vessels are located, says Riley, who is also the Packard Children’s obstetric anesthesiologist who cared for Adam during her delivery. “But it’s really hard to know, will they just peel off nicely or cause real problems?” he says.

“It can be very scary,” says high-risk obstetrician Deirdre Lyell, MD, who is the medical director of the Program for Placental Disorders within the Division of Maternal-Fetal Medicine at Lucile Packard Children’s Hospital, which now treats 15 to 20 placenta accreta patients per year. Lyell, who is also an associate professor of obstetrics and gynecology at the School of Medicine, and her colleagues are among a handful of researchers tackling the disease nationwide. “Women with accreta can bleed very quickly.”

Why does it happen?

“THE PLACENTAL TISSUE IS KIND OF REMARKABLE. IT BEHAVES LIKE CANCER, invading into the uterus,” says placenta accreta researcher Robert Silver, MD, professor of obstetrics and gynecology at the University of Utah. He’s describing the normal process by which a pregnancy takes hold, beginning when the new embryo implants in the uterus and the placenta begins to form about a week after the egg is fertilized. “Then there’s a signal — we don’t know what it is — that puts a brake on and stops the invasion,” says Silver.

The placenta is supposed to attach only to the uterine lining, a temporary layer, distinct from the uterine muscle, that is shed at delivery. If the placenta grows into the muscle, it sticks. Small adhesions — what scientists call “focal accretas” — may cause chunks of placenta to stay in the uterus after delivery, increasing a woman’s risk for postpartum infection or hemorrhage. In more serious cases of accreta, the whole placenta adheres to the uterine...
muscle and invades deeply into the uterine wall (“placenta increta”) or grows completely through the wall (“placenta percreta”).

Scientists aren’t sure if the problem originates from a too-invasive placenta or a defect in the ability of the uterus to stop it. As Lyell puts it, “Is the placenta or the uterus driving?”

Her team is part of a multi-institution effort to look for clues. Researchers at Stanford Medicine, Columbia and the University of Utah are creating a tissue bank of normal and adhesive placenta samples, which Stanford’s Julie Baker, PhD, an associate professor of genetics, is testing for genetic or molecular signatures of abnormal invasiveness. Early results from other research suggest overly invasive placentas over-produce growth factors and signals associated with formation of new blood vessels, and make too little of certain proteins that act in other situations to curb the growth of cancers. Such findings hint that the placenta partly drives excess invasion.

But epidemiologic data about placenta accreta patients imply that the uterus also plays a role. Accreta risk increases if a woman has uterine scarring, such as that left by caesarean sections, surgeries to remove uterine fibroids, or dilation and curettage (D&C) procedures used to empty the uterus after a miscarriage. If the placenta attaches to a scar, where the uterine lining may already be defective, it’s a recipe for trouble. The risk of developing placenta accreta is 0.3 percent for women with one prior C-section, for instance; it rises to 2.4 percent for those with three prior caesareans.

The position of the placenta is even more important: Lower in the uterus, where the uterine lining is less robust, the placenta is more likely to stick. And if the placenta implants across the exit from the uterus — a condition called complete or central placenta previa — the woman’s risk of developing placenta accreta rises enormously. Five percent of women with placenta previa and no uterine scars get placenta accreta. Women who have placenta previa and have had one prior caesarean have an 11 to 25 percent risk of developing placenta accreta, while those with placenta previa and two prior C-sections have a 40 percent risk of developing placenta accreta. Patients who had both placenta previa and a history of three prior C-sections, face an accreta risk of as much as 60 percent. Physicians have also noted that, in rare cases, women with no obvious risk factors can get placenta accreta, too.

Beyond understanding how an overly adhesive placenta forms, researchers also want to know if the condition could be prevented. “Maybe something as simple as a change in C-section technique could reduce the risk,” Silver says.

**Before the birth**

While physician-scientists conduct research to understand the science of placenta accreta, they are also making strides to help patients. Early, accurate diagnoses are enabling tightly planned care.

Often, as in Adam’s case, the condition shows up on a routine prenatal ultrasound. After the diagnosis, says Seeff, “we were doing what everyone said we shouldn’t do, which was to look online and see how dangerous it was and what to expect. It was quite frightening just reading some of the experiences.” For her part, Adam’s medical training helped to reassure her that her doctors knew how to manage her situation. Even so, she says, “I’m glad I’m not a specialist in that area; I would not have wanted to know exactly how bad things could get.”

Physicians begin to get a sense of how bad things are from their first ultrasound views of the affected placenta. An abnormally adherent placenta has “a Swiss-cheese-like appearance,” Lyell says. Her team has specialized tools, such as a near-field ultrasound probe for visualizing placental tissue, to gather as much diagnostic information as possible. A thin muscle wall or poor borders between the placenta and uterine muscle are other telltale signs. If the placenta invades nearby organs, the doctor may also see blood vessels at odd angles around another organ, such as the bladder. “It’s very disconcerting,” Lyell says.

After Adam was diagnosed at 20 weeks’ gestation, her obstetrician, Christie Coleman, MD, of the Palo Alto Medical Foundation, prescribed bed rest beginning at 30 weeks. Adam’s placenta extended across the uterine opening and down into her cervix, sending blood vessels into the muscles that kept her uterus closed. This was a hazardous situation because the lower portion of the uterus expands so much in late pregnancy. The growth could shear a major placental blood vessel, causing both the mother and fetus to quickly bleed to death. “If I had any bleeding, I was supposed to get to the ER as quickly as possible,” Adam says.

It’s risks like this that cause some women with severe cases...
of placenta accreta to end their pregnancies. “I have one patient who recently terminated her pregnancy at 11 weeks because the placenta had implanted all the way through her C-section scar,” says Daniela Carusi, MD, assistant professor of obstetrics, gynecology and reproductive biology at Harvard Medical School. Such an early, extreme placental defect can rupture the uterus during pregnancy. “This patient said, ‘I just don’t want to die,’” says Carusi, who is also director of the Program for Surgical Obstetrics at Brigham and Women's Hospital in Boston. “She had a little boy at home, and wanted to keep herself healthy and her family intact.” Many patients in this situation have subsequent normal pregnancies, Carusi adds.

Adam and Seeff wanted to continue her pregnancy. “When the condition was first diagnosed, we didn’t imagine that our case would become so life-threatening. It was only later, during the third-trimester imaging, that the results suggested that ours could be a much more serious case,” Adam says. And bed rest was extremely challenging. In addition to their worries about her health, and the fact that they had two young children to care for, Adam had a new job at Stanford as a lecturer in human biology. (“I had to tell Stanford, ‘I can’t teach spring quarter,’ and that was the hardest thing I had ever done,” she says.) And she’s not one to sit still, even while pregnant — during her prior pregnancies, she was in medical school and worked until delivery. But nor is she easily daunted. (In the spring of 2013, she developed and taught an online Stanford course on child nutrition and cooking. More than 22,000 people signed up.) To stay sane through the long weeks of inactivity, she kept a blog. “We were holding our breath to see how long we could keep the fetus inside,” Adam says. She made it to 37 weeks’ gestation; at that point, her medical team called for a scheduled C-section to avoid risking the possibility that she would go into labor.

Coleman planned for a complicated delivery, warning Adam that a hysterectomy would probably be necessary, and enlisting both Riley, an experienced Packard Children’s obstetric anesthesiologist, and a gynecologic oncologist to assist. In some cases, specialists from other disciplines also participate in placenta accreta surgeries, including vascular surgeons, who operate on blood vessels, and interventional radiologists, who help block off blood vessels to prevent hemorrhaging.

On June 16, 2010, before Adam was wheeled into one of the main operating rooms at Stanford Hospital “they put hoses, basically, in my arms in preparation for giving large amounts of blood fast,” Adam remembers. As Seeff stood near her head, the surgeons delivered baby Milan with an incision made high on Adam’s uterus to avoid her placenta. While the couple got their first glimpse of the new baby, the doctors got their first in-person view of the entwined placenta and uterus.

“The desire to preserve the uterus and preserve fertility is terrific,” says Utah’s Silver. “It deserves research.” Some teams, particularly in Europe, leave either the entire placenta...
or adherent portions in place after delivery in the hope that they will later detach, Silver notes, or they take active steps to help the retained placenta disengage, such as blocking blood vessels to retained segments, using radiofrequency ablation to destroy the retained placenta, or giving the chemotherapy drug methotrexate to destroy its blood supply. All of these approaches, however, require waiting days or weeks for the placenta to disintegrate and be reabsorbed.

After trying about 10 cases with such approaches, Silver is wary: “In several of those cases the patients had major complications with bleeding or infection and ultimately required hysterectomy. I’m not very enthusiastic about it other than in very experimental circumstances.”

But Boston’s Carusi, recalling a case she saw during her training that inspired her to study placenta accreta, cautions against a too-aggressive approach to removing a placenta that sticks unexpectedly. “From that case years ago, the lesson for me was ‘Respect the placenta,’” she says. “If it won’t come out, don’t fight it. You can end up doing a hysterectomy in someone who didn’t want one, or having a severe hemorrhage to control.”

For now, says Lyell, Packard Children’s placental disorders team avoids leaving pieces of the placenta behind inside the uterus. Before resorting to a hysterectomy, they sometimes try a combination of drugs that contract the uterus and a D&C procedure to try to remove pieces of placenta that are reluctant to detach. But they are also closely watching research from groups attempting alternate methods that involve leaving pieces of the placenta in place for longer periods.

Meanwhile, the Packard Children’s team is taking a new approach for another category of difficult cases. They’re staging post-delivery surgery over two days — a technique borrowed from trauma surgeons treating combat wounds in Iraq — for some patients whose placentas have grown through the uterus to invade other organs. In these cases, even a hysterectomy isn’t enough to get rid of the net of placental blood vessels, so the Packard Children’s team, in conjunction with David Spain, MD, the chief of trauma and surgical critical care at Packard Children’s and a professor of surgery at the School of Medicine, decided to try something different.

“When patients have bled so heavily and received so much blood that they’ve become unstable, there comes a point at which you can’t keep trying to get the placenta out,” Lyell says. Transfusing large amounts of blood can cause coagulopathy, in which the signals that trigger blood clotting stop working. When this happens, instead of continuing surgery, the team clamps everything that is bleeding, transfers the patient to the intensive care unit overnight and resumes surgery the next day. In the interim, the hormonal and vascular shifts that normally follow childbirth can occur, the patient is monitored closely and transfused as needed, and coagulopathy resolves. “When we’ve gone back the next day, it’s a completely different surgery,” Lyell says. “It’s a lifesaving move.”

For Adam, such extreme measures were fortunately unnecessary. But her surgery was far from simple. Coleman was glad for the assistance of Palo Alto Medical Foundation gynecologic oncologist Alfred Pisani, MD, who is an expert at distinguishing normal from abnormal pelvic tissues. As Coleman and Pisani operated, they knew that getting the placental blood vessels out would cause unavoidable bleeding, so they warned obstetric anesthesiologist Riley to be ready to transfuse blood each time they approached a vessel that looked difficult to remove. “We did get into really tremendous hemorrhaging, with her blood pressure going down quickly and her heart rate up,” Riley recalls. In each instance, with meticulous teamwork between the doctors, nurses and the blood bank, the team was soon able to bring Adam’s vital signs back under control.

During her two-hour operation, as Seeff went back and forth between the nursery where baby Milan was being cared for and the spot outside the operating room where Adam’s parents and sister also waited, he grew increasingly concerned about his wife. “It was very unnerving; the longer it kept going, the more worried we became,” he says. “But we were lucky that we were at a very sophisticated...
labor day
THE C-SECTION COMES UNDER REVIEW
By Julie Greicius

PREGNANT WOMEN KNOW A THING OR TWO ABOUT CURVES. But, beyond the unmistakable silhouette of a mother-to-be, the curve that may have defined modern childbirth more than any other is on a graph developed in the 1950s by an American physician named Emmanuel Friedman, MD. Today, scientists have challenged Friedman’s curve, which charts the progress of what was considered normal labor.

A convincing body of evidence shows that labor for American women is different today than it was in the 1950s, says Yasser El-Sayed, MD, obstetrician-in-chief at Lucile Packard Children’s Hospital. That’s because women themselves, along with advances in pain management, medical technology and monitoring during labor, have changed. Today, labor generally takes longer because the period of rapid cervical change, which Friedman called the “active” phase, starts later than it did for women in the 1950s.

An understanding of what makes labor normal is, of course, necessary for understanding what makes it abnormal. Obstetricians have traditionally used Friedman’s labor curve to help decide if it’s time to intervene, either with a caesarean section — the surgical delivery of the baby through the lower abdomen — or with operative vaginal delivery — using a grasping tool such as forceps to help. But C-sections, performed more often today than ever before, present their own risks, including predisposing women to disorders in future pregnancies. So, one major benefit of the new “normal” could be fewer C-sections, making childbirth safer for both mother and baby.

The new understanding is that, instead of a single definition of normal, there are several variations, all of which allow a woman to remain in the early (latent) phase of labor for two, three or even four hours longer than in decades past, before labor is considered abnormal. This is
especially important for first-time mothers, who tend to labor longer than in subsequent pregnancies.

While the new research and labor curve catches up with the modern woman, there’s no question that Friedman’s study laid the groundwork for a common understanding of the progress of labor and the beginning of safe labor practices. In 1955, Friedman completed a real-time study of 500 Caucasian women giving birth, which he used to establish the progress of what would be for decades considered normal labor, segmenting it into stages, which were themselves broken into phases. He graphed the progress as a curve showing the opening, or dilation, of the cervix in relation to time. His curve, charted with time as the horizontal axis and dilation as the vertical, shows a line rising gradually until it reaches a cervical dilation of 4 centimeters, then steeply, as the cervix opens from 4 centimeters to 10 centimeters.

According to Friedman, a healthy, first-time mother should reach the active phase of the first stage of labor — when the cervix begins to open more rapidly and contractions increase and intensify — when her cervix has dilated 4 centimeters. Friedman expected the second stage of labor — beginning when her cervix is fully dilated (10 centimeters), and she starts to push the baby out — to take two hours. After two hours, if labor was not progressing — meaning the baby was not descending through the birth canal — Friedman advocated intervention with forceps or C-section.

Friedman gave doctors a standard for the outer limits of safety, which, over the years, became one of the primary justifications for medically necessary interventions. Other factors, like the baby’s heart rate, weight and position and the health of the mother, were also critical considerations.

Since then, the U.S. C-section rate has climbed, in part because the increasing safety of the surgery itself made it an appealing alternative when a difficult vaginal birth was anticipated. This expectation of safety and an uncomplicated delivery bred a threatening legal climate with severe and costly implications for doctors accused of not performing a timely C-section. This expectation also fostered an increasingly broad range of indications for C-section. Physician and patient preference may have played a role, although to a lesser degree: The ability to schedule the birth held a strong allure. Mothers who feared risks from vaginal birth — such as urinary incontinence — might choose an elective C-section. For doctors and pregnant women, C-section seemed a way to control risks, rather than a risk factor itself. All of these issues contributed to the U.S. C-section rate reaching an all-time high in 2009 at about 33 percent of all births, where it has held steady.

But with so many C-sections, their dangers have become easier to see. The mother’s recovery is harder, and she is more likely to face surgical risks such as infections and blood clots. Her chance of needing a C-section for later births rises dramatically. Worse, women who become pregnant following a C-section are at greater risk of placenta accreta, an abnormally deep attachment of the placenta to the wall of the uterus. [See story, page 18.] In many cases, a woman with placenta accreta must undergo hysterectomy — complete removal of her uterus — to avoid the risk of bleeding to death when the placenta is separated from her uterus.

“Placenta accreta has become a national epidemic,” says obstetrician-in-chief El-Sayed, who’s also a professor of obstetrics and gynecology at the Stanford University School of Medicine. “During my four-year residency in the early 1990s, I saw a handful of cases. We’re now treating two a month. And this is happening all over the country.”

**NEW LABOR DATA**

With their study of labor published in 1986, David Peisner, MD, and Mortimer Rosen, MD, of Cleveland Metropolitan General Hospital, concluded that labor generally progressed more slowly than Friedman had found. Their results, based on data from twice as many women as Friedman had studied, showed that only 50 percent of labors were active by 4 centimeters of cervical dilation. They wrote, “A patient who is not progressing in labor at 4 centimeters cervical dilation is not necessarily abnormal.”

Time would show that such patients were, in fact, the new normal. In 2010 the National Institute of Child Health and Human Development’s Consortium on Safe Labor, led by Jun Zhang, MD, PhD, looked back at the medical records of 62,415 first-time mothers to assess the labor patterns of women with a healthy, full-term delivery. They found the patterns at the turn of the millennium were very different from their mid-century cohorts. Most women in Zhang’s study weren’t transitioning to the active stage of labor until their cervix was dilated to 6 centimeters. What’s more, it was possible for at least two hours to pass in the active phase without much additional dilation.

What did this mean for the C-section rate? The consortium published a separate paper in 2010 based on 228,668 detailed labor and delivery records from 19 hospitals across the United States between 2002 and 2008. This study focused on the first delivery for each of the women, 30.5 percent of whom delivered by C-section. They found that 65 percent of C-sections performed due to “abnormal” labor
On any given Friday, shortly after dawn, one or two dozen doctors and nurses gather in a darkened room on the first floor of Lucile Packard Children’s Hospital at Stanford. Over the course of an hour, a monitor at the front of the room displays the radiological scans of six or seven patients. Some have ill-developed bones; others have misplaced internal organs or malformed hearts. For each, the doctors and nurses — specialists across many disciplines — discuss the chances of survival and a plan of care, yet it will be weeks or months before any of these patients will even be born.

It’s clear that advances in fetal imaging techniques have increased the discovery of abnormalities before birth, allowing care teams to prepare for the mother’s and baby’s needs before, dur-
ing and after delivery. For many pre-natal diagnoses, the ability to address problems — either in utero or after delivery — has also made great strides. “But ensuring good outcomes from these advances depends on input from a diverse team of care providers and their tight coordination,” says Susan Hintz, MD, medical director of the Center for Fetal and Maternal Health at Packard Children’s, and a professor of neonatology at Stanford.

On a Friday in December 2011, attention in that darkened room at Packard Children’s focused on the image of a tiny pulsing heart — the heart beating inside Colleen Doria’s developing child. Colleen, 24 weeks pregnant, and her husband, Michael, both first-time parents, were at their home outside New York City, awaiting the outcome of that meeting with desperate hope.

A FEW WEEKS EARLIER, Colleen’s doctors on the East Coast had given her devastating news: Her baby’s heart had a hole in the wall between the two lower chambers, and there was no pulmonary artery. The baby, who would be named Teagan, had a complex heart malformation called tetralogy of Fallot.

One of the most common congenital heart defects, tetralogy of Fallot can be surgically repaired at almost any children’s hospital. But Teagan’s case represented the most complex scenario: Most tetralogy of Fallot patients have a narrowed pulmonary artery, the vessel that carries blood from the heart to the lungs; a small subset, of which Teagan was a member, lack it completely. To compensate, the fetus develops “collateral” vessels, scattered side branches that provide blood flow to the lungs. Before a child is born it’s impossible to know how many collateral arteries have developed, or how well they support lung function.

"PATIENTS LIKE TEAGAN" don’t usually die at birth, but — when the condition goes undiagnosed or untreated — about half will die by the time they are a year old, and 90 percent will die by the time they are 10,” says Frank Hanley, MD, director of the Children’s Heart Center at Packard Children’s. “Because most institutions consider the absence of a pulmonary artery an inoperable condition, seeing this condition on a fetal echocardiogram would tell them that this child is doomed to a horrible, very short life. And they would counsel parents about ending the pregnancy.”

Talking with their doctors about their child’s prognosis was one of the hardest conversations of Colleen and Michael’s lives. “They told us our baby would probably never leave the hospital,” says Colleen. “Or she’d go into hospice and pass away. They said that even if she had surgeries, she would still have poor quality of life.”

After visiting heart teams at two hospitals on the East Coast, Michael, a New York City police officer, and Colleen, a special education teacher, weighed the decision to terminate the pregnancy.

“I would never judge anyone for making that choice,” says Colleen. “It just wasn’t the choice for us.”

Colleen’s doctors warned her that searching the Internet for information about her baby’s condition was likely to be fruitless and upsetting. But she got online anyway, and found a mother’s blog describing her own baby’s diagnosis of tetralogy of Fallot with the absence of a pulmonary artery. It also described the surgery her baby had received, a procedure called “unifocalization” developed and performed by Hanley at Packard Children’s.

“It’s the most complicated operation in the field of congenital heart surgery,” says Hanley, a professor of cardiothoracic surgery at Stanford. “You have to find the collateral arteries, wherever they may be, reroute them, bring them together, and actually create a new pulmonary artery by sewing them together. We’ve done about 800 of these with excellent outcomes, so I know there’s a 98 percent chance we’re going to be able to make a difference. We’re able to counsel a family when they get the prenatal diagnosis at 20 to 24 weeks’ gestation that there is not only hope for this condition, but the prognosis can be quite good.”

Over the phone, Hanley confirmed the Doria’s baby’s diagnosis and gave them a very different picture of her future. “After hearing nothing but bad news,” recalls Colleen, “Dr. Hanley told us, ‘I feel encouraged that I would be able to help your daughter.’”
Finally, Colleen felt that her choice to continue the pregnancy was the right one. She and Michael decided she would give birth at Packard Children’s and have the baby’s heart surgery there as well.

That the Dorias had any choice at all was a wonder — and a measure of how far diagnosis and care for complex fetal conditions has come. Prenatal diagnosis of congenital heart defects like tetralogy of Fallot became available in the late 1980s. Before then — and even today, without adequate prenatal care — the baby’s condition would have been discovered only after her birth, and perhaps only when it was too late. Doctors would have rushed to learn everything they could about the newborn and only then would have assembled the medical team needed. At Packard Children’s, the crucial coordination is provided through the Center for Fetal and Maternal Health.

“You need the integration — the human integration and the technological integration. What makes the difference is the breakdown of silos between disciplines,” says Yasser El-Sayed, MD, obstetrician-in-chief at Packard Children’s and director of maternal-fetal medicine and obstetrics at Stanford. “In isolation none of these variables can do the job.”

In other words, the right people need to talk to each other starting as early as possible in a high-risk pregnancy. Because of this, Packard Children’s has made weekly fetal-care meetings standard practice. These meetings assemble physicians, surgeons, radiologists, obstetricians, neonatologists, respiratory therapists, genetic counselors, neurologists, cardiologists, nurses, social workers — literally anyone who might have expertise relevant to a patient’s needs. For complex patients like Teagan, smaller meetings among care providers happen daily.

Colleen and her baby would need careful medical management in the weeks leading up to delivery and in the months and years to follow. Hanley planned to do Teagan’s surgery three months after her birth, when risks of lung and cardiac complications were lowest. As a congenital heart disease patient, Teagan would also need follow-up care at least annually for the rest of her life. But first, ensuring the best outcome meant coordinating a thousand small details — everything from securing insurance coverage and housing during their stay, regular communication with Colleen’s doctors on the East Coast, and creating a precise list of doctors, nurses and equipment to be at the bedside ready for any number of complications at the moment of Teagan’s birth.

While Neves took care of logistics and cross-country communication, genetic counselor Meg Homeyer gathered the results of the tests Colleen had taken at a New York hospital. “If there is a genetic component that we can identify, it helps us explain to families what to expect and plan for,” says Homeyer. The Dorias were lucky: Though tetralogy of Fallot is sometimes a consequence of DiGeorge syndrome, a widely variable, sometimes debilitating genetic condition, the test showed this was not the case for Teagan.

“We think about a complex fetal anomaly not just as a fetal problem, but as an issue for immediate post-delivery care and for childhood — what is best for the fetal patient, the baby and the child later on,” says Hintz, the center’s medical director. “It’s an enormously positive thing that we’re involved in,” says Hintz. “We’re helping to plan for the future of the family.”

In March 2012, the Dorias left a fresh snowfall and flew across the country to have their baby at Packard Children’s. Admitted right away for monitoring and testing, Colleen met Neves, who walked her to her appointment at the perinatal diagnostic center and then to consult with cardiology and neonatology specialists. The next day, Hintz met with the Dorias to plan for the birth and for Teagan’s care. Hintz also gave them a tour of all the settings for the birth and treatment — from labor and delivery, to the neonatal intensive care unit and the cardiovascular intensive care unit. In her room, Colleen met with a social worker, a care coordinator, several imaging technologists, anesthesiologists, intensive care nurses, and cardiologists, and her baby’s heart surgeon, all of whom helped her prepare for what was to come. “They made it so seamless,” says Colleen. “There was nothing we had to do except walk into the hospital that day.”
Counseling, preparation and ongoing support of parents are key factors in care coordination, says Hintz, because, no matter how significant a baby’s medical need may be, the parents are the most important people in their child’s life.

Members of the Center for Fetal and Maternal Health team have multiple conversations with the parents, says Hintz. “We really try to emphasize to families that if they have questions they can ask anything they want, even if we’ve already covered it.”

“Stephanie [Neves] understood how special the situation was for us,” says Colleen. “I could finally have a conversation with someone about my baby and the tone was normal. She never spoke to us as though we should be scared. All of that stress and all of the odds and ends that we’d have to worry about — she took that away. I could be a normal mom. I thought: This is how other women must feel.”

Unexpectedly, just a few days after Colleen arrived, she began having contractions. Since the baby’s position in the uterus was breech, delivery would be by caesarean section. In the delivery room were nurses, doctors and an anesthesiologist caring for Colleen, and a team from the NICU, including a neonatologist, neonatal nurse practitioners and nurses to care for Teagan’s immediate needs. In the NICU, cardiologists, a respiratory therapist, nurse specialists and others waited for Teagan’s arrival, ready with a ventilator in case she needed oxygen.

“Dr. Hintz had told me, ‘There’s going to be a million people in the delivery room and then, all of a sudden, the baby’s going to be delivered and then there’s only going to be a few people, because most will go with her to the NICU right away,” says Colleen. “They let me choose whether to have Michael stay with me or go with the baby. I wanted him to go with her.”

Teagan didn’t need the ventilator. Although she had no pulmonary artery, her body had compensated by developing major aortopulmonary collateral arteries to supply blood to her lungs. Until she was born, there was no way to know exactly how many. Teagan, it turned out, had lots of them. The con-

‘SHE NEVER SPOKE TO US AS THOUGH WE SHOULD BE SCARED. I COULD BE A NORMAL MOM. I THOUGHT: THIS IS HOW OTHER WOMEN MUST FEEL.’ COLLEEN DORIA

cern, then, was not whether she was getting enough oxygen but whether she was getting too much.

The next morning, Colleen had recovered enough to go with her husband to visit Teagan in the NICU. She found her snuggled in an isolette with monitors tracking her heart rate, blood pressure and oxygen saturation. “She is one strong little girl,” one of the nurses told Colleen as she passed the baby into her mother’s arms for the first time.

AFTER TEAGAN SPENT TWO WEEKS in the NICU, she was able to go home for three months. Her parents had been trained to care for her until the return for her heart surgery with Hanley.

“They showed us how to give her medications and how to put in her nasogastric tube,” says Colleen. Inserted through the nose and leading to the stomach, the tube would allow the Dorias to give their daughter medications and supplemental high-calorie surgery — the standard duration of the complex procedure — Hanley gave them the happiest possible news. “He said there’s no reason she can’t live the normal life that every kid around her is going to have,” says Colleen. “She’ll play sports, go to birthday parties and school. There’s nothing she won’t be able to do.”

“It’s an exciting time,” says Hintz. “There are things we’re doing now for patients that we could not have done even a few years ago. Prenatal testing for life-threatening metabolic diseases, for example, allows us to diagnose early, pretreat intravenously during labor and delivery, and treat the baby immediately after delivery. What we’re really trying to do is get as much information as possible before the baby is born so that we can get the best teams and treatment in place for the baby.”

It worked for Teagan, now a thriving 18-month-old. “I’m not gonna lie,” says Colleen. “She’s really cute. When I take her out, her face just lights up. Last week we visited a restaurant that had a sandbox. She walked right up and waved, like she’s saying, ‘Hi everyone! I’m here!’”

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Few moments are as life-changing as the appearance of that blue line in a positive pregnancy test. But for many, after that first heart-stopping catch of breath comes a litany of questions and decisions: “Is my baby OK? How can I be sure? What should I eat, drink, do?” I well remember that anticipation — and the stress during my three pregnancies. During my last, about 10 years ago, I had the ignominy of, at the age of 35, falling into the “advanced maternal age” category. Babies of women of my age, I was reminded, are more likely to have genetic abnormalities than those born to younger women. Thankfully, even at that time a variety of tests were available to screen or diagnose affected pregnancies. I just had to choose which, if any, to undergo. Amniocentesis — accomplished by inserting a needle through my abdomen to collect amniotic fluid? Or chorionic villus sampling — also carried out with a needle in my abdomen or a catheter through my cervix to gather pieces of my placenta? These diagnostic tests would give a solid answer as to whether my baby had an abnormal number of chromosomes (the most common genetic problem seen in pregnant women of my age and the cause of Down syndrome), or carried the gene for cystic fibrosis or sickle cell anemia, for example. But neither of these procedures is risk-free: About one in a few hundred women (depending on the procedure and where it is performed) experience a miscarriage as a result. Or maybe I wanted to go with noninvasive screening methods based on blood samples and ultrasound scans. These are safer for the baby, but give answers in likelihoods, rather than yeses and nos. Currently, every pregnant woman in California is offered prenatal screening through a combination of blood tests and ultrasounds for genetic abnormalities through the California Department of Public Health. The $162 cost is often covered by insurance. If the preliminary screen
indicates an elevated risk, the woman is offered follow-up genetic counseling, ultrasounds and amniocentesis at no additional charge.

Screening was important to me: It would help me prepare if my baby were to have a severe health problem. And some women choose to abort a fetus if the child would have a serious health condition.

The stakes of my choice felt very high. Get a firm answer while risking my baby’s life? Or stick with a safer, less accurate bet? As many as 5 percent of women taking these traditional screens receive a false-positive result — resulting in weeks of unnecessary worry. I still get a little anxious thinking about it.

Things have changed. It's now possible to deduce the entire fetal genome from a single sample of a woman's blood (although this is not yet offered clinically), and new, noninvasive blood tests can identify about 99 percent of Down syndrome cases as early as 10 weeks of pregnancy. False-positive rates reported by the companies hover at around 0.1 percent for detecting Down syndrome, and false negatives for the condition appear to be even more rare. The tests can also identify several other chromosomal abnormalities that would affect a baby’s health, although with slightly less accuracy. The me of 10 years ago would have jumped at the chance for such screening.

This new type of prenatal screen, called cell-free fetal DNA testing, stands to significantly reduce the need for invasive, costly and risky diagnostic procedures. Not surprisingly, these cfDNA tests have become hugely popular since they were introduced two years ago, and will undoubtedly transform prenatal genetic screening — an estimated billion-dollar market — in the United States.

Not surprisingly, these cfDNA tests have become hugely popular since they were introduced two years ago, and will undoubtedly transform prenatal genetic screening — an estimated billion-dollar market — in the United States.

In 2008, however, Stanford professor of bioengineering and applied physics Stephen Quake, PhD, published a new approach based on combining a molecular counting principle with advances in DNA sequencing technology. By simply comparing the relative levels of each chromosome in the mother's blood, Quake, a Howard Hughes Medical Institute investigator, could identify women carrying a fetus that was contributing more or less than the expected ratio (a sign of an abnormal number of chromosomes, or aneuploidy). For example, a fetus with Down syndrome has an extra copy of chromosome 21, which would be reflected as a higher-than-normal ratio of chromosome 21 to other, unaffected chromosomes. The same approach works, although it is slightly less accurate, for other chromosomes like 18 and 13 as well as the sex chromosomes X and Y. (Abnormal ratios of these
chromosomes can also cause serious, sometimes life-threatening, developmental disabilities.)

The test is much more accurate, and can be performed earlier in a pregnancy, than traditional screening tests for aneuploidies in chromosomes 21, 18 and 13. These traditional tests have sensitivities ranging from 75 to 95 percent and false-positive rates around 5 percent. Finally, the cffDNA test devised by Quake can be performed at any point after 10 weeks of pregnancy; traditional screens are accurate only when performed at very specific windows of time after conception.

“There’s no question that the cffDNA screens are more sensitive and more specific than conventional screening,” says Louanne Hudgins, MD, a professor of pediatrics and director of perinatal genetics at Stanford. “They will also enable us to make accurate genetic diagnoses in the third trimester without the risk of preterm labor.” Hudgins is a co-author of Quake’s first paper describing the cffDNA analysis.

Stanford patented Quake’s test and licensed it to Verinata Health, but other companies have developed similar technology. San Diego-based Sequenom was the first to begin to offer the test in October 2011; since then Verinata, Ariosa Diagnostics and Natera have begun offering similar screens.

“This is the fastest adoption of medical technology that anyone has seen in our lifetime,” says Quake, who serves as an unpaid advisor to Verinata and receives a small percentage of Stanford’s royalties from the patent. “It’s truly amazing. In 2008, I thought it could take a decade to fully enter the clinic. But within days of publication I started to get emails from people around the world asking where they could get it done.”

Currently the cost of cffDNA tests ranges from about $795 to $2,700, depending on the company, and insurance coverage for the tests varies. The four companies are engaged in lawsuits, battling for the exclusive right to the approximately $1.3 billion market.

The American Congress of Obstetricians and Gynecologists currently recommends cffDNA tests only for women already shown by established screening methods or age to be at higher-than-normal risk, and they urge women to confirm any positive result with an invasive procedure such as amniocentesis or chorionic villus sampling.

Illumina, the company that owns Verinata, estimates that around half a million women will use a cffDNA prenatal test this year. “If 500,000 women are choosing this test, rather than invasive procedures like amnio or CVS,” says Quake, “that means in 2013 we will have avoided around 1,600 unnecessary fetal deaths. I find it absolutely remarkable, and it’s something of which I’m personally quite proud.”

So what’s not to like?

Despite its rapid uptake, the cffDNA test is still in its infancy. Questions remain as to how the test performs when a woman is carrying more than one fetus, or how to deal with the fact that as many as 5 percent of women (usually those with high body mass index) will have too little fetal DNA in their blood for analysis. Furthermore, different companies use different DNA sequencing techniques for their analysis, which can vary in their sensitivity and outcome, and the way they report their results varies widely.

Many observers expect the U.S. Food and Drug Administration to step in within the next year to establish ground rules for providing the tests.

“We’ve taken the whole phenomenon of cffDNA testing and commercialized it at a time when there is very little regulation or oversight,” says bioethicist Mildred Cho, PhD, a Stanford professor of pediatrics.

Until the tests are proven to have clinical utility in large groups of low-risk women (most were tested on women at high risk for these types of disorders), and until it’s certain that women and their providers thoroughly understand the strengths and weaknesses of the tests, it may be best to use them in combination with other, more traditional types of screens, some say.

“We’re in a very early stage right now with these tests,” says associate professor of genetics Kelly Ormond, a Stanford medical ethicist and certified genetic counselor. “I’m concerned that clinicians and patients who are jumping straight to the cffDNA tests may be overestimating what they can learn from them at this point.”

In an era when genetic information is
touted as the key to personalized health care, it’s hard to argue that it can be better to know less. But Ormond and others say it’s important that women consider and discuss with family members and their clinicians what information, if any, they would like to receive from prenatal tests. They are concerned that the ease of the cfDNA test may mean that women will undergo the procedure without considering its implications.

“Women may not give a lot of thought as to whether they want the cfDNA test, whereas, someone presented with the possibility of an amnio will think long and hard about whether she wants a needle in her stomach,” says maternal and fetal medicine expert Mary Norton, MD, a former professor of obstetrics and gynecology at Stanford. Norton has recently taken a position as the vice chair for clinical and translational genetics at the University of California-San Francisco.

Cho cites studies indicating that physicians’ attitudes toward informed consent — that is, making sure that a patient fully understands and agrees before undergoing medical tests — may be more lax if the method is non-invasive. She and others recommend against combining the blood draw for the cfDNA test with any other routine blood sampling procedures to avoid confusion, and urge that the patient be offered genetic counseling before and after testing.

“It’s clear that the cfDNA tests have some tremendous advantages and strengths,” says Norton. “And, if all you care about is Down syndrome, it’s a really great option. But I think it’s important to step back and realize that the current recommended screening tests do pick up things that cfDNA doesn’t.”

For example, traditional screening, which combines a maternal blood test with prenatal ultrasounds in the first or second trimester, can detect a variety of problems including the likelihood of preterm delivery, structural abnormalities of the fetus and preeclampsia, which can result in a dangerously high blood pressure. Combining cfDNA testing with ultrasounds and blood tests for signs of these other conditions may be an effective approach, Quake believes.

Norton is an investigator on a large, multicenter clinical trial comparing the cfDNA test offered by Ariosa Diagnostics with traditional, first-trimester prenatal screening in 19,000 low- or average-risk women. Conventional first-trimester screens use a blood test and a specialized ultrasound measurement of the back of the fetal neck to estimate aneuploidy risk. They deliver results earlier than other conventional screens, but are less accurate than those that also incorporate a second-trimester blood test. Results from that trial are expected in early 2014.

**THE BIGGER PICTURE**

There’s every reason to expect that cfDNA tests will one day be used to recognize fetuses with problems other than abnormal numbers of chromosomes. For instance, if a fetus is likely (because of the family’s medical history) to carry a mutation for a specific disease, it’s possible to sequence only the relevant genes.

“This is potentially very clinically important,” says Quake. “We could create a screen that would identify metabolic disorders, immune deficiencies and other problems. In principle we could learn this before the child is born, and be prepared to offer treatment right after birth rather than finding it out when the baby gets sick.”

Most experts agree cfDNA screening technology has the potential to revolutionize prenatal care, particularly if fetal whole-genome sequencing ever becomes commonplace. (Last year, Quake and another research group at the University of Washington independently showed that it is possible to sequence a fetus’ entire genome from a maternal blood sample.)

“Ultimately it is likely that anything we can figure out by studying an adult’s genetic sequence, we will be able to figure out for a 10-week-old fetus,” says Stanford law professor and bioethicist Hank Greely, JD. But do parents want to know whether their child will have a higher-than-normal risk for Alzheimer’s disease? How about obesity? Gum disease?

“No technology is all good or all bad,” says Greely. “In every instance, a new advance can be used well, or it can be used poorly. But it’s clear this test is spreading rapidly all over the world. It’s useful and it’s likely to play a bigger and bigger role in prenatal care in the coming years.” For instance, the cfDNA test for abnormal numbers of chromosomes 21, 18 and 13 will soon be part of the California prenatal screening panel as a way to follow up on troubling results from initial screens.

“Eventually we will be able to use this approach to ask any genetic question we want about a fetus,” says Quake, “and learn about any mutation we might be interested in.”

Ten years ago, I didn’t have this option. I finally decided on just the standard blood tests and ultrasounds when I was pregnant with my son. They didn’t indicate any increased risk, so, like every other pregnant woman for centuries, I held my breath and hoped until the day he was born.

He was fine.

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almost
without
hope

In the emergency room of the Rosebud Indian Health Service Hospital, suicide attempts by drug overdose are seen nearly nightly. Alcohol-related car accident injuries fill many of the small hospital’s beds, competing for space with tuberculosis, pneumonia and liver and kidney failure. Diabetes is common, leading to loss of life and limb. • The physical complications of poverty, joblessness and epidemic rates of alcoholism, diabetes and depression spill over into the wards here at the only hospital on the Rosebud Reservation, which has a population of 13,000 and stretches across 1,970 square miles of South Dakota prairie. Life is short, violence high and health care lacking in Todd County, the second poorest county in the nation. • “There are three ‘spiritual’ paths here: Native Lakota, Christian or alcoholism,” says Rick Emery, a physician assistant here for the past 13 years. He's hunkered down in command central, a small office in the ER, awaiting the arrival of an assault victim. It’s late March — spring break for the local schools. Drug- and alcohol-related cases are up. The staff morale, down. • “Bath salts, meth, Sudafed, anything that's cheap,” Emery says. His hair is gray, his kind face weathered. “It's worse when school's out, when kids on the reservation have nothing to do. We get young people, 17, 18 years old, coming in with chest pains.” Sometimes they’re drug-induced, sometimes not. The night before, a 16-year-old came in with a severe anxiety attack. The night before that, a 25-year-old male who had hung himself arrived too late to save. • Cursed with some of the highest suicide rates in the country, tribal leaders declared a state of emergency here back in 2007 making headlines in The New

by Tracie White

ILLUSTRATIONS BY JEFFREY DECOSTER

FALL 2013 STANFORD MEDICINE
York Times. But today, six years later, not much has changed. Across the United States, American Indian and Alaska Native youth ages 15 to 24 are still committing suicide at rates three times the national average of 13 per 100,000 people for their age group, according to the U.S. surgeon general. On the Great Plains, the suicide rate for Native Americans is 10 times the national average. Unemployment hovers at 80 percent, and the life expectancy for males is in the upper 40s, about 30 years lower than the U.S. average.

The ambulance arrives with the assault victim — a middle-aged Native American male with a blood alcohol content of 0.2 and a wide gash across his skull. Someone attempted to choke him, then bashed him in the head with a piece of firewood. The patient before him was a 26-year-old woman and former meth addict suffering severe vaginal bleeding. The patient after him: a 2-year-old boy with a raging dental infection who will have to be helicoptered out to a hospital hundreds of miles away to get the care he needs.

“These were all Sioux land from the Missouri River in South Dakota west through eastern Wyoming into southern Montana,” says Emery, referring to the wide swath of land that stretches across the northern Great Plains. Emery is a member of the Lakota Sioux. He worked as an Army medic for 17 years before returning home to his reservation and this hospital. The military has provided a way out of poverty for many here. “Lakota were nomadic tribes who followed the buffalo. Then the government put us in these desolate places. ‘We’ll take all this land in exchange for health care forever,’ they told my people. They just didn’t say what standard of health care that would be.’”

I can only wonder: How did things get so bad out here in the middle of the windswept prairies, land of majestic sunsets and home to once-proud warriors? Is there any hope for the future?

I’VE FOUND MY WAY into this emergency room as a writer covering Stanford students in a class on rural health care and Native American health disparities. The course ends with a weeklong trip to the Rosebud Reservation, where students volunteer in the hospital and help build low-income housing for Habitat for Humanity [see sidebar: page 38].

Few communities in the United States, perhaps some in the outer reaches of Montana or Alaska, are so isolated. To get here, I fly from San Francisco into Sioux Falls, one of the two major cities in South Dakota, then rent a car and drive west across hundreds of miles of empty ranchland, Laura Ingalls Wilder territory. Traveling Highway 90, I cross the Missouri River, then turn left at the town of Murdo, population 468, and head into Indian Country. The Rosebud Reservation is at the end of a highway, down a road, around a bend that leads to nowhere.

Three hours of driving brings me to my destination, the town of Mission. The Indian Health Service hospital is situated midway between the two largest towns on the reservation, Mission and Rosebud, both with populations of about 1,500. The students are staying in the Habitat for Humanity dorms, and I plan to meet with Shane Red Hawk before connecting with them. Red Hawk is a community leader who, along with his wife, Noella, helps at-risk teens at the Buffalo Jump Café and Teen Center near the center of town. It won’t be hard to find, I’ve been assured. It’s on the street corner next to the only stoplight in town.

Downtown Mission is about half a mile long with few landmarks. There’s a Wells Fargo, a Subway sandwich shop, a few express loan businesses, an Episcopal church and a post office. The buildings look both temporary and unfriendly — lots of aluminum siding, few windows — like a community was forced to move here that didn’t plan on staying long.
There are no malls, no movie theaters, no bowling alleys. Leading into town, there’s a large, tribal-owned grocery store empty of both food and customers — no one seems to be able to tell me exactly why. The parking lot, on the other hand, is busy. Cars line up at the drive-through alcohol kiosk, and teenagers and families hang out, chatting. One young man, his boot resting on the bumper of a pickup, wears a T-shirt that catches my attention: “Not just another Third World country.” I drive on, turn right at the stoplight and park in front of Buffalo Jump.

The sounds of video games ping from the corner of the dark, cozy cafe. Two teens laugh together. Red Hawk, tall and imposing, with a long, brown ponytail, sits alone at a corner table. He nods me over and waits for questions. Red Hawk grew up on the reservation, then left to join the Navy at 17. He returned home in 2006 after hearing about how young people were killing themselves here. He came back with Noella, opening the center as a safe place for kids to hang out and to introduce them to the forgotten ways of Native spirituality.

“I’ve had kids brought to me after being cut down from trying to hang themselves,” he says. “It’s humbling when a teenager arrives with swollen lips and fingers still blue.”

He continues: “My heart’s always been here. But dysfunction and oppression, alcoholism are a way of life here.” Our interview ends abruptly, interrupted by a phone call. Red Hawk apologizes; he has to leave for the funeral of a child in a neighboring town. For the rest of the week, a sign hangs in the Buffalo Jump window: “Gone to funeral.” I head off to check in to a hotel.

The next morning, I wake to the sound of native drumming from the radio alarm clock. I’m staying in the Quality Inn Rosebud Casino near the Nebraska border, about 40 minutes from the hospital, and worry about finding my way there before dawn in the dark. The weather’s turned colder, spitting icy rain on the windshield of my rental car. Tumbleweeds skitter across the highway as dawn breaks, a long, thin orange line drawn across the horizon. There are few addresses on the reservation, mostly P.O. boxes; GPS rarely works, and cell phone service is spotty. Mostly I rely on friendly tips for directions.

The Rosebud hospital is a modern building constructed inadvertently on top of a rattlesnake nest, surrounded by open land. Patients travel sometimes 100 miles over rough roads to get here, though finding transportation often isn’t easy. Still, the 35-bed hospital is consistently over capacity. Getting an appointment can be difficult to near impossible because of a lack of staff and an overabundance of patients.

I join the Stanford students at the morning staff meeting, listening to Ira Salom, MD, chief medical officer, talk about impending cutbacks of about $200,000 due to the automatic budget cuts known as sequestration which have hit the already underfunded Indian Health Service hospitals and clinics especially hard.

“We’re looking for quarters under seat cushions,” says Salom, who was recruited to the hospital from New York City where his wife still lives. “If I don’t make these cuts soon, we’re going to run out of money.” A staff member pokes his head into the room to inform him that the technician who runs the CT scanner is out sick with a migraine, leaving no one to fill in. Also, there’s no night staff available to cover the first week of April in the ER. He sighs and turns the meeting over to the chief pharmacologist, who discusses options for cutbacks, such as lidocaine patches, Lubriderm lotion and statins — non-lifesaving supplies.

THE ROSEBUD HOSPITAL is run by the Indian Health Service, which is part of the U.S. Department of Health and Human Services. The IHS is responsible for providing health care to 2 million Native Americans and Alaskan Natives who belong to more than 575 federally recognized tribes in 35 states. It was set up by the federal government to honor a long history of treaties in which Indian tribes exchanged land with the

‘for tribes here, health care is a right. they were promised health care “for as long as the river is running.”’
United States in return for food, education and health care.

“For tribes here, health care is a right,” says Sophie Two Hawk, MD, CEO of the hospital and the first Native American to graduate from the University of South Dakota medical school, in 1987. “They were promised health care ‘for as long as the river is running.’”

It’s well-documented that the government’s attempts to meet these obligations to the Native Americans have failed miserably; the primary cause is insufficient funding. Currently, prisoners receive significantly higher per capita health-care funding than Native Americans. The U.S. Commission on Civil Rights reports the federal government spends about $5,000 per capita each year on health care for the general U.S. population, $3,803 on federal prisoners and $1,914 on Indian health care.

“One of the most pressing inequities of the federal government’s attempts to meet these obligations, according to advocates such as the National Indian Health Board, a nonprofit in Washington, D.C., is that while the biggest federal health and safety-net programs such as Medicare, Social Security and veterans’ health are protected from sequestration cuts, the IHS is not. It stands to lose 5 percent of its $4 billion budget this year, a percentage that is expected to increase next year if sequestration continues, IHS administration officials say. These cuts will be devastating for many tribes.

Other Native health-care advocates, led by the Association of
American Indian Physicians, push for greater funding for the federal government’s student loan program for health professions.

“One of the main goals of the AAIP is to increase American Indian representation in the health-care workforce,” says Nicole Stern, MD, AAIP president, who points to the perpetual labor shortages faced on reservations, which hover at 15 to 20 percent for physicians.

IHS administrators say they are hopeful that the passage of President Obama’s health-care law, the Affordable Care Act, will ease these ongoing budget and staff shortages. The law, which began providing government-subsidized insurance plans Oct. 1 to low- and middle-income individuals, makes permanent the reauthorization of the Indian Health Care Improvement Act, which authorizes Congress to fund the Indian Health Service — a positive step, Native health advocates say.

Also, by providing health insurance to many of the same low-income patients that the IHS currently cares for, the new law should allow the IHS to seek reimbursement for services that it would otherwise pay for itself.

“The act should free up more funding for referred inpatient and specialty care,” says Margo Kerri-gan, California area director of the IHS. “We hope it does, but Indian people will need to apply for these alternate resources.”

If someone shows up with a torn ACL,
we can’t afford to fix it. He will walk with a limp.

ONE AFTERNOON DURING A VISIT to the hospital, I walk from the ER to a separate wing to find the CEO, Two Hawk. Her door’s ajar, and she waves me in. She’s dressed in the military-style uniform of the U.S. Public Health Service Commissioned Corps, her long, gray hair pulled back in a braid that drops down her back. She’s doing paperwork — denying a pile of requests from her physicians for additional care for their patients. The requests are appropriate, she says, but the hospital just doesn’t have the money to pay for the care.

“If someone shows up with a torn ACL, we can’t afford to fix it,” she says. “He will walk with a limp.”

Two Hawk, like many others, links the poor health statistics of Native Americans not only to the lack of adequate IHS funding but to the community’s tragic history. The hopelessness, the despair — it’s rooted in history.

For Rosebud, that history began in 1868 when under the terms of the Fort Laramie Treaty the Lakota Sioux, known as Sicangu, were placed on one large reservation that covered parts of North and South Dakota and four other states. After defeats in the Plains Wars of the 1870s, 7.7 million acres of Indian land were taken by the federal government and smaller reservations were created. The Sicangu Lakota were sent to live on the Rosebud Reservation. It’s a familiar story, repeated over and over again, throughout the American West: massacres, followed by relocations, followed by broken treaties. About 500 reservations remain today spread across the nation.

The term “historical trauma” is used to name the psychic wounding caused by massacre, destruction of culture and dislocation of the Native Americans in the name of Manifest Destiny. This history is still felt strongly on the reservation, Two Hawk says.

The forced relocation of Native American children to faraway boarding schools is a particularly ugly chapter in this history, which deeply damaged the Sioux. Native children were sent to boarding schools where they were forced to wear white man’s clothes and were beaten for speaking their native language. Almost every Lakota had a close relative who had been taken from home by white government agents in the early 1900s and sent to one of these schools. For decades, there were reports of abuse and malnourishment.

The long-term effects on health have been disastrous. The National Rural Health Association in a 2006 study reports: “The forced relocation of children into Bureau of Indian Affairs boarding schools ... led to cultural distortion, physical, emotional and sexual abuse, and the ripple effect of loss of parenting skills and communal grief.”

CONTINUES ON PAGE 48
Bacteroides thetaiotaomicron is one of the good guys. Known simply as Bt, it is an abundant member of the estimated 500 to 1,000 species of bacteria that live in the human intestine and one of the lead players in a remarkable symbiosis between man and microbe. Bt does what our bodies can’t. It ingests complex sugars and breaks them down into usable nutrients that can then be absorbed by our digestive system. We may be stardust, but we are also microbe excrement.

- Inflammatory bowel disease, in contrast, is about as unpleasant as the name implies. The complex condition has baffled science for decades. Among its peculiarities is the fact that the bacteria in the guts of sufferers vary significantly in type and number from those of healthy humans, Bt chief among them.

- “Unfortunately, we don’t know whether these variations in the bacterial populations are a root cause or a resulting symptom of inflammatory bowel disease, and, until recently, we were very limited in the tools available to answer that question,” says Justin Sonnenburg, PhD, a Stanford assistant professor of microbiology and immunology who

By Andrew Myers

PHOTOGRAPHY BY LESLIE WILLIAMSON

DREW ENDY

Endy’s an engineer who uses biological molecules to build microscopic computers.

One of his goals: Make it easy to compute inside living cells.
studies relationships between gut microbes and health. He’s in the vanguard of scientists applying a new research tool that provides unprecedented control of microbes.

That tool is a computer, but not a computer made of silicon, metal and plastic. It’s a computer made of DNA, RNA and enzymes, residing within the confines of a single cell.

**THE BUILD**

This biological microcomputer sprang from the mind of Drew Endy, PhD, an assistant professor of bioengineering at Stanford. In three scientific papers released over a 13-month span in 2012 and 2013, Endy and a team of researchers from his lab showed how they used ordinary genetic engineering techniques to turn the bacterium *E. coli* — that stalwart of the Petri dish — into a machine capable of the basic functions of a computer: logic, data storage and data transmission. They also showed that their techniques will work in any type of living cell, not just bacteria.

And while others have accomplished similar feats, Endy’s system has the singular advantage of being able to amplify the information flow.

“Amplification is what makes this system the best,” says Endy. “It’s the equivalent of the transistor in an electronic device. It’s what makes our computer really useful.”

So it’s a cool bit of engineering, but it’s more than that.

The work “… clearly demonstrates the power of synthetic biology and could revolutionize how we compute in the future,” said fellow biological engineer Jay Keasling, PhD, at the University of California-Berkeley, quoted in the *San Jose Mercury News*.

Other researchers echoed this opinion, as did the *Journal of Biological Engineering*, which recognized one of the three articles — “Engineered cell-cell communication via DNA messaging” — as its Publication of the Year.

Speed-wise at least, IBM won’t feel threatened by the bio-computer. “The microbial processor operates in the millihertz time frame — about one cycle every 1,000 seconds, or about four times per hour,” Endy says, “But in biology it doesn’t always matter; slow can be beautiful.”

The biological computer opens up a host of research avenues never before imagined, much less pursued. Microbes could be engineered to detect cancer, for instance, and then tag malignant cells with fluorescent markers for easy identification. Other cells might be programmed to detect those markers and deliver with pinpoint accuracy pharmaceuticals they themselves manufacture on the spot, much as Bt produces and excretes nutrients. Biological computers might even someday be able to reprogram cancer cells to shut off their own growth.

Unfortunately, at first biologists often have a hard time understanding his work, Endy says. “When I talk about this to groups of biologists, the initial response is usually, ‘Harrumph. That’s not how biology does it,’” he says. “They’re not used to thinking like engineers.” Once he explains that he’s using biology to build something simpler and easy to control, something useful, they begin to warm up to the idea.

Endy knows of several scientists starting projects using his system and he hopes many more will take it up. An advocate of open-source technology (which, as with open-source software, makes its discoveries and technologies free to the public), he has made the instructions available free online. A video primer is also on YouTube (http://stan.md/15u6OrC); it’s been viewed nearly 30,000 times.

**IT STARTS WITH A MEMORY**

The biological computer has been a quest of five years for Endy and the researchers in his lab. The first step was creating the data-storage component. To do that, Endy, postdoctoral researcher Jerome Bonnet, PhD, and graduate student Pakpoom Subsoontorn worked to master the precise interaction of two enzymes that, when working together, can flip a DNA sequence end for end and flip it back again. The key to biocomputing is that the microbe produces the enzymes, so it controls which direction the sequence points. With this bit of biotechnology, the researchers have created an equivalent to the 1s and 0s of binary data storage that are at the heart of most every computer today.

“If you are reading along a particular section of DNA and it reads one way, we can arbitrarily label that section a zero. If it reads the opposite way, we can call that orientation a one,” Endy explains.

Such a biologic memory device is the equivalent of a lone binary digit — a “bit” in computer shorthand — a quantity that is infinitesimal in storage terms. It takes eight bits to form just a single “byte” of data. A byte, in turn, is enough to store just one typed character of information. It would take some 15,000 bytes — or 120,000 of Endy’s bits — to store
This article. But, like the biocomputer’s slow clock speed, in biology such small amounts of data amount to a lot of computing power in the hands of the right people.

Endy’s team has gone a step beyond, formulating a clever way to retrieve the data that doesn’t require DNA sequencing. By engineering the microbe to glow different colors under ultraviolet light depending upon the direction the memory bit points, reading the data becomes as easy as shining a UV light on the microbes. If the section of DNA points one way, the microbe glows red. If the section points the other, it glows green.

To grasp how this might work, imagine a microbe that is programmed to detect the telltale chemical signature of cancer in the intestine. To start, one would swallow a million or so replicas of this specially programmed microbe. Once in the intestine, any of the microbes that encountered the signature of cancer would kick into gear and produce the enzymes necessary to flip its memory bit. Then, after the microbes exit the body (in a bowel movement) the researcher could illuminate them with UV light and know immediately whether cancer was present in the patient.

“Of the three core components of the biological computer, digital data storage was by far the hardest to create,” Bonnet says. “It took us three years and hundreds of tries to get just a single bit working right every time.”

The Biological Internet

After conquering the data-storage challenge, Endy and team created a way to transmit data between cells. Their technique enables the data to literally go viral, using an innocuous virus known as M13 that makes itself at home in bacteria, living off nutrients cadged from its host. Like a freelensing household guest texting its friends across town, M13 broadcasts its own genome to other cells. This is the infection stage of M13’s life cycle, and Endy and his team have repurposed it to fashion a biological Wi-Fi able to transmit virtually any DNA sequence between cells.

The technique requires a bit of genetic subterfuge. Normally, M13 works by sealing its own DNA within an additional brief genetic sequence, a sort of genetic package. To transmit a message, all the microbe has to do is add this packaging sequence and M13 will send it off to other nearby microbes, oblivious that the message inside the package is not its own DNA. Endy has parasitized the parasite.

“We can send any genetic messages we want and we can send them to specific cells within a complex microbial community,” says Monica Ortiz, PhD, a former graduate student working in Endy’s lab and now a postdoctoral researcher at Harvard. M13 can send genetic codes measuring in the tens of thousands of characters. While that’s a modest bandwidth compared with gigabit Ethernet, it’s plenty for biocomputing.

Researchers now have the means to control the behavior of not just a single microbe, but an entire community of cells. Cells engineered with M13-based communications might be orchestrated to start growing or stop growing, to cluster together or swim away. A group of microbes could turn on the production of insulin en masse when they detect sugar, morphine in the presence of pain, or anti-inflammatories at the site of ulceration. Contemplate for a moment the concerted effort that even a small portion of the trillion bacteria in the intestine might produce if working in a coordinated, pre-programmed fashion.

A Logical Conclusion

The last function Endy tackled was logic. Most computers are built to perform Boolean logic — named after George Boole, the mathematician who proposed a system of logic in the 19th century. Boolean logic in an electronic computer typically takes the form of 1s and 0s. One is true; zero is false. Answer true, gate opens, electrons flow. Answer false, gate closes, electrons don’t flow. With just these two yes-or-no states, binary computers are able to accomplish all the astounding things they do today.

“In a biological setting, the possibilities for logic are as limitless as in electronics,” says Bonnet.

In the biocomputer, the silicon gates are replaced by genetic gates that open and close to similarly control the flow, but instead of electrons the flow in this case is an enzyme that travels along a DNA strand. Answer true, enzyme flows. Answer false, enzyme doesn’t flow.

For example, one of the most basic logic gates is the “AND” gate, which gives an output of true when its two inputs are true — when “a” and “b” are both true. An “OR” gate, on the other hand, is true when either a or b, and possibly both, are true. Testing whether a or b, but not both, is true requires an “XOR” gate, known as an “exclusive or” gate. And so it goes, until there is a gate for every possible logical combi-
nation. Endy’s team has demonstrated biological equivalents for all the major logic gates known to electronic computing.

AMPLIFICATION
It is in the combination of logic and data transmission, however, where the biocomputer really begins to reveal its greater potential. The biological transistor is able to turn a tiny amount of information into a very large flow of data. In electronics, this is known as signal amplification.

With electronic signal amplification, a very small change in electrical flow is sufficient to open and close gates that control massive rivers of electrons. “The biological transistor, what we call a ‘transcriptor,’ does the same thing. A small change in gene expression can produce a very large change in cell behavior,” Endy says.

The transistor, often described as the greatest technological advance of the 20th century, was conceived precisely with amplification in mind as a way to replace unreliable vacuum tubes in relaying telephone calls across the continent. Electrical signals attenuate, weakening as they travel. By boosting the fading signal with transistors — by amplifying signals — it is possible to rebroadcast them across great distances.

Biological systems are no different. Genetic signals can now be amplified as they move through a community of cells, enabling the orchestration of large numbers of cells.

CALCULATING POSSIBILITIES
Sonnenburg and postdoctoral scholar Weston Whitaker, PhD, were familiar with Endy’s work from the published papers, but they had been thinking about using biological parts to build machines for a long time. Whitaker learned many of the techniques of the field at Berkeley. Folding in his own ideas and adding the genetic parts from Endy’s lab, they were off.

“Conceptually, the biocomputer is fairly straightforward. Technically, however, there are many issues, as you might expect when trying to transfer genetic parts between E. coli, where Endy worked, into Bt — two organisms separated by more than 2 billion years of evolution,” says Sonnenburg.

“Weston is clever, but such work often includes screening hundreds of variants of a genetic part to find just the right ones for Bt, so things are proceeding, but slowly.”

When Sonnenburg imagines the trillions of bacteria in every human colon, however, he sees only potential. “On a sheer numbers basis, there are 10 times more single-celled microbes on and in our body than all the remaining cells of our body combined,” he notes. “We’re just beginning to explore the implications of computing within these cells.”

The biological computer means that Sonnenburg could record each time one of his programmed Bt cells encounters certain environmental factors, such as inflammation in an intestine riddled with Crohn’s disease or ulcerative colitis.

“These tools will be useful immediately at the basic science level, helping us to better understand relationships of microbes to human health. In the long term, they open the possibility of altering the microbes’ community structure and function to prevent and treat diseases,” Sonnenburg says.

A research proposal drafted by Whitaker describes a three-pronged strategy to put the biocomputer to work. First, he plans to program microbes to detect inflammation. Already he has designed a genetic logic switch to detect inflammation in a mouse colon afflicted by colitis. Wiring this switch to the production of a fluorescent protein would allow programmed Bt microbes to tag afflicted areas for easy identification.

Second, using Endy’s logic and data storage tools, Whitaker and Sonnenburg plan to program microbes to gather and record information about what’s happening in the intestine that will help them understand the factors contributing to inflammation.

Third, they plan to program therapeutic bacteria and coordinate groups of them to produce and deliver immune-suppressants directly to the site of inflammation. The programmed bacteria would be research probe and drug factory in one. All three research directions were impossible before the biological computer.

MORE BIOCOMPUTING?
Endy says the long-term goal for his work is to make biology easier to engineer — and the more people working on that goal the better. Toward that end, he created a public benefit charity, the BioBricks Foundation, and developed the Bio-Brick Public Agreement to make it easier for people to freely develop uses of genetic computers.

He has formally donated the transcriptor and biological logic gates to the public domain via the BioBrick Public Agreement. That means anyone is free to use them. A similar declaration for the biological Internet is in process.
The only piece of biocomputer technology Stanford and Endy have patented is the biological digital memory.

“Some other groups have patented technologies claiming to accomplish a similar goal,” explains Endy. “If we have a patent, we can assure the technology is free and available to all simply by not pursuing our patent rights. But if we don’t have a patent, someone else could claim the technology and restrict its use.”

Meanwhile, Sonnenburg, Whitaker and graduate student Liz Stanley have begun working with programmed microbes in laboratory mice, and Bonnet has returned to his native France to apply the biological computer to studying diabetes.

All of these researchers say they recognize that years of clinical testing and regulatory review lie ahead before the biocomputer can be used in humans, but the fact that they can contemplate the possibility for the first time is profound.

asked to predict possible directions the biological computer might venture, Endy hesitates for a moment, wary of overstatement. “I’m not entirely certain where the biological computer might lead from a clinical or therapeutic perspective,” he says. “But, I do know that very modest amounts of computing inside living cells will be incredibly useful.”

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From disparate fields to study both the clinical causes of preterm births — what happens in the body that causes a woman to go into labor — as well as how environmental and sociological factors can impact this biology.

The center has established teams of researchers to tackle the issues, and is looking at not only the possible genetic factors involved in preterm births, but how bacteria in the gut could play a role, why infections increase the risk of preterm births and whether any molecules in a mother’s blood can predict her risk of going into labor early. Already, they’ve discovered a link between proximity to pollution in California’s Central Valley and preterm births; the data are not yet published.

“Right now, we don’t understand the ultimate clinical mechanisms of premature birth,” says Wise. “We don’t understand what triggers the onset of early labor, and that makes it hard to make sense of these social forces.” That lack of scientific knowledge makes it hard to untangle the factors that play into the high rate of preterm births in the United States, he says, but also means that it’s important to study all angles of the problem. A breakthrough could come as easily from the

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'SOME OF THESE DEFECTS HAPPEN SO EARLY that they've already occurred by the time a woman even finds out she's pregnant.'

discovery of a new environmental factor — such as pollution — as from an experiment in a biochemistry lab. And the best breakthrough, they all agree, would be a discovery that offers a way not to better treat premature babies once they're born, but to stop preterm births from the outset.

Over the 20th century, small improvements in technology and approaches to treating preterm babies were constantly pushing earlier the gestational age at which babies were considered viable, and raising the survival rate for these tiniest babies.

“Now we’re at a plateau,” says Stevenson. “The outcomes haven’t been improving; we can’t push them beyond a certain limit in terms of survival.”

So lowering infant mortality, he says, will require preventing preterm births. And even when it comes to many known risk factors for preterm births — substance abuse, diabetes and high blood pressure, for example — physicians can do better at intervening early in pregnancy to optimize women’s health and reduce this risk.

A major focus in the field, Sunshine says, is to encourage at-risk women — such as those with diabetes — to see a doctor earlier in their pregnancy, get their health under control, and continue careful monitoring and regular doctor’s visits throughout pregnancy. “If we can get them in early pregnancy and get them in better condition, that can make a difference.”

In 2011, Kaiser Permanente revealed data from almost two decades of the Kaiser Permanente Northern California Early Start Program, an initiative aimed at getting care to at-risk women as early in pregnancy as possible. Women enrolled in the program, they found, were less likely to give birth preterm, have a stillbirth or a low-birth-weight baby. If the program were expanded to reach women across the nation, Kaiser calculated, it could save $2 billion in healthcare costs.

“Our problem with premature births is a problem with the poor health of women of reproductive age in our country and the lack of access to health care that many women in this group have,” says Wise. “Young women tend to have highly fragmented care.” Many of them lack health insurance, he says, and don’t see a doctor regularly enough for any clinician to even know that they have risk factors that lead to preterm births.

According to a 2010 report by the CDC, Americans in their 20s — peak childbearing years for women — were almost twice as likely to lack health care as older adults, and 12 percent of people in that age group had been unable to fill a prescription they needed because of cost.

Although the 2013 Save the Children report focuses on how to improve infant mortality rates in the developing world, several of its recommendations, including improving female education and nutrition, would have positive effects in the United States. Researchers like Wise and MacDorman emphasize the importance of both providing easier access to care for young women as well as educating them better about health during pregnancy.

Birth defects are another cause of infant mortality, and as is the case with preterm births, scientists don’t know many of the risk factors, or the developmental causes at a molecular level.

“Some of these defects happen so early that they’ve already occurred by the time a woman even finds out she’s pregnant,” says Shaw, whose research centers on structural birth defects such as spina bifida and congenital heart malformations. “That’s a window of time that’s very hard for us to study but critical to give scientists ideas about their causes and therefore potentially lead to prevention methods.”

The good news is that the latest numbers on infant mortality in the United States offer the first glimmer of improvement: Data released in April 2013 showed a drop in infant mortality rates between 2005 and 2011, after a plateau from 2000 to 2005. The overall rate dropped from 6.87 deaths per 1,000 births to 6.05, and drops were seen in nearly all causes of mortality, including birth defects and preterm births. The CDC report on the new data hypothesized that part of the drop is likely due to fewer doctors performing non-medically indicated early caesarean sections or inductions of labor, although more data is needed to be sure. And the 6.05 rate still keeps the United States low on the list of international infant-mortality rankings.

“The takeaway message is that the status quo is unacceptable,” says Wise. “The infant mortality rate in many ways is a synoptic judgment on our health-care system and our society. It’s telling us that we must do better — and we can do better, especially when it comes to eliminating social disparities in medicine.”

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patients. It makes them feel very mortal — it’s often the first time they’ve had to think about death, and that has huge impacts on them.”

For Adam, focusing on keeping things normal at home for Kiran and Misha helped pull her through. She was in intense pain from the surgery and, like many placenta accreta survivors, she produced insufficient milk to breastfeed. Her sister and parents helped Seeff to care for her and for Milan, and the boys’ cousins were on hand to play with Kiran and Misha. “We kept it light,” Adam says. “We have video footage of them blow-drying my hair while I was resting on the couch. They understood that something was wrong, but we made it seem as if ‘After the baby comes, the mother has to lie down all the time.’ We didn’t want to scare them.”

Today, Adam and Seeff are taking joy in watching their three sons grow and develop distinct personalities. Kiran is a fan of the sciences and enjoys building things; Misha is the family comic. And little Milan, now 3, loves sports. “He’ll run after anything that looks like a ball,” as Seeff puts it. “The most rewarding thing about seeing them grow up is how well they interact with each other, seeing the creation of a family.”

Now, looking back, Adam says, “I tell my kids there are ‘big bads’ and ‘little bads.’ The ‘big bads’ are things you never completely recover from. We’ve had one big scare in our family history and come through that without lasting scars. I put that in the category of ‘little bads.’” And the harrowing experience has given her a new appreciation for life. “I feel that I need to find a way to make every day meaningful,” she says. “These days were given to me for a reason. It’s my job to find ways to use them well.”

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**FEATURE**

**Too deeply attached**

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hospital with very experienced surgeons and doctors.”

Adam received 22 units of blood, more than 7 liters total. “She lost more than two times her normal blood volume,” Riley says.

**TIME TO HEAL**

When Adam was finally transferred to the intensive care unit at Stanford Hospital where she spent the next 24 hours on a ventilator, she had two thoughts: relief that the baby was OK and a desperate desire to get home to her older sons. After her breathing tube was taken out, the nurses gave her an incentive spirometer to blow into; receiving so much transfused blood had caused fluid to pool in her lungs, and the blowing action exercised her lungs and helped clear the fluid. But it also put a painful strain on her surgical incisions.

Her daily visits with Milan, who was being cared for in the hospital nursery, were incredibly motivating.

“I blew into that machine day and night,” she says. “They could not believe how determined I was, but I had two kids at home and I had told them I would only be in the hospital for a few days.”

Two days after she had entered the hospital, she was well enough to be transferred to Packard Children’s regular maternity ward, where she wept when the implications of her experience began to hit. “I realized how close I had come to not being here for my children.”

Complicated reactions in the aftermath of placenta accreta are common, the experts say. “The difference between making a choice to no longer have your fertility and hav-

**‘A NUMBER OF PATIENTS HAVE POST-TRAUMATIC STRESS DISORDER AFTER PREGNANCY BECAUSE THE DELIVERY IS SO STRESSFUL... IT MAKES THEM FEEL VERY MORTAL — IT’S OFTEN THE FIRST TIME THEY’VE HAD TO THINK ABOUT DEATH.’**

ing that choice thrust upon you is very difficult emotionally,” says Silver.

Yet some women, after months of worry about delivery, are relieved to know that a hysterectomy means they’ll never be pregnant again.

Still, even if they feel some relief, “a number of patients have post-traumatic stress disorder after pregnancy because the delivery is so stressful,” Carusi says. “We’ve struggled to find help for them because people don’t think of new mothers as PTSD patients. It makes them feel very mortal — it’s often the first time they’ve had to think about death, and that has huge impacts on them.”

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**FEATURE**

**Labor day**

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were done in the first stage; 28 percent were done before dilation had reached 6 centimeters. With current studies now indicating that a normal active phase may not begin until 6 centimeters dilation, it’s clear that the majority of these labors may not have been abnormal at all and that many of these C-sections could have been avoided on the basis of timing alone.

The Consortium on Safe Labor’s landmark studies resulted in a new labor curve, also published in 2010, capturing the more diverse experiences of the modern woman in
labor. Instead of a single line sloping up the graph to show full dilation over a set period of time, as Friedman's curve did, the new curve shows four sets of staircases that step gradually up the chart. Each one has a unique starting point based on how dilated a woman's cervix is when she is first admitted to the hospital in labor. Depending upon where she starts — 2, 3, 4 or 5 centimeters dilation — her progress toward 10 centimeters is measured differently, with a range of time allowed for each step.

Consortium researchers also looked at evidence as to why labor lasts longer today. For starters, moms today are slightly older and tend to weigh more than their Mad Men-era counterparts. That’s one finding from a 2012 study by Sarah Laughon, MD, of the National Institutes of Health, that compared the medical records of 39,491 women who gave birth between 1959 and 1966 with those of 98,359 women who gave birth between 2002 and 2008. And as Zhang’s study on C-sections showed, women who are overweight are more likely to have a C-section; as obesity rates in the United States have risen, so too have C-section rates.

“For both spontaneous and induced labors, C-sections were being done based on an understanding of labor that was informed by 1950s patients, as opposed to an understanding of labor that is steeped in data from a contemporary population,” says El-Sayed. “If we don’t understand what’s normal, then we end up doing interventions that may not need to happen.”

In February 2012, the National Institute for Child Health and Human Development, the Society for Maternal-Fetal Medicine and the American College of Obstetricians and Gynecologists gathered in Dallas for a workshop on reducing C-sections by preventing a woman’s first caesarean. They provided many recommendations for clinical practice, from which papers were distributed to obstetricians nationally. Many hospitals, like Packard Children’s, have adopted these new guidelines. The challenge for American hospitals and obstetricians now is to put these guidelines into routine practice everywhere.

“Changing practice takes a lot of time and involves a cultural change, but it will have a great impact. It’s wonderful news for mothers and babies,” El-Sayed says. SM

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FEATURE
Almost without hope

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Leaving Two Hawk, I head to the office next door where another Native American hospital employee, psychologist Rebecca Foster, PhD, works. When I knock on her office door, she’s taking a break to cradle her week-old grandson. Foster and her husband, Dan, also Native and a psychologist at the hospital, have 14 children — seven of those adopted from relatives on the reservation who were unable to care for them. All seven of those children are special needs, like the baby’s father, who was born with fetal alcohol syndrome.

Foster’s goal was always to get an education, then return to help her people. She has served as a role model over the years. Young people gape at the degrees she’s hung on office walls, she says.

“They are always amazed to see a Native person who has accomplished things. I went to reservation schools. My parents stressed education. We came back to the reservation. ... There are a lot of very positive and wonderful things on the reservation, the strength of the community’s ties, the connections with ceremonies and traditions. I grew up in a community where you are related to hundreds of people. We take care of one another. We perform ceremonies together. There are real deep ties with home.”

She, too, attributes much of the destitution and despair on the reservation to history.

“I’m Blackfeet Dakota, from Montana,” she says. “We had Glacier Park. The government took it. The population was decimated from 60,000 to 6,000 from disease. ... We are the only group in the U.S. still under the jurisdiction of the federal government. We didn’t become U.S. citizens until 1924; freedom of religion was not granted until 1978.”

Tribes like the Sioux that followed the buffalo lost both their way of life and their food source due to western expansionism. Forced to live on the most desolate land and to turn to unfamiliar agrarian lifestyles, they were left with food from the government’s commodity program — flour, pasta, rice, peanut butter, canned food — a diet distributed from warehouses on reservations, devoid of fresh food. Today, it’s still nearly impossible to find fresh fruit and vegetables on the Rosebud Reservation.

The relocations of masses of people onto the least profitable lands in South Dakota have resulted in some of the lowest living wages in the country. The average family income is $18,000. Housing is poor, with family members crowded into unheated trailers; there are few jobs beyond some
in minor agriculture and ranching; the difficulty recruiting teachers to the isolated location has resulted in poor schools with high school dropout rates of 50 to 60 percent. For the few Natives who do make it to college throughout Indian Country, a staggering 98 percent return within the first two months, homesick for the close community and culture that doesn’t exist for them in the outside world.

“I see a lot of kids who are depressed, who talk about sui-

‘I GREW UP IN A COMMUNITY WHERE you are related to hundreds of people. We take care of one another. We perform ceremonies together. There are real deep ties with home.’

cide,” she says, then pauses to look into the eyes of her grand-
baby. “And yet, kids are still resilient. They still have a desire to have a good life, to be happy, to accomplish things. No matter where you come from, you can never completely destroy that. There are very few kids here who don’t have a dream.

“What I tell young people is that there is a difference between having to stay here because you are trapped and choosing to be here because you have something to give. One’s a prison, the other is a home.”

NEARING THE END of the week, the Stanford students make bison fajitas for dinner at their dormitory and discuss their experiences — the good and the bad, the tragic and the heroic.

“It opened my eyes,” says Roxana Daneshjou, an MD/PhD student. “I don’t think I had a very good understanding of what living on a reservation was like. It was shocking. Just seeing a health-care delivery system not working. We are not taking care of our people.”

Daneshjou talks about the patient she helped treat who had returned to the hospital after suffering a severe fracture in her arm two months ago. Because of the lack of orthopedic care, the patient was back again, her arm still in pain.

“It’s just awful. If we were at Stanford, she’d go see a very good orthopedic surgeon and it would be fine. It’s the worst feeling in the world to know that the ability exists to fix something, and just not see it get done.”

But undergraduate Layton Lamsam, Osage, who grew up getting care at Indian Health Service clinics on a reservation in Oklahoma, felt differently about his day. The hard-working, short-staffed professionals who provided the best care they could in some of the worst circumstances impressed him. His goal: to help improve this care someday.

During my flight home, my thoughts wander back to the Buffalo Jump Cafe and a 15-year-old Native American girl who walked in just before I left, a pink-strapped travel bag thrown over her shoulder. Two years ago, the girl had threatened to hang herself. School officials sent her to Shane and his wife to talk. She joined us at our corner table. When I asked about suicide, she covered her face with her hands. Tears leaked slowly between her fingers.

Since she was too upset to talk, we left the cafe to walk around the neighborhood, past the worn-out drunks, the church, the high school basketball courts. She’s more hopeful about the future now, she said. She’s thinking about becoming a nurse. But it’s hard to get to school most days. She lives with a large family in a small home with little money. Alcohol use is high, and family support low. She desperately wants to leave the reservation some day. But, then again, this is her home. It’s all she’s ever known.

“This is where my heart is, where I belong,” she said. “Of course I want to leave. But I want to come back and help my people.”

The wide open prairies disappear from my view as the plane takes off, and I catch my breath at the memory of the beautiful landscapes on the Rosebud Reservation and the brave people left behind there — at the end of a highway, down a road, around a bend — fighting hard for a bright-

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“Did you know there’s been a plane crash at San Francisco airport?” • It was a little past 11:30 a.m. on July 6 when Eric A. Weiss, MD, the medical director of emergency management for Stanford and Lucile Packard Children's hospitals, learned of the crash landing of Asiana flight 214. A television in the emergency department waiting room had reported the news, which made its way to Bernard Dannenberg, MD, the director of pediatric emergency medicine, and then to Weiss, both of whom, fortuitously, were working that day.

Weiss knew that if there were casualties, Stanford — one of only two level-1 trauma centers within 25 miles of the airport, and the only one with a helicopter-landing pad — would be well equipped to treat them. He had a committed, well-drilled staff, and many key emergency responders were already on site.

He also had good luck. Just three weeks before the crash, the ED had drilled the “code triage” response: exactly what they were about to face.

At 11:50 a.m. Weiss got the call he was waiting for. It was San Mateo County Emergency Services asking for a count of available beds.

“We can take as many as you need,” Weiss said. At 12:05 p.m., he paged about 800 staff with a “code triage-standby” message, indicating an extraordinary situation that might call for additional manpower and supplies.

He also dialed his partner in disaster response, Brandon Bond, administrative director of the office of emergency management for the two hospitals. As Bond arrived, a helicopter approached with two patients in critical condition, and an ambulance was coming with four more. A few minutes later, 12:47 p.m., Weiss activated the disaster plan with the code “triage-major.”

“This told everyone ‘all hands on deck, expecting major casualties, open the command center, clear out the emergency department and deploy the caches of disaster equipment that had already been pulled out and pre-staged,’” Bond says.

Within 30 minutes they had mobilized over 150 health-care providers and had set up a mass triage area in the emergency department parking lot and another area for less urgent casualties. Activated staff included physicians, nurses, technicians, clerks, registration personnel, transporters, social workers and translators.

David Spain, MD, chief of trauma and critical care surgery, was on site when patients began arriving by helicopter, ambulance and bus. The most common injuries were spine and rib fractures. Some were serious, a few requiring surgery, he says.

Most of the flight’s 307 passengers and crew were Korean or Chinese citizens. By the end of the day, close to 200 had been cared for at nine Bay Area hospitals. Ultimately three girls died of crash-related injuries. Fifty-five, including 16 minors, were evaluated at Stanford; 11 were admitted to Stanford and seven to Packard Children’s.

“As often happens in a crisis, many individuals stepped up and worked tirelessly to provide the best possible medical and social care to patients,” says Lloyd Minor, MD, dean of the School of Medicine. “But it was more than a willingness to help that was on display; it was the work of professionals trained to respond in an emergency situation.” — ROSANNE SPECTOR
It's tempting to imagine our two most recent common ancestors — sometimes referred to as Y-chromosomal Adam and mitochondrial Eve — skipping through the tulips hand in hand. The illusion is fueled by the recent discovery that the two lived during roughly the same time period. Very, very roughly, that is: The man lived between 120,000 and 156,000 years ago, the woman between 99,000 and 148,000 years ago. It's clearly unlikely that they knew each other. But that they could have lived at the same time comes as a surprise. Previous research had indicated that the man lived much more recently than the woman, says Stanford professor of genetics Carlos Bustamante, PhD, who in August published a study in Science on our most recent common ancestors.

Despite the Adam and Eve monikers, these people weren't the only man and woman alive at the time or the only people to have present-day descendants. They simply successfully passed on specific portions of their DNA through the millennia to most of us, while the corresponding sequences of others have largely died out. The crux of the new study was a comparison of Y chromosomes of 69 men from around the globe to create highly accurate inheritance trees. The researchers also studied the DNA in these men's mitochondria — structures that serve as cells' power plants and carry their own DNA.

Bustamante focused on these particular sequences because of the unique way they are inherited: The Y chromosome is passed only from father to son; the DNA in mitochondria is passed from a mother to her children. Both are useful for tracking ancestral relationships because they undergo much less of the shuffling and swapping of genetic material that occurs routinely in most human chromosomes.

What does the apparent overlap between the male and female sequences mean? It's possible that it indicates a time when only a few sequences were passed on after others died out because of an unknown external event. A catastrophic volcanic eruption? A deadly virus? But it's also quite possible that the timing is simply a fluke. — KRISTA CONGER