

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

Fall 2011

special report

ON THE  
VERGE OF A  
REVOLUTION  
CANCER'S NEXT  
STAGE

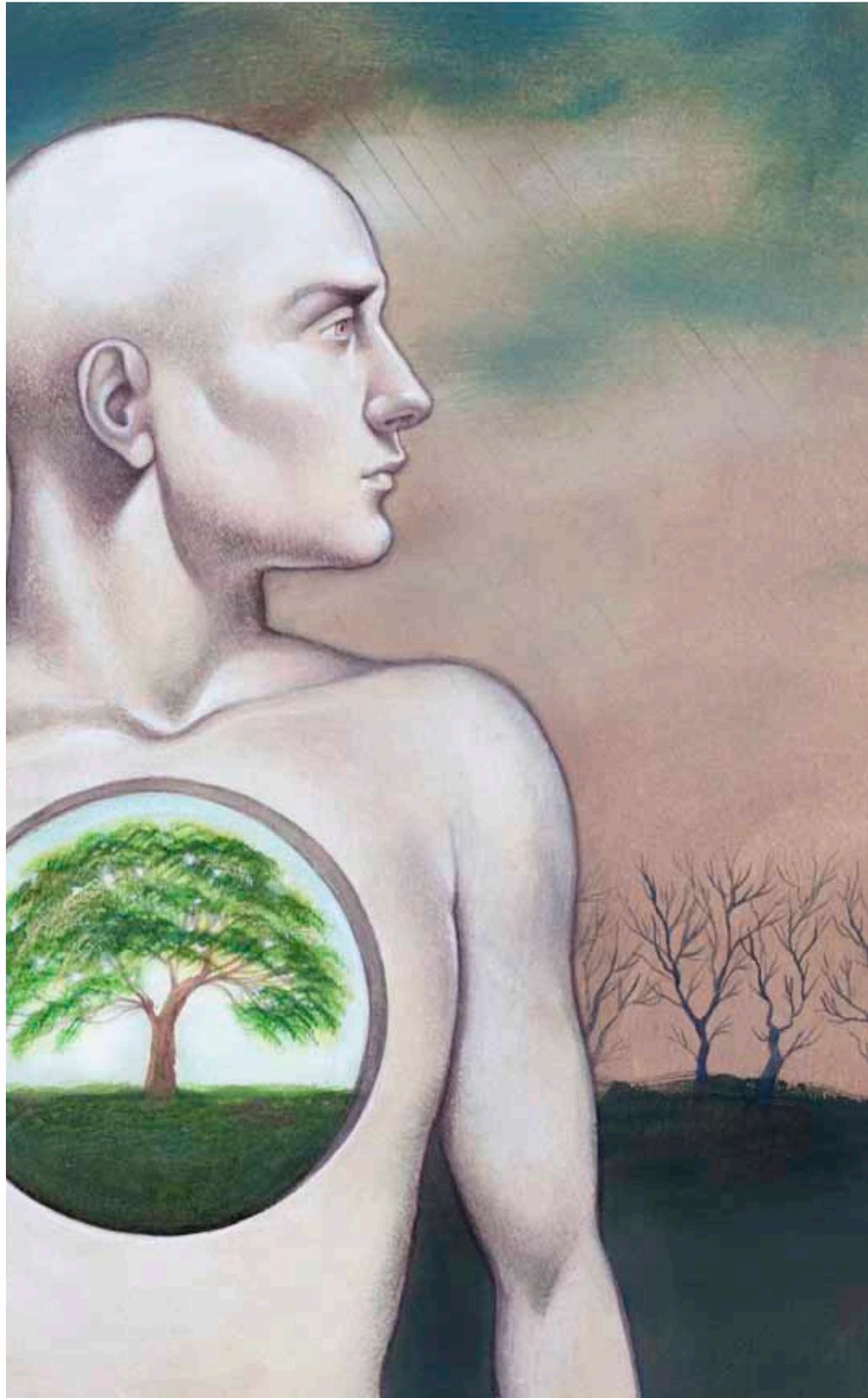
Baby on board  
Chemo while pregnant

The  
malady's biographer  
A conversation with  
Siddhartha Mukherjee

Pain killers  
Palliative care demystified

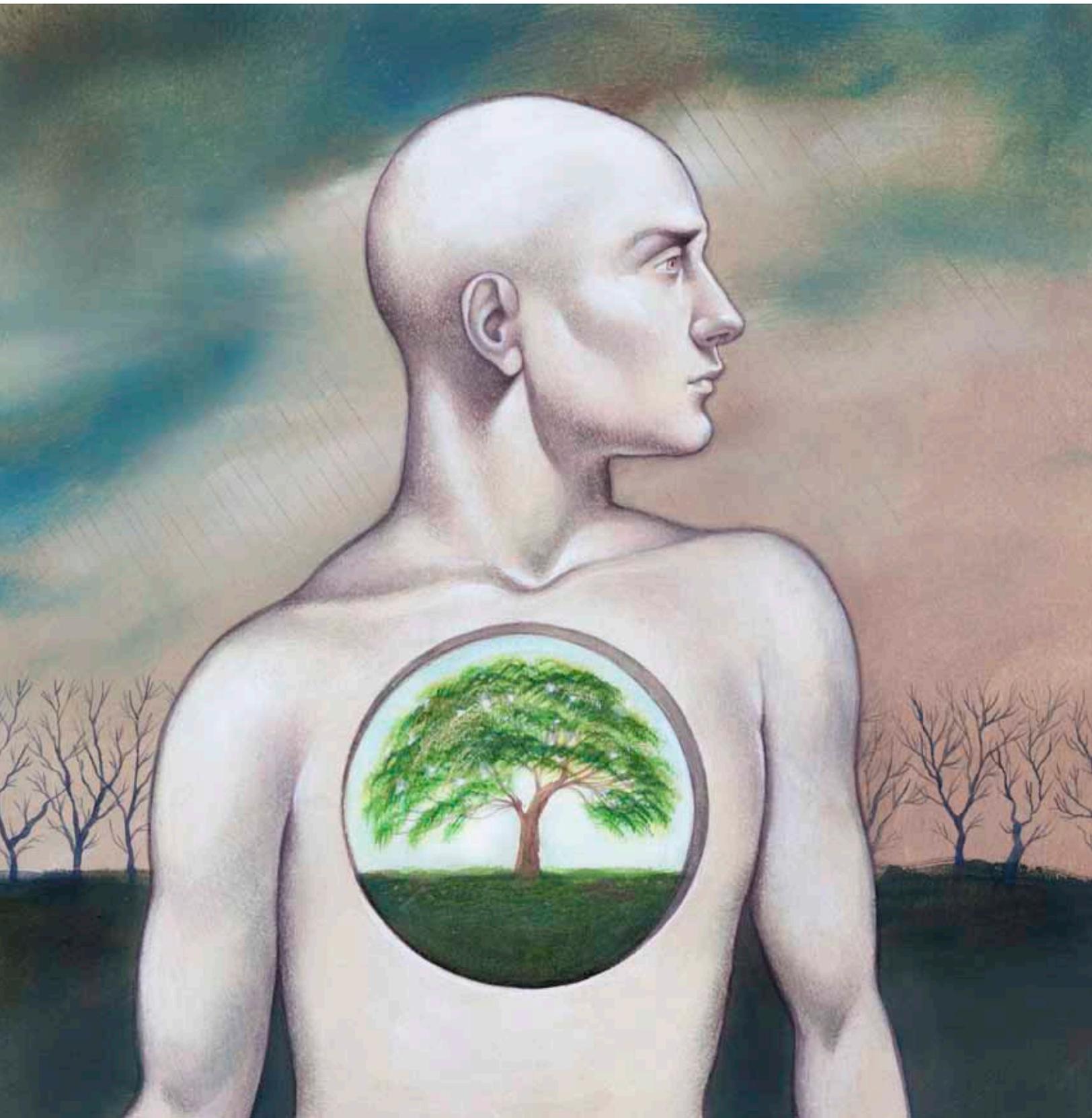
You've beaten cancer  
Is the nightmare over?

DIY cancer research  
Laboratory skills not required



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# A GOOD SCARE

## SOME STRESS COULD FIGHT CANCER

Stress can slow skin cancer, at least sometimes, and **Firdaus Dhabhar, PhD**, and his

colleagues have the evidence to prove it. • But it's not so simple. Dhabhar also has evidence that stress can hasten cancer. • You see, there's stress and then there's *stress*. • First, Dhabhar, associate professor of psychiatry and behavioral sciences, investigated the bad stress: chronic stress that goes on for weeks and months. This kind of stress reduces the immune system's ability to fight diseases, including skin cancer, according to his mouse studies. • But the idea that all stress is bad didn't add up for Dhabhar, who looks to nature for clues about health. Unlike chronic stress, an affliction mostly limited to modern man, acute stress is an important response to dangerous situations, the fight-or-flight rush felt when you're chased by a tiger or, more realistically, in a near accident on the freeway. Acute stress sends immune cells coursing through your blood and on to their battle stations, ready for action if you are hurt. What's more, Dhabhar had previously shown in humans that an adaptive, acute-stress response during surgery can speed recovery.



It's reasonable, then, that acute stress might affect cancer differently, and could even help fight it. "Often, biology defeats pathology and we don't even realize it," says Dhabhar.

So he and his team studied how the immune-boosting effects of acute stress affected skin cancer. The researchers exposed hairless mice to about 10 minutes of UV-B light three times a week — each treatment akin to staying out a bit too long in the sun. For a short-term stress that mimicked the natural danger of a collapsed burrow, half the mice were placed in small, ventilated plastic tubes that restricted their movement for a couple hours before some UV sessions. After 10 weeks, the restrained rodents developed fewer tumors than the unstressed mice. The protection came from ramped-up defensive immune genes, and more immune cells invading the tumors of the stressed group.

While short-term stress helped, its protective effects didn't last forever. After 22 weeks, nearly all animals had tumors, although the short-term stress group had fewer and smaller tumors until week 26, when the tumor burden evened between the two groups. Dhabhar's lab is now investigating whether an acute-stress immune boost at later stages of tumor development is also protective.

If visions of oncologists prescribing public speeches and bungee jumping are floating through your head, you may want to know that Dhabhar hopes

to find ways to behaviorally (think virtual reality or brief exercise) and pharmacologically mimic the good effects of acute stress. Other research from Dhabhar's group has shown that stress hormones mediate the protective redistribution of immune cells to the skin. Now, he is teasing apart the molecular and cellular mechanisms of that redeployment. Those details could inform the amount, timing and location of hormones needed to mimic the acute-stress response in patients so doctors can best exploit nature's immune-boosting system.

Dhabhar's lab has also shown that chronic stress can suppress the beneficial acute-stress response. "Therefore, the key is to keep chronic stress levels low so the protective acute-stress response can spring into action when needed," he says. So forgo your anxiety about that demanding boss or those bills. Save it for when the tiger comes to bite. — SUSAN L. YOUNG

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SPECIAL REPORT

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# letter from the dean

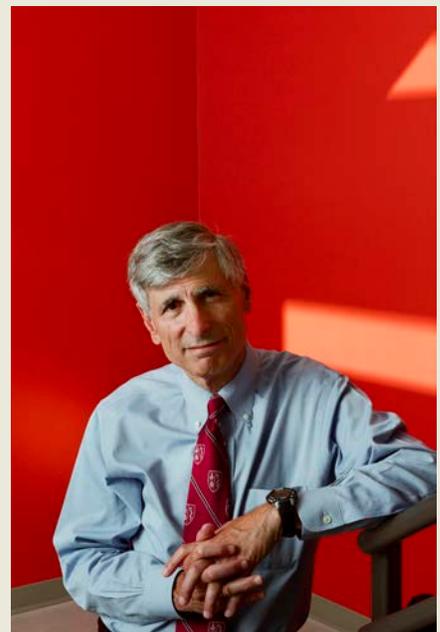
Advances in medicine often begin with an insight in the laboratory or at the bedside, when physicians and scientists believe they have discovered a better way to treat a disease or solve a clinical problem.

However, without rigorous evaluation, innovations cannot be assumed to be either effective or safe. Indeed, the annals of medicine are filled with seemingly great ideas that proved ineffective or even harmful to patients when they were carefully evaluated. Today, we require proof — usually a clinical trial before recognizing a new drug, biologic therapy or device as a standard of treatment. Of course, it is also important to recognize that today's standards of therapy will almost invariably be replaced tomorrow. The cycle of innovation to assessment and reassessment is one of the foundations of medical science.

Yet this cycle is facing a crisis, in part because too few patients are enrolled in clinical trials. The gap between the knowledge advancement we could have and the nearly stagnant reality is especially evident in cancer research. Clinical research for childhood malignancies (which account for less than 2 percent of all cancer) stands as the unparalleled exemplar, with the vast majority of children participating in clinical trials as part of their treatment. For children with cancer, clinical trials are accepted as the norm by physicians, patients and their parents. In fact, data on children's clinical trials suggest that simply participating improves outcomes, even if the therapy being studied is not fully effective. This reflects the fact that clinical trials reduce the variability of treatment modifications, such as physicians' more subjective changes in dose or regimen. In all, U.S. childhood cancer death rates declined by more than 50 percent from 1975 to 2006, averting 38,000 deaths.

But meanwhile, less than 5 percent of adults diagnosed with cancer enter a clinical trial, in part because they are largely treated by oncologists in private practice — unlike children, who are primarily treated at academic medical centers. The low rate of participation in clinical trials hurts the development and regular renewal of national standards of cancer treatment, the collection of biological samples from large populations of patients and the ability to comprehensively monitor outcomes.

Given the cost and complexity of modern cancer care, it is incumbent on physicians to assess the diagnosis and management of oncology patients objectively, rigorously, efficiently, constantly and successfully. Innovations need to be complemented with the assessment and reassessment of presumed standards of care. From my perspective, this is best done through clinical trials and protocols, modeling what has been done over the past decades in childhood cancer. That standard should be incorporated into adult cancer care, although this will require oncologists and patients to transform their attitudes and recognize clinical trials as essential to improving the outcome of cancer.



Sincerely,

Philip A. Pizzo, MD

Dean

Stanford University School of Medicine

Carl and Elizabeth Naumann Professor, Pediatrics,

Microbiology and Immunology

# upfront

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

## Hard knocks

NEW RESEARCH HAS SHOWN THAT CHILDREN'S RISK for learning and behavior problems and obesity rises in correlation to their level of trauma exposure, says the psychiatrist at the School of Medicine and Lucile Packard Children's Hospital who oversaw the study.

The findings could encourage physicians to consider diagnosing post-traumatic stress disorder rather than attention deficit/hyperactivity disorder, which has symptoms similar to PTSD but very different treatment.

"Contrary to some people's belief, children don't get used to trauma. These events remain stressful and impact children's physiology," says senior author Victor Carrion, MD, associate professor of psychiatry and behavioral sciences.

The study was published online June 8 in *Child Abuse & Neglect: The International Journal*.



The findings provide compelling evidence that pediatricians should routinely screen children for trauma exposures, says Carrion,

who is also a child psychiatrist at Packard Children's. "As simple as it may seem, physicians do not ask about trauma," he says.

The study builds on earlier work that linked worsening health in adults with their dose of exposure to nine types of adverse childhood events, in-

cluding being subject to various kinds of abuse or neglect; having a household member who abused alcohol or drugs, was incarcerated or was mentally ill; having a mother who was treated violently; and not living in a two-parent household.

To perform the study, the researchers evaluated medical records from 701 children treated at a primary-care clinic in Bayview-Hunter's Point, a San Francisco neighborhood with high rates of poverty and violence. Each child's exposure to adverse events was scored on a scale from 0 to 9, with one point given for each type of adversity. The researchers also evaluated the medical records for evidence of obesity and learning or behavior problems.

#### ADVERSE EFFECTS

Two-thirds of the children had experienced at least one category of adversity, and 12 percent experienced four or more categories. An adversity score of 4 or higher left kids 30 times as likely to show learning and behavior problems and twice as likely to be obese as those with a score of 0.

Prior research has shown that about 30 percent of children in violent communities have symptoms of post-traumatic stress disorder, which can include the learning and

behavior problems detected in the current study, Carrion notes. However, a physician unaware that a child had experienced trauma, and noting the child's physiological hyperarousability and cognitive difficulties, may diagnose ADHD instead of PTSD.

That's a problem because the two disorders have opposite treatments, he says. Kids with PTSD need psychotherapy, not the stimulant medications given for ADHD.

"Children can recover from PTSD with the appropriate treatment, which is one of approach and not avoidance," Carrion says. "By not asking about trauma, we're utilizing avoidance. We're perpetuating PTSD."

It's important to expand access to psychotherapy, even if only short-term, for impoverished children with PTSD, says Carrion. He's working with collaborators and community partners in San Francisco to launch the Center for Youth Wellness, combining pediatrics, mental health services, educational support, family support, research and child-abuse response. It's set to open by mid-2012. — ERIN DIGITALE

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*The research was funded by the Lennar Urban Corp., the National Institute of Mental Health and the Evans Foundation.*

## Autism redux

A NEW SCHOOL OF MEDICINE STUDY OF TWINS suggests that non-genetic factors play an unexpectedly large role in determining autism risk, turning upside down recent assumptions about the cause of this common, disabling developmental disorder.

From prior studies of shared autism in twins, scientists had estimated that 90 percent of autism risk was attributable to genes and only 10 percent to non-genetic environmental factors. But the new study — the largest ever of twins in which at least one in each pair has autism — shows almost the opposite: It found that genes account for 38 percent of autism risk, with environmental factors explaining the remaining 62 percent.

"It took me a bit by surprise that the heritability of autism was so much lower than previous studies calculated," says Joachim Hallmayer, MD, associate professor of psychiatry and behavioral sciences and first author of the new paper, which appeared in the July 4 issue of *Archives of General Psychiatry*. "Our work suggests that the role of environmental factors has been underestimated."

Although the study does not identify specific environmental factors, they could in-

clude any non-genetic factors that influence autism risk.

The children studied were 192 pairs of twins identified from a California-wide registry of children who receive services for developmental disabilities. The large size of the study and the fact that the subjects were drawn from California's entire, highly diverse population means the study's results are more reliable and apply more broadly than those from prior studies, which examined small, homogeneous groups of children in Northern European countries, Hallmayer says.

The study included 54 pairs of identical twins and 138 pairs of fraternal twins. At least one child from each pair had been diagnosed with full-blown autism or a less severe form of autism spectrum disorder. The scientists conducted standardized evaluations to verify the children's diagnoses, a step that had been omitted in many prior studies.

To calculate the relative contributions of genes and environment to autism risk, the researchers then examined the difference in shared autism rates between identical and fraternal twins. Identical twins share all their genes, fraternal twins share half of theirs, and both types of twins share most elements of their

Scientists had estimated that 90 percent of autism risk was attributable to genes. The new study found that genes account for 38 percent of autism risk, with non-genetic factors explaining the remaining 62 percent.

environment from conception through childhood. As the scientists expected for a disease that is partly explained by genes, the identical twins were more likely to share an autism diagnosis than the fraternal twins. Identical twins did not always share their diagnosis, hinting that non-genetic factors contribute to autism. The surprise came, however, in the calculation of environmental contributions to autism risk.

“The dizygotic [fraternal] twins are more similar than you would expect if you take only genetic factors into account,” Hallmayer says. The higher-than-expected degree of similarity between fraternal twins confirmed that something other than genes was at work — in other words, the twins’ shared environments helped explain their shared diagnoses.

And what might the unknown environmental risk factors be? “That’s the multimillion dollar question,” Hallmayer says.

— ERIN DIGITALE

*The research was funded by the National Institute of Mental Health and Autism Speaks.*

### Jittery bugs

IF YOU WERE THE SIZE OF A BACTERIUM, the lining of a stomach would seem like a rugged, hilly landscape filled with acid-spewing geysers, says Manuel Amieva, MD, PhD, assistant professor of pediatrics and of microbiology and immunology.

*Helicobacter pylori*, the



bacterium that causes ulcers and some cancers, must navigate through the treacherous terrain to find sanctuary in the mucous layer that coats the inside of the stomach. In a study published in *mBio* on July 26, Amieva and others identified a protein that regulates *H. pylori*'s ability to seek slimy shelter. That protein could be a target for therapies that specifically combat *H. pylori* while leaving our friendly gut bacteria alone.

*H. pylori* makes a living in

about half the people on Earth and typically goes unnoticed. But in about 15 percent of those infected, the microbes cause ulcers. Yet worse, *H. pylori* infection increases the risk of gastric cancer.

Although it takes up residence in our stomachs, *H. pylori* can't stand our caustic digestive juices. To avoid getting burned, the microbes use whiplike appendages called flagella to power their corkscrew bodies into the mucus that protects our stom-

ach cells. While it was known that the bacteria colonize the stomach's surface mucus, the School of Medicine researchers found that they also live deep in some of the glands that tunnel down from the stomach's inner surface.

A protein called ChePep helps the bugs find their way into safe areas, the researchers discovered. Without it, the bacteria behaved erratically, doing a lot more backward swimming than normal, as if always trying to

escape toxic conditions.

"They weren't taking the nice arcing trajectories that you see with normal *H. pylori*; they were moving herky jerky, taking short swims, then stopping, then turning and swimming off again," says lead author Michael Howitt, PhD, a former graduate student in Amieva's lab.

Microbes use their so-called chemotaxis machinery to move based on the chemical composition of their surroundings, swimming toward good conditions and away from bad.

"If the bacterium isn't sensing anything bad, it'll rotate the flagella in one direction and swim straight," says Amieva, senior author of the study. "But if something bad is seen, it'll activate a clutch, stall the flagella and switch directions." The newly discovered ChePep helps regulate when that clutch gets activated.

The researchers were surprised to find an unknown part of the chemotaxis machinery. "The chemotaxis system is the best-studied biochemical signaling system ever. Finding a new player was totally unexpected," says Amieva.

While most components of the chemotaxis machinery are shared in all bacterial families, ChePep is unique. Its uncommon nature means ChePep could be a good drug target for fighting *H. pylori*. "If you blocked ChePep, the beneficial bacteria in our guts would still have



their chemotaxis machinery intact," says Howitt. — SUSAN L. YOUNG

*The work was supported by the National Institutes of Health, the National Cancer Institute and the National Institute of Allergy and Infectious Diseases.*

### Sleep interrupted

GETTING ROUSED FROM A GOOD SNOOZE is not only bad for your mood, it could be bad for your memory, according to a new study in mice.

Experts have long hypothesized that sleep continuity is

important for memory, but it has been difficult to investigate, in part because a preferred research subject — the mouse — is so jumpy. Once you wake a mouse up, it gets stressed (which itself affects memory), and it doesn't fall back asleep for a long time.

In addition, any kind of sleep manipulation affects all features of the sleep — not only continuity but also duration, quality and percentage of rapid eye movement sleep, explains Luis de Lecea, PhD, associate professor of psychiatry and behavioral sciences,

who co-led the study with H. Craig Heller, PhD, professor of biology.

So the researchers' challenge was this: How could they fragment sleep into shorter episodes without affecting sleep intensity or duration and without invoking a stress response, so they could see its effects on memory?

They turned to optogenetics, a technique in which specific cells are genetically engineered to be controlled by pulses of visible light. The researchers used the method on the type of neurons that

## The challenge: How could they fragment sleep into shorter episodes without affecting sleep intensity or duration and without invoking a stress response, so they could see its effects on memory?

play a key role in switching between sleep and wake, and found that by stimulating these cells with 10-second bursts of light, they could fragment the animals' sleep without affecting total sleep time or quality and composition of sleep.

After manipulating the mice's sleep, the researchers tested their memories. They presented the mice with two objects: one that they had seen before, and another that was new. Rodents' natural tendency is to explore novel objects, so if they spent more time with the new object, it would indicate that they remembered the other, now familiar object.

The result: Mice with fragmented sleep explored the novel object no longer than the familiar one, showing that their memory was affected.

While the study does not reach any conclusions about the amount of sleep needed to avoid memory impairment in humans, it does suggest that memory difficulties in people with apnea and other sleep disorders are likely connected to the compromised continuity of sleep caused by such conditions.

The findings were published online July 25 in the *Proceedings of the National Academy of Sciences*.

— MICHELLE L. BRANDT

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*The study was funded by the National Institute of Mental Health and the Klarman Family Foundation.*

### New digs

STANFORD UNIVERSITY MEDICAL CENTER has begun laying the groundwork for its much-anticipated, \$3 billion renewal project, which will bring new state-of-the-art patient care and research facilities to the community.

The six- to seven-year renewal project includes construction of a new Stanford Hospital and laboratories at the School of Medicine, and the expansion of Lucile Packard Children's Hospital.

"At the heart of the project is the hospitals' and medical school's need to deliver rapidly advancing medical science to a growing community of patients and providers in the safest, most future-thinking and seismically sound environment," says Mark Tortorich, vice president of planning, design and construction for the hospitals.

Site preparation work began this summer. One of the first projects is an upgrade to the Hoover Pavilion on Quarry Road. Originally built in 1930 as the Palo Alto Hospital, the site today houses outpatient and administrative offices and the Arboretum

Children's Center. The building will be modernized and improved, yet preserved through a facelift so it will better resemble its historic image. A new parking garage will also be added to the site.

On Welch Road, major utility upgrades are being made for the new buildings. Water services, gas lines and information technology infrastructure — located under Welch Road between Pasteur Drive and Quarry Road — will be replaced over the next 18 to 24 months. Welch Road will then be repaved, with a center-turn lane and new bicycle lane. The landscape and median strips will be improved, benefitting all the Welch Road buildings.

### PACKARD ADDITION

This fall, demolition of the buildings at 701 and 703 Welch Road will clear ground for the addition to Packard Children's Hospital, which will add 104 beds to the hospital's capacity. In early 2012, utility lines that serve the current Packard Children's Hospital — which, like Stanford Hospital, will continue to care for patients throughout the renewal process — will be redirected to make way for construction, which will take about 18 months. By the fall of 2012, says Tortorich, "you'll begin to see a large hole in the ground" as excavation begins for the addition to the children's hospital.

The underground parking structure and floors will be built first, then the above-ground work will become visible, with steel framework scheduled to rise in summer 2013. Construction is expected to be completed by 2016.

At the medical school, the 1959 Edwards, Lane and Alway buildings, which do not meet current seismic standards, will be replaced with three laboratory buildings to be called the Foundations in Medicine buildings. Construction for the first FIM structure is scheduled to begin April 2013 with occupancy scheduled for July 2015.

At Stanford Hospital & Clinics, some facilities and services currently at 1101 Welch Road will be moved into the renovated Hoover Pavilion to help prepare for construction, Tortorich says. The Welch Road building and the Blake Wilbur parking structure then will be removed and prepared as the site of the new Stanford Hospital.

Shovels will go into the ground in the beginning of 2013 with steel framework for the new, 600-bed Stanford Hospital to go up in August 2014. The new hospital, including an enlarged and enhanced emergency department, will be completed in 2017, with planned occupancy the following year. — JULIE GREICIUS

# GAME CHANGE

## ON THE VERGE OF A REVOLUTION

SYLVIA PLEVITIS  
WAS EXCITED.  
IT WAS DECEMBER 2003,  
AND SHE HAD JUST  
LEARNED THAT THE NATIONAL  
CANCER INSTITUTE WAS  
OFFERING MILLIONS OF DOLLARS TO RESEARCHERS  
IN A VARIETY OF NON-BIOLOGICAL  
FIELDS TO STUDY HOW CANCEROUS TUMORS  
BEHAVE AND GROW.

SHE TOLD HER BOSS, GARY GLAZER, MD, CHAIR OF STANFORD'S RADIOLOGY DEPARTMENT, "THIS IS MY CHRISTMAS PRESENT. THEY ARE TALKING TO ME." • So Plevritis, who has a PhD in electrical engineering, emailed mathematicians, computer scientists, engineers and biochemists across the campus — anyone she thought would be interested in pursuing the grant. Her message went viral as recipients sent it on to others who might want to be involved. • At the time, Plevritis was deep into her second career: a public-health-focused effort to optimize magnetic resonance imaging technology to diagnose breast cancers. But she wasn't a laboratory scientist, or a physician. • "At first I wasn't focused on the molecular biology of the tumor, but on how to deliver data that a health policy-maker would need to recommend new clinical guidelines," she says. "But as I grew more curious about cancer progression, I'd read papers discussing the effect of one gene on one pathway in a cell, and I'd think, 'We're looking at this disease in a very narrow way. We need to think methodically of an underlying network of hundreds or thousands of interactions that drive a cell to divide.'" In other words, a kind of a circuit. • With that, Plevritis faced another conundrum. "I spent four years building a funded research program to study breast cancer screening, but I was increasingly interested in the natural history of the disease. There was only so much I could squeeze out of the clinical data to understand cancer progression, and I felt I needed to dig deeper. I needed to learn about the molecular world of cancer, and that put me at another crossroads in my career. I could either continue with public health, or change direction again."

By KRISTA CONGER  
Illustration by Anita Kunz



In the end, she decided to make the switch. But she wasn't on her own. Increasingly, investigators are realizing the advantages of viewing cancer as a system, rather than individual mutant cells. Combined with the many advances we've made in the past few years in understanding the molecular biology of healthy and cancerous cells, we stand a chance of finally making significant inroads against a disease that has captured the fear and imagination of our nation for four decades.

"Revolutions in cell and molecular biology, biomedical engineering and information sciences are creating the potential for a new generation of more effective and less toxic cancer therapies," says Beverly Mitchell, MD, who directs the Stanford Cancer Institute. "We can now systematically identify many of the molecular roots of disease and employ powerful computational systems to interpret a dizzying amount of data."

**T**HE FUTURE HASN'T ALWAYS LOOKED SO PROMISING. • Since President Richard Nixon declared a "war on cancer" on Dec. 23, 1971, we've seen a slow and steady decline in the death rates for several common forms of the disease, but many cancers remain deadly. With the exception of a few precious triumphs, the diagnosis still often feels like nothing less than a heartbreakingly punctuated death sentence: Treatments can lead to disease-free intervals, but about 50 percent of adult cancer patients can still expect to die from their disease.

As Mitchell points out, this is poised to change. In the decade since the first drafts of the Human Genome Project were completed, eye-opening discoveries have become commonplace. As we've burrowed into the complexities of our genetic material, it has become easier to identify abnormalities in tumor DNA. We've learned about corrupted molecular signaling pathways, cell cycle missteps and drug resistance. We can watch in real time as cancer-killing cells home in on tumors in a human patient and even calculate the phenomenal physical force faced by the cells as they leave the shelter of the tumor and enter the bloodstream.

"We're now prepared to ask some game-changing questions," says Jerry Lee, PhD, deputy director of the National Cancer Institute's Center for Strategic Scientific Initiatives. "We have an amazing amount of data. Now we need insight."

But more than scientific insight is needed to eliminate some of the biggest obstacles to treatments and cures: a dysfunctional cancer clinical trial system, disastrous drug shortages and a health-care system unable to deliver cancer care at an affordable price. Without meaningful change at the policy level, many experts worry that we will squander the opportu-

nity to bring these discoveries from the lab to patients.

"It is clear that our nation is at an important crossroads, where the science before us presents unprecedented opportunities to create new and better medical products and promote better health for the public," writes Food and Drug Administration commissioner Margaret Hamburg, MD, in an October 2011 FDA report. "But we must act now and work together to capitalize on this groundbreaking science in order to bring safer and more effective treatments to American families and keep our position as the global leader in scientific innovation."

"Basic scientists have opened a fire hose of information," agrees biostatistician Phil Lavori, PhD, who chairs Stanford's Department of Health Research and Policy. "There are many, many good ideas. But there are real problems in the ways we test these ideas and bring the resulting therapies to patients. If we can't resolve these, we're risking an incredible opportunity to make progress."

Indeed, optimism about the scientific side of cancer research is pervasive. Concepts such as cancer stem cells, immunotherapy and oncogene addiction (a tumor's dependence on the activity of a single gene) have exploded on the scene in the past 15 years. They've left us teetering on the precipice of finally understanding what makes a good cell go bad, and how we can mitigate the damage when it does.

Emboldened by these advances, researchers have begun to tackle the bigger picture of who gets cancer and why, and what can be done about it. For example, the National Cancer Institute recently launched the Provocative Questions endeavor, seeking answers to "important but non-obvious" questions, such as the role of obesity in cancer incidence, how an organism's life span affects the molecular mechanisms of cancer development, and whether it's possible to enhance survival — not by killing a tumor, but simply by keeping its growth static. Then the institute invited researchers to submit proposals by mid-November this year to answer one of 24 of these questions; about \$17.5 million is up for grabs.

"We're looking to change the research paradigm," says NCI's Lee, "by looking beyond the horizon. And we can do that by not only asking these types of questions, but also by providing the framework for robust data sharing that will allow researchers to ask and answer their own questions."

The net effect of these advances is an exciting mix of getting up close and personal with the genes and molecules that drive uncontrolled cell growth while also taking a deliberate step back and striving for a more global understanding of the behavior of the many, varied disorders we call cancer. This wide-angle approach is embodied in an emerging concept called systems biology — precisely what the NCI was seeking to encourage in 2003 with the grant announcement that sparked Plevritis' imagination.

### **A Breathalyzer-style test for lung cancer? It's not your usual cancer diagnostic test, but if**

**you think about it,** it makes a lot of sense. Breath carries molecular clues about your health, especially about your lungs. And unlike chief alternatives for lung diagnostics — biopsy and CAT scans — a breath test causes no harm.

Daya Upadhyay, MD, who runs Stanford's lung nodule clinic, has used her molecular biology skills to make just such a test, which she hopes will give patients a head start on fighting cancer. But does her test work? A seed grant

from the Stanford Cancer Institute will help Upadhyay find out.

In addition to funding the seed grants (\$850,000 to 17 investigators this year), the institute manages and monitors Stanford's cancer clinical trials system; holds seminars, lecture series and other meetings to bring together potential collaborators from multiple fields; sponsors cancer educational programs; and organizes core facilities where researchers can share critical technologies that are too expensive for individual labs to buy.

As a National Cancer Institute-designated cancer center, the Stanford institute integrates multidisciplinary cancer research, training and education with comprehensive clinical care. It is made up of over 300 experts — investigators and clinician-researchers from more than 30 academic departments throughout the medical school.

"Patients receive comprehensive personalized cancer care from an integrated team of specialists, in an environment of discovery and learning," says institute director

Beverly Mitchell, MD. Patients also have the potential to contribute to the study of cancer by participating in clinical trials.

"The Stanford Cancer Institute builds on a long tradition of cancer discoveries and new treatments developed at Stanford," says Mitchell. "It also taps Stanford's significant intellectual resources in academic departments outside the School of Medicine. Simply stated, the institute's goal is to mobilize the enormous potential of Stanford University in the fight against cancer." — MICHAEL CLAEYS

### SYSTEMS BIOLOGISTS OFTEN TALK OF AN EFFORT TO CRACK THE "BLACK BOX" OF A CANCER CELL — IN EFFECT MAPPING A COMPLEX CIRCUIT OF CELL GROWTH AND DEATH HONED BY MILLIONS OF YEARS OF EVOLUTION.

The goal, explains Plevritis, now an associate professor of radiology and a Stanford Cancer Institute member, is to "look at cancer as an integrated system. In the past, people have studied metabolism, or cell death, or oxygen use, or any number of other events in cancer cells. We want to look at all these processes simultaneously and how they regulate one another."

For example, taking such a long view of cancer can identify parallel gene signaling pathways, or networks that contribute to drug resistance. Knocking out one pathway with a targeted therapy may slow the cancer's growth, but the cell can still use the alternative route. Blocking both simultaneously takes advantage of a concept known as synthetic lethality and can be a way to specifically kill cancer cells while sparing normal tissue.

"This is a powerful approach that is just in its infancy," explains Amato Giaccia, PhD, professor and director of radiation oncology research at Stanford. "In this scenario, neither of the two drugs alone will have much effect, but together they can be lethal to the cancer cell."

Furthermore, the cancer cells may have established unique pathways rarely used in normal cells. "I believe that the number of ways that a cell can become cancerous is not infinite," says Plevritis. "There are specific drivers, or gene mutations, that orchestrate this transition. If we can identify these drivers and then target and manipulate them, we may be able to move cancer cells into a more benign state."

Some of these are oncogenes, genes that when mutated,

drive uncontrolled growth. Others are genes that govern processes like differentiation that funnel cells into developmental dead ends, where they can do little harm.

Plevritis speculates that there may be as few as 100 drivers. "It should be manageable to understand the system. Once we uncover a network of relationships on a molecular level, when we perturb the system, we can understand how the network responds and design more effective therapies."

### SYSTEMS BIOLOGY MAY BE ONE OF THE NEWEST KIDS ON THE CANCER THERAPY BLOCK, BUT IT OWES ITS EXISTENCE TO A MORE FAMILIAR CONCEPT —

personalized medicine. Stanford immunologist and oncology division chief Ron Levy, MD, pioneered the technique in the mid-1980s when he hit upon the idea of using monoclonal antibodies to attack cancer-specific molecules on the surface of lymphoma cells. The technique required generating a new batch of unique antibodies for every patient, thus personalizing their treatment.

"For some types of cancer, monoclonal antibodies totally changed the game," says Levy. "However, although this type of treatment can put people in remission, it only cures a few of them. We need to take them up another notch in potency, to make them work better, and to take advantage of these remissions we're inducing." Levy believes the key lies in further activating the immune system against the cancer.

While some personalized medicines, like the prostate cancer therapy Provenge, follow Levy's original model of generating a unique treatment for each patient, others, like the breast cancer drug Herceptin, work by sorting patients into

smaller subgroups and assigning treatment based on the pattern of gene expression in their tumors.

“Personalized medicine is an age-old idea,” says Levy. “Physicians have always been thinking about how best to treat individual patients. But advances in technology and understanding about tumor biology have allowed us to add a whole other dimension. Now we can test the gene expression levels and DNA sequences in each person’s tumors and match them with a therapy most likely to work for them. The potential is amazing.”

Health economists are quick to point out that this potential sometimes comes with a staggering price tag: Three rounds of Provenge, marketed by the Seattle-based company Dendreon, costs about \$90,000. Roche’s Zelboraf — a new treatment for advanced melanoma patients whose tumors carry a specific mutation — costs \$56,000 for six months, and Seattle Genetics’ Adcetris, which links a tumor-targeted antibody with a cell-killing drug, costs about \$108,000 per year.

“I wonder if we’ve now entered a mode where \$100,000 per year is an acceptable price for a cancer drug,” says Stanford associate professor of pediatrics and bioinformatician Atul Butte, MD, PhD. “As drugs become more and more targeted to subsets of patients, the price tends to increase. I think the real challenge of personalized medicine now is to figure out how to get costs down.”

Levy disagrees. “It’s not automatic that the overall course of treatment will be more expensive,” he says. “There is a real possibility that we can drive down costs by making better treatment choices for patients. If we pick a treatment most likely to work, while also delivering fewer side effects, that can be cost-saving. Non-targeted cancer drugs can also be expensive, especially if they are associated with hospitalization for side effects. Then the cost to the system can be much higher than the new targeted agents.”

### THE OUTPOURING OF HUMAN GENETIC INFORMATION OVER THE PAST DECADE IS BEING TAPPED AS A RESOURCE FOR CANCER TREATMENTS.

Some of Butte’s work is an example of this. Butte, chief of the division of systems medicine in pediatrics, has used information from publicly accessible databases of gene expression patterns and genetic changes in cancer cells to identify which

signaling pathways are likely to be disrupted in specific types of cancer and other diseases. He then pairs the diseases with existing drugs that target the same pathways. In this way, he’s found some unlikely combinations: a widely available, inexpensive medication for ulcers that seems to work in an animal model of a lung cancer called adenocarcinoma, for example. “It’s as if we’re panning for gold,” says Butte. “If I can find these types of associations in my bioinformatics lab, without first doing a wet experiment, we start to think, ‘Wow, how the world has changed.’”

### YET WITH CANCER RESEARCH GOING GANGBUSTERS, YOU CAN’T HELP BUT WONDER: WHERE ARE THE CANCER TREATMENTS WE WERE PROMISED?

Many are stuck at the human testing stage, it turns out. According to a 2010 Institute of Medicine report, “the system for conducting cancer clinical trials in the United States is approaching a state of crisis. ... If the clinical trials system does not improve its efficiency and effectiveness, the introduction of new treatments for cancer will be delayed and patient lives will be lost unnecessarily.” The report estimated that only about 60 percent of NCI-sponsored trials are completed and published — a figure it called “a terrible waste of human and financial resources.”

On the face of it, the concept of a comparative clinical trial is simple: Give one group of patients a proposed treatment and not the other group. Watch to see who improves. Variations on this theme are described in ancient texts, and a similar technique was used in the 1700s to show that citrus fruits can cure scurvy. To make the comparison fair and unbiased, randomly assign people to treatment groups and, to make it more precise, start with a homogenous group of patients.

Until now, we’ve had only a few ways to assess the variability among patients and their tumors. But in an age of personal genomics, clinicians can make many more distinctions. Unless you have an identical sibling, no one else can lay claim to the particular assortment of nucleotides that makes up your DNA. (Even if you have an identical twin, genetic modifications in utero are likely to confer subtle yet important regulatory differences in how your cells respond.)

As the depth of our understanding grows, it becomes

‘I WONDER IF WE’VE NOW ENTERED A MODE WHERE \$100,000 PER YEAR IS AN ACCEPTABLE PRICE FOR A CANCER DRUG.’

clear that the old model of one condition, one drug, one large group of — theoretically homogenous — patients, and the luxury of years in which to come up with an answer is simply inadequate. The pace of medicine today, the need to tailor treatments to the genetic background of a patient and his or her tumor, and the concept of dynamically responding to changes in cancer growth all demand new clinical trial designs. We need rigor without rigidity.

Of course, any changes to the system must still lead to an outcome that will help patients: new treatments or drugs approved by the Food and Drug Administration.

“We are very interested in the possibility that some people will respond better to a drug than others,” says Robert Temple, MD, the deputy director for clinical science at the Center for Drug Evaluation and Research at the FDA. “We also support trial designs that include adaptive elements if a tumor marker predicts survival. If you find a marker that predicts no response, you could drop those people out of the study, for example. But the basic requirement for getting a drug to the marketplace will always be to show that it works in a defined population.”

**A**DAPTIVE DESIGN ALLOWS RESEARCHERS TO ALTER participants’ treatment plans during the study in response to ongoing measurements of efficacy. Another concept, enrichment, involves enrolling only those patients who are most likely to benefit from the treatment tested. Doing so increases the likelihood of generating statistically significant, useful results.

“We want to learn with each patient we treat,” says Stanford Cancer Institute associate director Branimir Sikic, MD. “Right now, we markedly overuse chemotherapy drugs. Maybe half of all patients with common cancers are resistant and don’t benefit from the treatment. But they all get toxic side effects. Now we’re slowly but surely matching up what we know about key mutations and critical pathways in cancer with drugs targeted to those vulnerabilities.” Sikic’s upcoming ovarian cancer trial capitalizes on this knowledge to predict which of five chemotherapies commonly used to treat the disease will work best for each patient.

“We’re trying to harness the power of genomics to answer questions about drug sensitivity,” says Sikic. “If we predict that a patient’s tumor will be sensitive to a particular chemotherapy, and we’re right, the next patient with a similar genomic background will have a higher likelihood of being assigned that drug. With a reasonably accurate test, we hope to get an answer about the effectiveness of treatment after treating fewer than 100 patients. This is very different from the traditional clinical trial model that looks for performance

in large groups of patients over long periods of time.”

Well-designed trials are useless, however, without patients to enroll in them, or drugs to use in them. “We’re going to have to get around the problem that less than 5 percent of adult cancer patients who could be participating in clinical trials are enrolled in one,” says Lavori. “The rate of participation is abysmal.”

The problem escalates rapidly when willing patients are stratified into smaller and smaller subgroups based on their particular combinations of biomarkers. Often many patients must be screened to find one who fits the necessary profile, and this process must be repeated for each enrollee.

In addition, chronic, worsening drug shortages are hampering the completion of even adequately enrolled trials. According to an October *Scientific American* article, 15 of the nearly 200 drugs in short supply in 2011 are cancer drugs required for clinical research; more than 150 NCI-sponsored trials involve medications with limited availability.

The drug shortage problem, which is considered by many physicians and patient advocacy groups to be a national emergency, has been worsening steadily since 2006. According to the FDA, about 75 percent of the shortages result from problems with product quality or delays in production or capacity. What’s not clear is what to do about the crisis. In February, U.S. Sens. Amy Klobuchar, D-Minn., and Bob Casey, D-Penn., introduced S296 — the Preserving Access to Life-Saving Medications Act.

The act requires prescription drug manufacturers to notify the FDA at least six months before any planned discontinuation or interruption in the production of critical drugs, or as soon as possible when unexpected events appear likely to cause a drug shortage. It would also require the FDA to notify the public of shortages and the plan to address them. However, as the agency’s Center for Drug Evaluation and Research’s Edward Cox, MD, noted in a public workshop in September, the FDA has no authority to require that a company produce certain types or amounts of drugs. Cox is the coordinator for CDER’s Drug Shortage Program.

“Manufacturing capacity is not something that we control,” says Cox.

### INADEQUATE ADULT CANCER TRIAL PARTICIPATION IS ANOTHER PROBLEM WITHOUT AN OBVIOUS SOLUTION.

In June, the Institute of Medicine’s Forum on Drug Discovery, Development and Translation held a workshop at the Mount Sinai School of Medicine to explore the promise of adaptive trial designs and how to increase public engagement

**As experts like to point out, cancer isn't just one disease.** And so understanding what causes

the various forms of cancer and pinpointing effective treatments requires the insight and investigative skills of scientists from several disciplines.

Many of these discoveries come from the Stanford School of Medicine, where more than 300 scientists and clinicians have made cancer their focus. Below is a small sample of the Stanford findings reported during the past year that are moving cancer research forward:

### Starving cancer cells

Researchers have identified a compound that kills kidney cancer cells by restricting their prime energy source: glucose. In animal studies, the drug halved the amount of glucose imported by tumor cells, slowed tumor growth and produced few side effects.

If successful in humans with kidney cancer, the compound may offer an improvement over current chemotherapy drugs that indiscriminately kill cancer cells and other rapidly dividing cells, like blood and hair follicle cells.

"This study demonstrates an approach for selectively inhibiting the ability of cancer cells to take up glucose, which is a pretty powerful way of killing those cells," says senior author Amato Giaccia, PhD, professor of radiation oncology, whose study was published in *Science Translational Medicine*.

### Potential therapy for skin cancer

People with a genetic disease called basal cell nevus syndrome develop hundreds, even thousands,

of skin cancers each year. Many require frequent surgeries and develop significant scarring. A clinical trial by Jean Tang, MD, PhD, assistant professor of dermatology, found that an experimental drug significantly slowed or stopped the development of tumors in each of 24 patients who received the drug, and caused existing tumors to shrink in size. Tang presented the findings at the annual meeting of the American Association for Cancer Research.

The results were so positive that the randomized, placebo-controlled trial was halted early to allow all participants access to the drug, Genentech's GDC-0449.

"Many of our patients enrolled in this trial not because of their own disease but for their children who have inherited the same mutation," Tang says.

### Predicting treatment responses

Measuring tumors' initial response to treatment allowed researchers to predict the efficacy of a gene-targeting lung cancer treatment, they reported in *Science Translational Medicine*.

Some forms of cancer are highly dependent on the activity of specific cancer-causing genes called oncogenes. Dean Felsher, MD, PhD, and his colleagues observed that inhibiting oncogenes caused some tumors to shrink in a rapid and distinctive way,

enabling the researchers to create a mathematical "signature" of an oncogene-dependent tumor. The formula's accuracy was validated in a trial of an oncogene-suppressing drug. Patients with robust initial response had the predicted sustained tumor regression.

"With some simple measurements, we found we can determine when a cancer is addicted to a particular cancer gene and will respond to therapy targeting that gene," says Felsher, associate professor of medicine and of pathology.

### Confirming the role of cancer stem cells

Leukemia patients whose cancers express higher levels of genes associated with cancer stem cells have a significantly poorer prognosis than patients with lower levels of the genes. The finding is among the first to show that the cancer stem cell hypothesis — that some cancers spring from and are replenished by a small population of hardy and self-renewing cells — can predict outcomes in a large group of patients.

The study published in the *Journal of the American Medical Association* was led by Ash Alizadeh, MD, PhD, assistant professor of oncology. To gather the data, he and his colleagues conducted a retrospective analysis of more than 1,000 acute myeloid

leukemia patients.

"The clinical implications of this concept are huge," says Alizadeh. "If we're not able to design therapies to target this self-renewing population of chemotherapy-resistant cells, the patients will continue to have a tendency to relapse."

### Cutting off a tumor's blood supply

A bioengineered protein has been shown to prevent cancer cells from creating new blood vessels, thereby restricting access to nutrients and impairing tumor growth. The protein blocks two chemical receptors that regulate new capillary creation — a process called angiogenesis. When tested in mice, the protein inhibited angiogenesis more effectively than single-receptor blockers.

"Samples treated with our dual-action protein have minimal blood vessel formation, similar to a sample in which angiogenic factors are absent," says lead researcher Jennifer Cochran, PhD, assistant professor of bioengineering. The study was published in the *Proceedings of the National Academy of Sciences*.

Beyond cancer, preventing angiogenesis could help treat such diseases as macular degeneration, one form of which impairs vision through unchecked capillary growth in the retina.

— M.C.

in clinical trials. Participants noted many factors that may impede enrollment: a lack of awareness by physicians and patients of relevant trials, the reluctance of patients to agree to the time commitment and travel required for complex trials, and the difficulty of overcoming pre-existing preferences for certain medications or interventions, among others.

Lack of institutional support for those conducting clinical trials was also a concern. Several programs at Stanford aim to address these issues. Their success is evident in the numbers.

"Currently at Stanford more than 50 percent of children with cancer are in a clinical trial, and about 14 percent of adults," says Sikic, who directs Stanford's Clinical and Translational Research Unit and co-directs its Spectrum program,

which helps researchers and faculty members better understand how to design effective clinical trials. "Nationwide only about 4 percent of adults with cancer are enrolled."

The Stanford Cancer Institute typically has about 330 clinical trials open for enrollment at any one time, both adult and pediatric — which have much higher participation. As a result, pediatric cancers, unlike adult cancers, have seen some astounding clinical successes during the past 20 years.

"Until recently, we've acted as if the patient doesn't have to be a partner in their care," says biostatistician Lavori. "I think we need to reach out to patients and explain why it's so important to participate in clinical trials." Lavori is testing a new concept called point-of-care randomization in a

pilot study at the national Veterans Affairs Cooperative Studies Program, which allows patients and physicians to quickly and easily participate in clinical research.

“Many times there are three or four possible treatments for a patient’s condition,” says Lavori. “There really isn’t a compelling reason for a physician to pick one over the other. At that point we would randomize the choice of treatments, and use an adaptive trial design to quickly feed back which approach is preferable for which patients. If there’s a winner emerging, we should be able to see it relatively quickly.”

He sees this as a way to increase clinical trial participation among adult cancer patients that will quickly and efficiently drive the identification of effective new therapies. According to Lavori, it’s absolutely critical to do so.

“We need to use our interactions with patients to their full advantage, and tell them, ‘If you don’t want your children dying of cancer in the coming decades, you need to demand and participate in clinical trials.’”

### A DYSFUNCTIONAL CLINICAL TRIAL SYSTEM. A NATION STRUGGLING TO MANAGE A CRISIS IN OUR DRUG SUPPLY LINE.

And a health-care system that doesn’t blink at offering new treatments that far exceed in price most people’s annual income. What’s to be done?

Many experts agree that within the next five years, a cancer patient’s ideal course of care will look very different from just 10 years ago. Dependence on chemotherapy, radiation and surgery will be reduced; instead treatment will likely emphasize sequencing of both the patient’s genome and the tumor, and analysis of the tumor’s potential drug resistance. Treatment will be tailored to each patient and carefully calibrated to avoid promoting the survival of the strongest, most resistant disease-causing cells. The patient’s immune system cells may even be trained to specifically attack the tumor cells. Principles of evolution, population dynamics and mathematics might be incorporated to predict how the cancer cell population will respond to treatment, which will be monitored with unheard-of imaging capabilities.

But revolutionizing cancer care clearly also hinges on making big changes outside the laboratory. It will require support and innovation at academic medical centers around the country. “New opportunities inevitably create new challenges,” says Stanford Cancer Institute director Mitchell. “Some critical research technologies are too expensive for individual laboratories and instead require core facilities to be shared by many investigators. And although our ability to divide major

categories of cancer, such as breast cancer, into many subtypes offers the potential for highly specific therapies, it also creates new demands on our clinical trials system.”

**P**ROGRAMS LIKE STANFORD’S SPECTRUM HELP BY TEACHING clinicians and researchers how to design clinical trials to test their laboratory-inspired ideas. And the Cancer Clinical Trials Research Office works to increase accrual of cancer patients and to lessen the administrative burden of ongoing trials.

But progress will also require many people like Sylvia Plevritis, who fight in the trenches and direct troops. When Plevritis realized she needed to know more about health care, she returned to school to earn a master’s degree in health services research to complement her PhD in electrical engineering. And when she heard about the NCI announcement, she brought together people who hadn’t tackled cancer before — mathematicians, engineers and even statisticians — with experts in genetics, cancer and medicine to brainstorm new ways to think about cancer. Their work paid off: In October of 2004 Stanford was one of nine institutions to receive funding to plan a full-scale center, and in 2010, Stanford received \$12.8 million over five years to establish a Center for Cancer Systems Biology. “We’re in a very good place,” says Plevritis, who directs the new center. “We finally have the information and the structure to make a significant contribution to cancer care.”

At the national level, there have also been signs of progress. Although legislative action addressing drug shortages and spiraling health-care costs has been stymied by political and budgetary wrangling, President Barack Obama issued an executive order on Oct. 31 aimed at reducing prescription drug shortages by broadening the requirement that drug companies report possible shortages and expediting review of new drugs — much like the pending Klobuchar-Casey legislation. The executive order, however, also calls on the FDA to investigate possible instances of stockpiling or price gouging. Meanwhile, organizations like the FDA, the Institute of Medicine and the National Cancer Institute are striving to work together to increase the efficiency, timeliness and enrollment in cancer clinical trials. Despite promising signs, however, significant change will likely take time — time stolen from people fighting cancer.

“If we don’t rectify these issues, we may not make the progress we could be making,” says Lavori. “I want my children and grandchildren to be as free of the threat of cancer as we are now in this country of the fear of polio paralysis that gripped our country during the first half of the 20th century. Right now we are falling woefully short of that goal.” **SM**

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# Cancer's biographer

A CONVERSATION  
WITH SIDDHARTHA MUKHERJEE

Although oncologist Siddhartha Mukherjee, MD, has written a magnum opus on cancer, he doesn't think his über-expert status will change how he interacts with patients. The 2011 Pulitzer Prize winner for nonfiction says, "I try to be very humble about the possibilities and achievements of what can be done and what cannot be done in cancer. I think, unfortunately, becoming an expert is as much a poison to writing a book as it is to treating a patient."

Mukherjee realizes that America's 40-year war on cancer (or for that matter the 2,500-year war since Queen Atossa of Persia had a tumor excised from her breast) is littered with hopes and dreams for cures that never appeared. *The Emperor of All Maladies: A Biography of Cancer* is a sober assessment of the state of cancer and makes no claims that defeating it is within our reach. Yet Mukherjee acknowledges a biomedical renaissance is under way, writing, "The tools that we will use to battle cancer in the future will doubtless alter so dramatically in 50 years that the geography of cancer prevention and therapy might be unrecognizable."

Paul Costello, chief communications officer for the School of Medicine, caught up with the Stanford graduate in August as Mukherjee was on vacation winding down from the year's non-stop action as a clinician, researcher and celebrated author.

**Costello:** *I was intrigued by your suggestion that quite possibly cancer is our normalcy. What did you mean by that?*

**Mukherjee:** The idea that we can eradicate cancer completely from our bodies and societies forever in the future, I think, is somewhat absurd. And that's not because I'm being pessimistic or nihilistic about this project. It's the very biological nature



of cancer that makes this true. The very genes that allow our embryos to grow, our cells to grow, our bodies to grow — if you corrupt those genes, then you get cancer. And in that sense, cancer is sort of the corrupted side of our normalcy.

And that is bolstered by what I call the statistical reality of cancer — that one in two men and one in three women will face cancer in some form or the other, and one in four men or women will die of cancer in the United States. So, if those are the numbers, we can barely start calling cancer an abnormal event in our life.

**Costello:** *You've said that one reason you decided to write the book was that you found a lot of what's been written about cancer vaguely insulting. Why insulting?*

**Mukherjee:** There's a simplification, which I was reacting to. I'm talking about a typical book on cancer, which

you find in the health and wellness section, which says, “Eat broccoli and cure cancer,” or “Take this magic diet and you’ll never get cancer.” I think those have a kind of insulting simplification about them. I mean, patients need to know more. We need to have a much more sophisticated conversation around what cancer is, how long it’s been with us, what is happening, how we got here, what is the Cancer Genome Project, what are the new directions in cancer therapy.

**Costello:** *Why did you choose the words The Biography of Cancer? Why “biography”?*

**Mukherjee:** The word “biography” in the title came very late in the process of writing the book. For the longest time, the book was subtitled “A History of Cancer.” I chose the word “biography” for three reasons. The first was that I was drawing a portrait of the same subject, looked at over time, several times over: cancer in 1885, and then again in 1892, and then again in 1922. And every time, much like human beings change their appearance, their persona, it seemed that the imagination of cancer had changed radically in the public life. So in that sense, it was a biography.

The second reason is somewhat more prosaic, and that is that the book is stitched together using the condensed biographies of various cancer researchers, various cancer patients, cancer advocates, men and women like Mary Lasker and Sidney Farber. So in a

way, the narrative structure of the book is biographical.

And the final reason, and perhaps the most complex, is that when patients describe their illness — Susan Sontag does this very movingly in the very first lines of the book — they describe it, often, as moving in or inhabiting an altered state. It is as if their biographical sense of who they are changes as well.

**Costello:** *You just had a piece in The New York Times about cancer prevention and politics.*

*Can you talk further about that?*

**Mukherjee:** We think of cancer prevention as a sort of silo, as a kind of entity in and of itself. But, in fact, cancer prevention has multiple dimensions, and every dimension needs action.

The first challenge of cancer prevention, I think, is a scientific or a biological challenge — how does one carefully, rigorously identify carcinogens and other biological phenomena that are linked to cancer?

But the other problems, I think, we tend to ignore. There is a political problem, and that is that once these carcinogens have been identified they might turn out to be involved in some industry or another. For instance, famously, the tobacco industry vigorously denied the carcinogenicity of cigarettes for decades and there was a lull between the discovery of the carcinogen as a biological entity and its revelation in the political realm. That lull was about 10 years, maybe even longer. So, for in-

stance, the first studies that linked cancer to cigarettes actually predate even the 1950s, but it’s not until 1964 that the Surgeon General’s report makes a definitive conclusion about this in the political realm and thereby kicks off stronger control on tobacco.

And the final challenge is that once you finally establish that carcinogen in the public realm, the carcinogen has the capacity to keep coming back. As we know now, there are pockets of America where young teens have started smoking again. This is not only decades but almost 50, 60 years after the first discovery of tobacco as a carcinogen. So that’s a social problem.

**Costello:** *Right now, the words that we use in cancer are “race for the cure,” “the war on cancer.” And I wonder if you think we need to change those words.*

**Mukherjee:** I think we do. I think we need to re-create narratives to understand what is happening. Harold Varmus [director of the National Cancer Institute] said to me, “Wars are things we win and lose, but solving cancer is like solving a jigsaw puzzle. And you don’t win or lose a jigsaw puzzle; you solve it or you don’t solve it.”

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



# THE UNEXPECTED

## CANCER DURING PREGNANCY

By Erin Digitale

Photograph by TrujilloPaumier

Minnie and Paul Narth spent their first wedding anniversary in the hospital.

It wasn't terribly romantic —

Minnie wore a hospital gown, and an IV fed medication into her arm as she toasted the day with a glass of grape juice — but the Narths were content. It was the evening of Aug. 8, 2009, and Minnie,

37 weeks pregnant, was having labor induced.

In a few hours, the Narths would meet their eagerly awaited baby boy.

And they had good news from Minnie's obstetrician, who thought she could avoid a cesarean section, which would carry high risks in her fragile medical state.

Minnie Narth's immune system was running a marathon. She had spent the last three months fighting an extremely aggressive form of lymphoma. • Twenty years ago, the happy scene in Minnie and Paul's delivery room at Lucile Packard Children's Hospital could probably not have happened. For decades, pregnant women with cancer were almost universally advised to terminate their pregnancies. Oncologists saw pregnancy as a liability — not only could cancer treatments harm the fetus, doctors thought, being pregnant might worsen the cancer prognosis. • The Narths were surprised to learn about Minnie's treatment options. • "Our concern was — give chemo while she's pregnant?" says Paul. The response he remembers from Stanford lymphoma specialist Ranjana Advani, MD, was, "Of course we can!" • The surprise is understandable, says Richard Theriault, MD, a breast oncologist at MD Anderson Cancer Center in Houston who has studied cancer and pregnancy for 20 years. Expectant mothers arrive for treatment having spent months avoiding pregnancy no-nos like poached eggs, sushi, aspirin. • "We basically tell them, don't breathe, don't do any of these things — but we're going to give you chemo," Theriault says. "It does sound really crazy, doesn't it?" • When Paul and Minnie married on Aug. 8, 2008, his parents and her large, close-knit Filipino family were ecstatic. The news of her pregnancy a few months later added to everyone's joy. She was 38 and hadn't been sure she would ever have children — the pregnancy felt like "such a gift," she says. • Then came the heavy bleeding and contractions, the rushed trip to her doctor, the ambulance ride to Packard Children's. • "The doctors came back and said it was cancer," says Paul, remembering the day in May 2009 that his six-months-pregnant wife was diagnosed with stage-4 diffuse large B cell lymphoma. "I went to pieces."

MINNIE AND PAUL NARTH FOUND OUT IN THE SECOND TRIMESTER OF HER PREGNANCY WITH THEIR SON, KIERON, THAT SHE HAD CANCER.

Minnie's first reaction was denial: "It's impossible that I have cancer everywhere, all of a sudden."

Her own doctor had thought the on-and-off bleeding Minnie experienced throughout the pregnancy was due to a benign dermatologic condition, lichen planus, inside her vagina. But Minnie also had a new lump in one breast, she told obstetrician Natali Aziz, MD, and the maternal-fetal medicine team at Packard Children's, who took over her care after she arrived at the hospital via ambulance. Suspicious, Aziz — who specializes in high-risk pregnancies — admitted Minnie to the hospital and called for a full diagnostic workup.

Minnie's parents happened to be arriving the next morning from the Philippines for a visit to Paul and Minnie's Menlo Park home. Paul picked them up at the airport, telling them all he knew — that the doctors suspected Minnie had cancer.

At the hospital later that day, the diagnosis was confirmed. An MRI scan, chosen because it wouldn't require radiation exposure, showed that Minnie had tumors in her vagina, breast and ovaries.

"The one thing I can never forget is my dad's face," Minnie says. At the news of her diagnosis, her father, usually a tremendously talkative person, was speechless.

A delayed diagnosis like Minnie's is unfortunately not unusual. Obstetricians see few cancers, so they sometimes mistake early cancer signs, especially with tumors of the breast or reproductive organs, for side effects of pregnancy. For instance, pregnant breast cancer patients are diagnosed two to six months later than non-pregnant women, researchers estimate. But as more women delay childbearing, cancer in pregnancy is becoming more common, with one in 3,000 to one in 10,000 pregnancies now affected by malignant disease.

In one sense, Minnie's late diagnosis was lucky. If the cancer had been discovered in her first trimester, she would have been strongly encouraged to abort, because chemotherapy can't be given while the fetal organs are forming. Fortunately, the scientific debate that raged during the 1980s and '90s about continuing pregnancy after a second- or third-trimester diagnosis has been resolved, with researchers concluding that staying pregnant does not impede a woman's ability to survive cancer.

Minnie was relieved to know that her disease could be treated without ending her pregnancy. The diagnosis became a motivation to fight for her family.

"It took me a while to find Paul, to even think that I was going to have a child," she says. "There was no way I was going to give that up without a fight."

"She's my hero," Paul says, listening to his wife. He began

learning all he could about lymphoma, a mechanism for coping with his fear that he would lose his wife, the baby or both.

Minnie urgently needed chemotherapy. But first, Aziz had to check on the baby and review obstetric considerations with Minnie and Paul. In theory, she could have performed a cesarean right after diagnosis, but it was highly debatable whether this would have been better for the baby than continuing the pregnancy while Minnie received chemo.

"She was only about 26 weeks along," Aziz says. "Delivering the fetus that early would pose significant prematurity risks, which are far greater than those posed by chemotherapy."

So Aziz performed an ultrasound and a fetal non-stress test to provide a baseline for monitoring the baby's growth. She gave steroids to mature his lungs as a hedge against early delivery. And she did a baseline echocardiogram of the baby's heart because Advani planned to give Minnie a cancer drug that could have cardiac side effects. The fetal assessment was the beginning of a well-coordinated dance between the high-risk obstetrics team at Packard Children's and the adult oncology team at Stanford Hospital & Clinics, as both groups kept watch over two intertwined lives.

The fetus evaluated, Minnie began receiving a standard mixture of lymphoma drugs: cyclophosphamide, doxorubicin, vincristine and prednisolone. A fifth drug, the monoclonal antibody rituximab, was omitted. Advani's decision not to give the medication illustrates a classic dilemma of cancer treatment in pregnancy.

"Rituximab is the one biggest advances in lymphoma in the last decade," Advani says.

However, the literature contains scant reports of its use in pregnant patients, and although the rituximab molecule is theoretically too large to cross the placenta, there are limited data available regarding its safety in pregnancy. "What if it's harmful to the baby?" Advani says.

There's no good way to find out. Ethical and practical restrictions prevent the clinical trials and pharmacokinetic studies normally used to assess chemotherapy drugs.

"A lot of the science is missing," says MD Anderson's Theriault. "We don't know what happens to these drugs in pregnant women — how they're cleared, what the levels are." Though there is more scientific literature on cancer and pregnancy than there was when he first treated a pregnant breast cancer patient in 1989, research is still sparse.

A few observations suggest that the body's handling of chemo drugs in pregnancy may not be straightforward. For one thing, pregnant women experience few side effects from chemo — they have much less chemo-related nausea than other patients, for instance. Also, "most of our pregnant can-

cer patients are bald at delivery, but the babies have a full head of hair,” Theriault says. “So that’s odd.”

Physiologic changes in pregnancy, such as greater blood volume and altered blood filtering by the liver and kidney, could theoretically change drug metabolism. Plus there’s the unknown factor of the placenta. The molecules of some chemo drugs are too big to pass through the placenta’s mesh-like membranes and cross into the fetal circulation, but many are quite small. Possibly the placenta filters some of them anyway, though no one knows how.

To improve the educated guesswork involved in giving chemotherapy to a pregnant woman, oncologists draw upon a few sources of information. Some chemo medications have clear contraindications for pregnancy. Thalidomide, known for causing birth defects in the 1960s, is today used for chemo in non-pregnant patients; it’s unequivocally avoided in pregnant women.

showed the little guy was growing and doing well.

Minnie’s tumors were shrinking, too. The vaginal tumor had originally been so large it would have obstructed delivery, but by the time her pregnancy reached 37 weeks, it was undetectable. Aziz was relieved. “The truly remarkable aspect of Minnie’s delivery planning was that we were able to decide from a medical standpoint that she was safe to have a vaginal delivery, considering the obstructive vaginal mass we saw at diagnosis,” she says. Aziz felt that a cesarean would have carried extra risks for Minnie’s chemo-weakened body and could have slowed her recovery from the birth and return to cancer treatment.

A few hours after Paul and Minnie toasted their anniversary, there was again a celebratory mood in the delivery room as Kieron prepared to make his appearance. “My older sister was there, and she was,” Minnie pauses, laughing, “filming the damn thing.”

## “A LOT OF THE SCIENCE IS MISSING.

WE DON’T KNOW WHAT HAPPENS TO THESE DRUGS IN PREGNANT WOMEN.”

Scientists are also tracking large groups of mother-child pairs who received chemo during pregnancy. Theriault is following more than 90 women who had breast cancer treatment at MD Anderson while pregnant; Advani is working with colleagues across the country to write up a series of outcomes for pregnant lymphoma patients.

And finally, oncologists rely on old-fashioned caution.

“I recheck with the pharmacy the safety of nausea drugs, antacids, things I normally prescribe and don’t think twice about,” Advani says, “When someone’s pregnant, there’s an extra responsibility.”

Obviously, no one would give a powerful drug to a pregnant woman without good cause. “You have to put it in the context of cancer — what the consequences would be of not treating,” Theriault says.

On this point, Advani is bluntly clear: “If you don’t do anything, the patient dies.”

As Minnie’s pregnancy progressed, Aziz continued to manage her obstetric course with the oncology team and monitor the baby, whom Paul and Minnie decided to name Kieron Anthony, a choice that combined their own middle names. (Paul’s given name is Paul Kieron Carl; Minnie’s middle name is Antonia.) Frequent ultrasounds and fetal non-stress tests

Then she grows more serious, describing how the nurses whisked newborn Kieron away so quickly for testing that she didn’t get to give him the first hug she’d imagined. “All I wanted was to hold him,” she says.

Nonetheless, Minnie and Paul were jubilant. Kieron was healthy and had — yes! — a full head of jet-black hair.

Advani soon came to Packard Children’s to meet the baby. “It’s a joy to see a newborn, especially when the mother has been through so much,” she says.

*A week after delivery, Minnie began having unexplained new symptoms and received a whole-body CT scan.*

The news was unexpectedly bad: She had tumors in her kidneys and her brain. She was switched to a different, more intense chemotherapy regimen, including methotrexate, a drug avoided in pregnancy because it induces miscarriage. She spent several days in Stanford Hospital in an extremely fragile state.

This was one of the hardest periods for Paul. Today, Minnie says she never seriously considered the possibility that she might not be around to see Kieron grow up; Paul’s response is, “She’s much better than I was.”

C O N T I N U E S O N P A G E 4 0

# AFTER CANCER'S CURED WHAT'S LEFT TO HEAL?

By Michelle L. Brandt

PHOTOGRAPH BY TRUJILLOPAUMIER



It's a spring day in 2006, and Shariann Tom is walking gingerly through the sun-drenched atrium of the Stanford Cancer Institute, away from the last round of her cancer-fighting regimen. She has successfully completed not one, but four separate fights with Hodgkin's lymphoma and her oncologist has just given her a tentative clean bill of health. This pretty, petite woman in her mid-40s is, for the moment at least, cancer-free. • But the Pacifica, Calif., wife and mother of two hardly looks or feels like a victor. Her chest is pounding, her eyes brim with tears, and her normally warm smile is absent. With trepidation, she approaches the sliding doors that separate this therapeutic womb from the uncertain, and much less welcoming, outside. • “Inside the building, everyone is cheering for me, congratulating me, telling me to go live my life,” Tom says much later. “But as soon as I’m on the other side of those doors, I feel fired, dropped, alone. Other than knowing I have to go home, I don’t know what I’m supposed to do.” • Tom walks to her car and wets the steering wheel with her tears as she drives away.

[MORE PEOPLE TODAY ARE SURVIVING CANCER THAN EVER BEFORE](#), thanks to improvements in detection, diagnosis, treatment and follow-up care. One in 20 adults in the United States is a cancer survivor, and the number of survivors has quadrupled since 1971. Patients like Tom are also increasingly surviving multiple cancer experiences.

The disease may be gone for Tom and her 12 million cancer-survivor counterparts, but the consequences of the disease and treatment remain: Physical problems, depression, financial woes and future cancer diagnoses are a few of the challenges they face. There's a need for our health-care system to get better at helping these warriors stay healthy in body and mind, and this need will only grow as more people slay the cancer beast. A recent report estimates that by 2020 the number of survivors will reach 18 million.



A health-care system that provides adequate support and resources to survivors would represent a shift. As Julia Rowland, PhD, director of the National Cancer Institute's Office of Cancer Survivorship, puts it, those in the cancer field were "just grateful that people made it through therapy. We were focused on keeping people alive, not on other possible consequences of diagnosis and treatment."

Those who work closely with patients know now there's more to it. "It's not like you have active cancer, but you have active consequences," says survivorship expert Patricia Ganz, MD, a professor of health services and medicine at UCLA. "It doesn't go out of your life — it's not like getting your appendix removed."

SHARIANN TOM HAS GONE THROUGH FOUR BOUTS OF CANCER, BUT HAS NOW BEEN FREE OF THE DISEASE FOR FIVE YEARS.

EIGHT YEARS BEFORE FACING those sliding doors, Tom ran her fingers over the smooth skin of her neck one day and felt a bump at the precise spot where the handsome, shirtless hero on the cover of a romance novel typically kisses the object of his affection. Tom wasn't worried: "I come from a bumpy family."

But this particular bump didn't go away — it grew and changed shape until "one day it felt like it had legs" — and her primary care physician ordered a biopsy. Tom's cell phone rang on a September evening when she was visiting her parents in San Francisco; she took the doctor's call in the dark dining room, away from the clatter of dishes and pans and the laughter of her small children in the kitchen.

The ominous report sprang from her phone: "You have lymphoma."

"What's lymphoma?" Tom asked, swallowing hard as a lesson in medical terminology was delivered. She heard cancer, lymphatic cells, lymph nodes. "What are lymph nodes?" she whispered violently. "Can we just cut it out?"

After she hung up, Tom approached the kitchen doorway and stared at her mom before breaking down. "This wasn't my life, this wasn't me," she recalls thinking. And: "Oh, God, I'm going to die." She was 37 years old.

CANCER IS CONSIDERED a disease of older people: According to NCI data, the median age for cancer diagnosis is 66. Yet more than 40 percent

of cancers occur in adults under the age of 65 — which means that many people, like Tom, could have decades of post-cancer living. And post-cancer coping.

Cancer survivors face a plethora of health consequences: Cancer and the various treatments often leave in their wake pain, fatigue, organ damage, sleep disruption, sexual dysfunction, fertility issues, limited mobility and cognitive disarray, such as memory difficulties. Some survivors experience difficulty completing everyday tasks (treatment-related neuropathy in her hands, Tom says, causes her to "write like an old lady"); some, like Tom, who left a position at computer services company Netscape shortly after her first cancer experience, find themselves unable to resume work. (A recent study in the *Journal of Health Economics* showed that two to six years after diagnosis, survivors are less likely to be employed than

their healthy adult counterparts.)

The problems can linger. According to a Northwestern University survivor study presented at the American Society of Clinical Oncology annual meeting in June, many survivors experience symptoms three to five years after treatment ends. The most common health issues reported were fatigue (16 percent), disturbed sleep (15 percent), cognitive difficulties (13 percent) and pain (13 percent). “We were surprised to see how prevalent these symptoms still are,” study co-investigator Lynne Wagner, PhD, commented at the time.

Survivors also face an increased risk of getting other cancers: Roughly 16 percent of new incidences each year are in people who have had a previous cancer. And radiation and chemotherapy are known to increase a patient’s risk of heart

“I came here and they wanted me to have a bone marrow transplant, chemotherapy and radiation,” she recalls. “I wanted it out of my body completely — I would have given it the kitchen sink if I could. But it was the hardest thing I’ve ever done. The treatment took me down to zero.”

The experience also affected her family life — her husband, Gerry, became the primary caregiver for their children, then “still in the single-digit ages” — and her family’s finances. She had been the breadwinner of her household but knew she couldn’t return to a demanding corporate job after this experience. “Cancer treatment turns your whole life upside down,” says Gerry Tom.

Shariann experienced emotional turbulence, as well. She couldn’t help but question herself and her strength both dur-

“YOU’RE DONE AND  
YOU FEEL  
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YOU FEEL LIKE YOU’RE ON YOUR OWN.”

problems. Indeed, as Kevin Oeffinger, MD, director of the Adult Long-Term Follow-Up Program at Memorial Sloan-Kettering, points out, “Most women who have breast cancer will be more likely to die of cardiac disease than their cancer.”

The disease plays such a large role in a patient’s physical well-being that Oeffinger, who has done extensive work on survivorship, refers to the cancer experience as “a looking glass through which all future health and illness behaviors of the survivor must be interpreted.”

**THE TREATMENT THE FIRST TIME AROUND,** Tom reminisces, wasn’t terribly taxing. “I didn’t have too many symptoms; I was tired, but I wasn’t doing badly,” she tells me in a cozy coffee shop on a cool, wet spring afternoon. “I glided right through it. I like to say I had ‘cancer lite.’”

Tom leans forward, pauses, blinks. “If I’m being totally honest, I don’t think I did it right.”

It wasn’t that she didn’t follow her doctor’s advice or show up for her appointments, but she felt, in a way, that she hadn’t suffered enough. “Cancer is supposed to be horrible, and the first time was not that,” she says. She thinks that’s why she wasn’t very surprised when her remission came to a halt after 13 months. Her doctor discovered another lump, and sent her to Stanford for care.

ing and after her cancer’s repeat performance. “I asked, ‘Am I less of a person because of this? What did I do wrong?’”

She had a lot of doubt, she says, about her strength and ability to move on.

**IT’S COUNTERINTUITIVE THAT SOMEONE** who just overcame the most grueling experience of his or her life should be in such a dark place: One would think a former patient would feel like Superman or Wonder Woman. (“I got through cancer. I can get through anything!”)

But those who work closely with survivors call the end of the treatment the second-worst time in a patient’s experience — the worst being the diagnosis. Studies have shown that depression affects 25 percent of cancer survivors. “You’re done and you should feel happy but in reality ... you feel like you’re on your own,” says Oxana Paless, PhD, director of survivorship research at the Stanford Cancer Institute.

A big reason for this is that once they reach survivor status, patients often lose their contacts and their routine. Most cancer patients have a built-in support network — the doctors and nurses who coordinate and carry out their care and cheer with them when the tests come back, and the relatives and friends who keep them company during the IV drip of chemotherapy and fold their laundry when their arms are too

weak. This network can vanish literally overnight.

And former patients often find themselves anxious and fearful about their future and uncertain over what to do with post-cancer life. “My sole job was to take care of myself, to get myself through treatment, to stay alive,” explains Tom. After treatment, she thought, “Now what do I do?” That’s the hardest part of the cancer journey.”

Over the past two decades, nurse practitioner Kelly Bugos, manager of the Stanford Cancer Survivorship Program, has seen people struggle with resuming their familial and societal roles when their intensive therapy ends. Often, she says, they grieve for the loss they’ve experienced — loss of energy, innate health, time and finances.

**SLEEP WAS TOM’S CLOSEST FRIEND** during her second cancer treatment: While undergoing the bone marrow transplant and chemotherapy, she would spend up to 20 hours a day in bed. She describes the fatigue as bone-wrenching.

Her husband, wanting to help and wanting her to rest, kept their two active children out of the house as much as possible — taking them to their grandparents’, the zoo, the mall. But the quiet house made Tom feel isolated and, in retrospect, she says it wasn’t a good idea for her or the kids. “I missed them, and it made it scarier for them because they didn’t get to see me,” she says.

Despite the fatigue and loneliness, Tom did her best to keep her eye on the prize, thinking constantly of getting the cancer out of her body. “We both felt that we were going to beat this and we were going to move on,” Gerry Tom says. But his wife couldn’t muster the emotional energy to think much about what “moving on” would look like.

When the treatment was over, it took a year before she stopped taking daily naps, before she felt physically ready to re-enter the world. “It’s not like the treatment ends and the pain stops — it doesn’t happen like that,” she sighs.

Instead, she inched her way back to her life.

**IN ITS 2005 REPORT, *From Cancer Patient to Cancer Survivor: Lost in Translation***, the Institute of Medicine called the transition from active treatment to post-treatment care “critical to long-term health” of cancer survivors. Yet, the transition is not a smooth one for many — some would argue most — cancer patients.

The majority of survivors return to their place of treatment for routine check-ups; according to Oeffinger, it’s common for patients to have fairly close follow-up in the first few years before gradually slipping away and disappearing into their new, post-cancer reality.

And even the initial follow-up might not be as complete as necessary. Cancer patients are often treated by a team of clinicians (oncologist, surgeon, radiologist and other medical professionals) but then monitored in the post-cancer era by just one person — who may not have all the details of that patient’s experience.

The IOM report identified this fragmented and poorly coordinated cancer care system as a major barrier to good survivorship care, along with a lack of guidance on the necessary tests and services that should be made available to patients. How often should a colon cancer patient be screened for recurrence? At what point is it safe for a patient with advanced breast cancer to transition fully to the care of her primary care physician? What therapies should be made available to those patients suffering from persistent insomnia? And who in the health-care system should be responsible for coordinating survivorship care? No clear answers exist for these types of questions. The IOM calls for research to answer them.

The National Cancer Institute agrees; in an effort to promote the science of cancer survivorship, it created in 1996 the office that Rowland heads. Rowland reports that between 1998 to 2007, the number of survivorship grants overseen by her office rose from 9 to 127 — a 14-fold increase — and continues to climb today, albeit more slowly. And at Stanford, Palesh was brought in last year specifically to study issues facing some survivors, such as fatigue, cognitive dysfunction and sleep disruption.

Still, it can be a challenge to get researchers to focus on this less-than-sexy line, points out Sarah Donaldson, MD, a Stanford oncologist and co-author of the IOM report. “You’re not going to be awarded the Nobel Prize for studying late effects,” she says.

**TOM THOUGHT SHE HAD THIS THING BEAT** after the first recurrence. But her cancer had other plans: A spot was discovered in her pelvic region in 2003 and, during a routine follow-up two years later, she was told there was a spot on her chest.

“How many times can I go through this?” she remembers asking her Stanford oncologist shortly after her fourth diagnosis. “As many as you do,” came the answer.

And so, she stayed positive — believing, her husband says, that “if your perspective is that there’s a chance for survival, the chance will be there.” And her chances wound up being good.

Tom knows she’s one of the lucky ones: She received good care, got through each recurrence and continues to be monitored closely by her oncologist. But she still feels that some sort of bridge — perhaps in the form of a written plan — should have been provided to help her navigate life post-treatment.

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As it was, she was sent off with nothing but an appointment card. She experienced firsthand the fact, as Gerry Tom put it, that “there’s no real exit strategy for patients.”

**AS DIRECTOR OF THE STANFORD CANCER INSTITUTE** and a practicing oncologist, Beverly Mitchell, MD, has heard from many patients about the difficulty of entering into the post-treatment world. “They’re in remission and they feel like they’ve been let loose without plan or goal; it’s a difficult time,” she says. “We need the transition to be made with the patient feeling empowered and in control.”

One of the best ways to empower patients and help their future clinicians is to arm patients with a “survivorship care” plan. That’s the view of the IOM panel, which outlined what such a plan would include: detailed information on the patient’s disease, treatment and possible consequences; timing of recommended follow-up visits; tips on maintaining a healthy lifestyle; and resources on psychological and support services. Such a plan, ideally, would go to the patient and his or her primary care physician and would help guide clinical care for the rest of the survivor’s life.

In an ideal world, Rowland says, a physician or other health-care professional would sit down with the outgoing patient and recap what he’s been through, assess lingering problems and talk about the future. “This is what we call a teachable moment — a time when people are willing to make changes in their life,” she says.

Many organizations are already doing this in various ways. UCLA’s Ganz describes some models that work: At a large academic medical institution, a nurse practitioner in a dedicated survivor clinic could meet with the patient at the end of treatment and then manage follow-up care. At a community clinic, a nurse navigator could help patients with post-treatment issues; in a managed-care medical group, the primary care physician could get the survivorship plan from the oncologist and oversee post-cancer monitoring.

At Stanford, a planning committee — of which several survivor advocates are a part — recently developed a program to promote physical, psychological and social well-being among cancer survivors. It includes a research component headed by Palesh and Stanford psychiatrist David Spiegel, MD, who has spent much of his career studying the psychosocial effects of cancer and how to treat them; a survivorship care clinic; and a wellness piece that builds on services that have long been offered through the Stanford Cancer Supportive Care Program, led by nurse Holly Gautier and the Stanford Center for Integrative Medicine. Those services include such things as psychotherapy, hypnosis, mindfulness

training, acupuncture and therapeutic massage.

“As an institution, we plan to provide the resources to help patients transition from cancer therapy to wellness,” explains Bugos, who leads the clinical program development along with Douglas Blayney, MD, the Ann & John Doerr Medical Director of the Stanford Clinical Cancer Center.

Among the committee’s other work: investigating ways to provide a survivorship plan and to partner with other members of a survivor’s health-care team, and planning a June 2012 community conference on survivorship issues — a collaboration with the Cancer Prevention Institute of California and the Stanford Health Library.

**A REMISSION ISN’T LIKE A GRADUATION**, in which a life phase officially, and permanently, closes. Which is probably why Tom didn’t initially celebrate the end of her last treatment.

But the days on the calendar slipped by, her children became taller and her new business — she became a life coach specializing in work with cancer patients — steadily grew. And with each follow-up doctor’s visit, she found herself in new territory: She had never before been able to say it had been three, or four or five years since her last treatment. “I wondered, then, if I should celebrate,” she says. “Or is it too late now?”

It wasn’t: One week after we met, Tom and her family, including her two children — now 20 and 17 — took a seven-day cruise to the western Caribbean. The getaway was in honor of her 50th birthday and the fact that she was five years cancer-free.

But five years hardly means her cancer experience is long gone, or long forgotten. Tom has lingering side effects from the treatment, she’s at an increased risk of heart disease and she’s under strict orders to exercise regularly and cut out red meat. Plus, she worries.

Tom had a dream right before we met. “It was one of those dreams where you’re sobbing in your sleep because it feels so real,” she tells me quietly. “They were taking my blood to see if the cancer was back.”

She pauses. “So, do I still get scared about the cancer coming back?”

“Yes.”

**NO ONE DISAGREES THAT SURVIVORSHIP** can be extremely difficult. But not all the consequences of a cancer diagnosis are negative.

Sloan-Kettering’s Oeffinger tells his patients that a post-cancer life can be a very healthful one. “If I influence lifestyle behaviors — making sure they don’t smoke and get on a low-fat

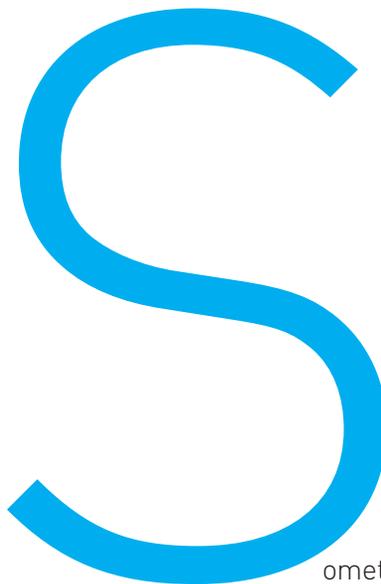
C O N T I N U E S O N P A G E 4 1



# STOP THE SUFFERING WHY NOT?

By Susan L. Young

ILLUSTRATION BY BRIAN CRONIN



Sometimes the pain is a whole body ache, as if all the bones in his body are broken. Other times, it feels like a knife is stabbing him under his joints, or, on this day, right in the groin. • Last holiday season, while standing and chatting with a friend at work in a Silicon Valley car-repair shop, Daniel Shaine was struck with a pain so intense that his legs buckled. “It doesn’t happen that way often,” says Shaine, a 67-year-old Campbell, Calif., resident. But around that time, such attacks started coming more frequently. • “The pain is there for a reason,” he says. “The doctors know there is something wrong and they are trying to discover how much this cancer has spread.” • The semi-retired automobile service writer has dealt with his cancer pain for more than a decade now, but only for the last year or so has he been getting help from a branch of medicine specifically dedicated to easing the symptoms of complex illnesses such as pain. • That branch — palliative care — is a relatively new discipline that helps seriously ill patients and their families maintain the best quality of life possible, and, as one study has recently shown, can even lengthen their lives. But prejudices and misconceptions about palliative care’s role in medicine stop many doctors from telling patients it’s an option. • It took a long time for palliative care to come to Shaine’s aid. His journey with cancer began in the wintry months of 2001 with a seemingly harmless act: picking up something heavy at work. “I felt something move in my lower back. The cancer was already there, it just manifested itself as a pulled muscle,” he says. • His eventual diagnosis was stage-4 prostate cancer, which had metastasized to his back and attacked his spine. His situation seemed so dire he received his last rites. But that proved too soon for the deeply spiritual Shaine. Half a year later, the test results that once suggested furious growth of his prostate cancer had dropped to near normal levels. His doctor could barely believe it.

"I had an appointment to see my urologist and when he walked in the room, he started to shake his head," remembers Shaine:

"You are a remarkable man, Mr. Shaine," said his doctor. "Do you go to work every day?"

"I pray for strength and courage to do that," Shaine responded. "We had a rough time last summer, didn't we, doc?" he said, not really needing an answer.



Not that Shaine got off easy. The cancer took five of his vertebrae and 6 inches off his height. Fortunately, his spinal cord was not damaged, so Shaine kept his mobility, his work life, his social life. But he could not escape the pain.

"The pain would explode and then tentacle out, mostly across my back," says Shaine. "It was if someone took a knife and just twisted it in." Although he has dealt with advanced cancer for nearly a decade, Shaine, a four-year veteran of the

Navy, did not work with a palliative care team until after he had switched from a Bay Area community hospital to the Veterans Affairs Palo Alto Health Care System in 2009.

As a team, palliative care physicians, nurses and social workers help patients with any serious illness manage such symptoms as pain, nausea and sleeplessness by recommending additional medications or suggesting alternate therapies. They help families cope with the stress and fear of disease, guide them through the maze of medical care, and have important conversations about a patient's goals for living with their disease and for their last days.

Although all Veterans Affairs medical centers provide palliative care services, not all offer outpatient clinics for patients like Shaine. In fact, most medical centers offering palliative care services assist only inpatients, those admitted to stay at least one night. That leaves many cancer patients without access to palliative care, as the majority of cancer care is provided in the outpatient setting.

Inpatient palliative care services aren't a guarantee either. In 2010, 63 percent of hospitals with 50 beds or more offered palliative care services, according to a study headed by Sean Morrison, MD, director of the National Palliative Care Research Center and professor of palliative care at the Mount Sinai School of Medicine in New York. However, the trend across the country is moving upward. In 2000, only 25 percent of hospitals with at least 50 beds had offered the care.

"We've seen really dramatic growth," says Morrison, who notes that in the mid-1990s, less than 5

percent of hospitals offered the team-based approach to improving quality of life. Stanford Hospital has offered inpatient palliative care services since 2007.

Even within existing palliative care units, more specialists are needed. In December 2010, the American Academy of Hospice and Palliative Medicine identified 4,400 hospice and palliative care physicians with either board certification or membership in the AAHPM in the United States. Most

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of these physicians, however, practice palliative medicine part time. Between 2,700 and 6,000 specialists are needed to fully staff the current hospital-based palliative care programs, the AAHPM estimates.

“The average person with cancer suffers from untreated and unnecessary pain and other symptoms,” says Morrison. “Palliative care teams do better at managing pain and other symptoms than usual care, they provide family support and help assure safe discharges from the hospital.”

And yet, patients sometimes aren’t referred until very late in their disease, even though they could benefit from earlier palliative care, says Morrison.

### LANGUAGE BARRIER

[A historical association with hospice and end-of-life care deters some doctors from introducing patients to palliative care teams.](#)

Palliative care grew from the modern hospice movement, which was founded in the United Kingdom in the late 1960s to provide specialized care for the seriously ill and dying. Although palliative care can help patients with many years ahead of them, some doctors assume these specialists work only with dying patients. Others are afraid their patients will think they’re giving up on them, either because of palliative care’s connection with hospice or the way some oncologists use it to mean “non-curative,” as in “palliative chemotherapy,” which doesn’t cure a patient of cancer but rather reduces cancer symptoms, usually by shrinking the tumors.

“While palliative care is not limited to issues surrounding the last stage of illness or end of life, that does reflect where providers currently view palliative care fitting in,” says Stephanie Harman, MD, clinical assistant professor of medicine and director of Stanford Hospital’s inpatient palliative care program. “It has been a limited view.”

The concern over the word “palliative” may exist more in the minds of providers than of patients. Public opinion research published in 2011 by the Center to Advance Palliative Care interviewed laymen and physicians alike and found that many health-care professionals frame the specialty as end-of-life care. The study concluded that physician attitudes hinder the field’s progress.

Conversely, the report also found that most consumers aren’t familiar with the term. But when they learn what palliative care teams can do, they want the service to be available for those who need it. “An enormous percentage of people, once they understood what it is, wanted it,” says Lisa Morgan, communications director for CAPC. The study found that the best way to communicate what palliative care does is to emphasize how it benefits patients and the relief and support it provides.

Shaine would recommend palliative care for anyone experiencing pain.

“The people I am working with are not pill pushers; they are trying to understand the best way to give me good quality of care,” says Shaine. “I have always been impressed with how much they listen to me and how they give me feedback to show the best procedure for keeping the pain under control.”

### A SEPARATE PIECE OF THE PUZZLE

[Palliative care isn’t meant to take the place of oncologists or other physicians but rather to support their efforts in treating patients with serious illnesses like congestive heart failure, lung disease or cancer.](#) While oncologists and others manage symptoms and the side effects of treatments as best as possible, sometimes the issues become complicated.

“For certain patients who have difficult-to-treat symptoms or issues like pain, constipation, stress or depression — issues that the primary provider is having difficulty dealing with — it may make sense to refer to a palliative care specialist,” says Kavitha Ramchandran, MD, clinical assistant professor of medicine at Stanford.

“In the same way that endocrinologists get more training in diabetes and hypothyroidism, we get more training to help deal with difficult symptoms,” says Ramchandran, who is both a palliative care specialist and an oncologist.

Likewise, technological breakthroughs happen in symptom management just as they do in tumor treatments and cancer prevention. “Oncologists are always reading up on the newest therapies and understandings of the mechanisms of deranged tumor cells,” says James Hallenbeck, MD, associate professor of medicine and associate chief of staff for extended care at the VA-Palo Alto. “What I’m reading about are the new understandings of shortness of breath, itching, depression, weakness and fatigue, or nausea and pain,” says Hallenbeck, who is also a member of the Stanford Cancer Institute.

Pain is a mysterious illness that eats up as much as \$635 billion in the United States each year for treatment and lost productivity, according to a recent report from the Institute of Medicine. For cancer, pain is a difficult symptom to manage and is rarely treated by simply setting up a morphine drip. In Shaine’s case, the typical treatment for bone pain could exacerbate another problem — previous medication damaged his jawbone, a condition known as osteonecrosis. So his palliative care specialist, VJ Periyakoil, MD, the director of Stanford Palliative Care Education and Training and a clinical associate professor of medicine at Stanford, has been working with Shaine to find an alternative.

For now, he takes pain medication twice a day, but sometimes he needs something stronger. The trick is, he doesn't want to be, as he says, "dopey." "As I have told them, I don't want to be a zombie," says Shaine. "That's not going to help anybody."

"Our palliative care recommendation was to order a bone scan and refer him to nuclear medicine for treatment with samarium-153, a bone-targeting radioisotope, to relieve bone pain," says Periyakoil. Results in hand, the next step for Shaine and his palliative care team is to discuss how samarium-153 treatment would affect his life.

In addition to seeing patients through the VA-Palo Alto, Periyakoil runs Stanford's Hospice & Palliative Medicine fellowship program.

"What my fellows and I care about most is what treatments can we provide to these people to promote not just quantity of life but also concurrently quality of life," says Periyakoil.

And evidence suggests palliative care does both.

#### CONVINCING ARGUMENT

A 2010 study conducted at the Massachusetts General Hospital in Boston showed that palliative care increased both the physical and psychological well-being of stage-4 lung cancer patients. Patients who saw a palliative care team from the moment of diagnosis reported less depression and received less aggressive end-of-life care yet lived almost three months longer than advanced lung cancer patients who did not.

"That *New England Journal of Medicine* study caused a sen-

Currently, Ramchandran and her team are seeing patients as needed in the outpatient oncology setting. "If a patient has refractory pain or depression, for instance, or wants to talk about goals of care, we can meet with them," says Ramchandran. To explore another method for connecting outpatients with palliative care, the new Stanford Women's Cancer Center will soon hold a once-a-week clinic in which patients, with their oncologist's referral, will make separate appointments to work with palliative care.

"One of the things we've been doing at Stanford is being as available as possible," says Ramchandran. "Once a provider has watched us help one patient, they'll refer another one. They just need to see it in order to believe it."

Beyond extending and improving lives, palliative care offers a boost to bottom lines. "When you provide palliative care, you increase the efficiency of health care and you reduce health-care costs," says Mount Sinai's Morrison. His studies showed that palliative care programs significantly reduced hospital costs for seriously ill patients while improving clinical quality, patient well-being and family satisfaction.

"Palliative care teams sit with patients and families to understand what their goals are, and then they match their treatments to their goals. Then what you really get is true, patient-centered care in the setting of serious illness," says Morrison.

For now, the demand for palliative care exceeds the supply of specialists. "Because the field is so new, many of our faculty never had any palliative care training," says Periyakoil. "There are too many cancer patients suffering from many

## "IT SHOWED THAT PATIENTS WHO RECEIVE PALLIATIVE CARE

ALONGSIDE NORMAL CANCER CARE LIVE LONGER."

sation in the cancer world because it showed that patients who receive palliative care alongside normal cancer care live longer. In fact, the impact of palliative care on survival was similar to a well-known expensive chemotherapy drug called bevacizumab (trade name, Avastin) in the same patient population," says Ramchandran. She hopes that palliative care teams can continue to chip away at the false impressions of their field by having an effective presence in clinics. To that end, Ramchandran is spearheading new programs for outpatient palliative care services at Stanford Cancer Institute.

distressing symptoms and too few palliative care experts. We still need to significantly bolster our efforts to train our community in order to better alleviate patient suffering," she says.

"I understand one of these days, this cancer is going to catch up with me," Shaine says. "But as long as I am talking with my doctors and say my prayers every day, I am comfortable. Through prayer and people giving me confidence, like the palliative care people, I have no fear." **SM**

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# old brain, new tricks

## WHAT BLOOD'S GOT TO DO WITH IT

COUNT DRACULA MAY HAVE BEEN BLOOD-THIRSTY, BUT NOBODY EVER CALLED HIM STUPID. IF THAT PRACTITIONER OF WHAT YOU COULD CALL "THE TRANSYLVANIAN TRANSFUSION" KNEW THEN WHAT WE KNOW NOW, IT'S A GOOD BET HE WAS KEEPING HIS WITS AS SHARP AS HIS TEETH BY RESTRICTING HIS TREATS TO VICTIMS UNDER THE AGE OF 30. • "Friends don't let friends drink friends," read the first slide of graduate student Saul Villeda's PowerPoint presentation as he kicked off his PhD thesis defense on Dec. 3, 2010. Considering what he was about to tell the audience, this was probably a prudent admonition. Working in the lab of associate professor of neurology and neurological sciences Tony Wyss-Coray, PhD, Villeda had helped uncover a relationship between blood and brain that may have huge implications for all of us non-vampire types who grow older day by day. • Aging takes a toll on all tissues, but its wrath is reserved especially for tissues with low regenerative potential — for instance, the brain. What Villeda and Wyss-Coray found — in mice,

By Bruce Goldman

ILLUSTRATION BY LARS HENKEL

to be sure — was that old blood has a detrimental effect on the brain. The hope: We humans might someday be able to rejuvenate our own aging brains with as-yet-unidentified factors circulating in young blood. • Extraordinary though this may sound, it's not without support. The research literature shows that muscle and liver tissue, and blood itself, renew themselves more easily in the presence of young, versus old, blood.

It seems that something in blood influences stem cells, those acclaimed protean spheroids resident in most of our tissues. Depending on cues they get from their immediate surroundings, stem cells can variously hibernate, multiply or produce differentiated daughter cells that renew or augment tissues in need of bulking up.

The brain is the body's most heavily vascularized organ, boasting a huge amount of surface contact with the maze of blood vessels that run through it. But liver and muscle have no barrier separating them from the circulating chemistry set that is our blood. The brain does. It is cordoned off from the circulatory system by a tight curtain of barrier cells, the better to keep it from crashing every time you nibble on a Twinkie, boosting the glucose levels in your blood to the



high heavens, or get an infection, triggering all kinds of molecular mayhem in the blood.

However, it's become clear that, **blood-brain barrier be damned, certain blood-borne molecules** whose levels rise with increasing age can get into the brain and mess up its ability to generate new nerve cells along with its capacity to do its job.

Wyss-Coray's team has pinpointed a few of these molecules in mice and is on the verge of identifying other blood-borne molecules that have an opposing, brain-rejuvenating, effect but whose numbers diminish in aging blood. There are hints that some of them affect human brains the same way.

"We're not talking about a disease," Villeda says. "This is

normal aging, the one thing none of us can escape from. This affects every single person on Earth. We're all getting old. There might be ways of changing that. That, to me, is just wild."

The substances suspected as damaging our brains' ability to form new nerve cells are immune-signaling molecules, produced in excess as we age. Can we protect ourselves from these detrimental effects?

Can we stay smarter for longer?

### Ask a mouse

Mice and people are different, but we have a few things in common. They like cheese, we like cheese (well, most of us do). Human and mouse brains are a lot alike, too. The same basic building blocks — nerve cells

and supporting glial cells — assemble into similar brain structures in both species.

It's now understood that the adult human brain is capable of producing new nerve cells, which are key to forming certain types of new memories and, therefore, to new learning. This is possible because the brain, contrary to the conventional wisdom of two decades ago, has its very own stem cells. These precious cells are not randomly distributed throughout the brain, though. Both mouse and human brains have been found to harbor stem cells — and to produce new nerve cells — in just a couple of specialized niches, very close to blood vessels. Here, stem cells can quietly incubate or, given appropriate cues, replicate or differentiate.

Alas, the numbers and activity levels of stem cells in the brain diminish with increasing age. So do certain mental capabilities, such as spatial memory: An example in humans is remembering where you parked the car. If you're a mouse, it could be recalling the whereabouts of an underwater platform you can perch on so you won't have to keep swimming in order to keep your nose above water.

In 2005, professor of neurology and neurological sciences Thomas Rando, MD, PhD, published a study in *Nature* showing that stem cells in the muscle and liver tissue of mice thrived when exposed to younger mice's blood. To demonstrate this, Rando's team used a surgical technique to join the circulatory systems of two mice. Connecting a young mouse to an old mouse this way let Rando and his colleagues measure the direct effects of exposure to young blood on a living older animal's tissues, and vice versa.

Rando also noticed changes in the number of stem cells in mice's brains, mirroring those seen in muscle and liver. But

sor of genetics Anne Brunet, PhD.

They plunged in, first by examining the brains of mice of different ages and confirming earlier reports by others that the older the mouse, the fewer new nerve cells its brain was generating in a key area called the hippocampus.

Next, Rando taught Wyss-Coray, Villeda and their peers the technique for connecting mice's circulatory systems. They compared the numbers of new nerve cells being generated in each partner of several old/young mouse pairs with the numbers they had previously observed in solitary mice of various ages.

Sharing blood with a younger mouse seemed to rejuvenate older partners' brains. Young partners of old/young pairs generated fewer new brain cells than unpaired young mice did, and old young/old mouse partners generated more.

"We saw a threefold increase in the number of new nerve cells being generated in old mice exposed to this 'younger' environment," says Wyss-Coray.

Clearly, something in the older mice's blood was affecting

## "We're all getting old. there might be ways OF CHANGING THAT.

spending the time to get enough supporting data to include these findings would have held up the study's publication. So he omitted them from the published work.

He did, however, tell Wyss-Coray about it. That conversation set in motion a five-year effort whose outcomes were published in a *Nature* study this fall. Villeda was the first author, Wyss-Coray the senior author and Rando one of its co-authors.

Wyss-Coray was already interested in blood-borne factors and the brain. In fact, he was on his way to publishing an article in *Nature Medicine* about proteins whose concentrations in blood correlate with the onset and progression of Alzheimer's disease and that might therefore allow an early diagnosis of the disorder.

Blood-brain barrier notwithstanding, the brain is affected by the so-called pro-inflammatory molecules secreted into the blood during the immune system's response to viral and bacterial infections. "Sleepiness, fuzzy thinking — these are behaviors generated in the brain," says Wyss-Coray.

Still, he says, "the prevailing theory at the time was you had to be insane to pursue the effects of blood-borne factors on the brain. Saul was crazy enough to do it."

Villeda, a new arrival in the Wyss-Coray lab, came with the right tools for the job. He had been looking at stem cells in the brain during a prior hitch in the lab of associate profes-

sor of genetics Anne Brunet, PhD. Whatever that something was, it wasn't cells. Wyss-Coray's group showed, for example, that just injecting plasma (the cell-free fraction of blood) from old mice into young mice's tails produced many of the debilitating effects of an out-and-out circulatory hook-up to an old mouse.

Next, Villeda, Wyss-Coray and their labmates checked for age-related differences in the levels of 66 immune-signaling chemicals in mouse blood. They found 17 whose amounts rose with age. Six of these substances also increased in younger members of young/old mouse pairs, compared with levels in mice whose circulatory systems hadn't been exposed to old blood.

One of the molecules they identified was eotaxin, a small protein that attracts immune cells called eosinophils to areas where it has been secreted by other cells. In blood and cerebrospinal fluid drawn from healthy people between the ages of 20 and 90, eotaxin levels increased with age, too.

Eotaxin is associated with allergic responses and asthma. This has aroused pharmaceutical companies' interest in drugs that block eotaxin, at least one of which is in clinical trials now. But eotaxin has never before been singled out as having any role in brain aging or cognition.

"All of this made exploring eotaxin further seem like a

good idea,” says Wyss-Coray. So they did. Injecting eotaxin alone into a normal young-adult mouse diminished its formation of new hippocampal nerve cells, just as injections of old-mouse plasma or a hook-up to an older mouse’s bloodstream did. The eotaxin-injected young mice also performed worse on spatial-memory tests.

Whether eotaxin actually crossed the mice’s blood-brain barrier is not certain, Wyss-Coray says — although it looks that way. Injecting substances known to incapacitate eotaxin into one hemisphere of a mouse’s brain, while injecting eotaxin into its bloodstream at roughly the same time, protected that hemisphere’s capacity to form new nerve cells.

In any case, crossing the barrier may not be strictly necessary, as stem cells in the brain are always found in proximity to the blood vessels that permeate the brain. Endothelial cells, critical components of blood-vessel walls, have receptors for eotaxin on them. Like Pyramus and Thisbe — those mythological love-struck teenagers who, forbidden to see one

produce new nerve cells and, therefore, to restore worn-out circuitry or incorporate new experiences.

Work by Palmer and others indicates that the inflammatory reaction to an infectious disease a woman might suffer during pregnancy could have a downside for the baby’s brain. And there is some evidence from epidemiological studies that anti-inflammatory drugs like aspirin or ibuprofen may reduce the risk of Alzheimer’s disease.

“I think it’s probably a safe speculation to say that inflammation-producing injuries or disorders may reduce new nerve-cell formation or even accelerate aging,” Palmer says.

The good news is that we may already have ways of countering that tendency. “There are some, no pun intended, no-brainers,” says Palmer.

“Give laboratory mice a running wheel, and they’ll run from 3 to 7 miles every night,” he says. That, in turn, seems to let their brains retain their ability to generate new nerve cells — which makes sense when you consider that steady exercise is known to reduce blood levels of various pro-inflammatory molecules whose concentrations typically rise as we age. Staying healthy and continuing to get exercise as you age is the way to go.

Wyss-Coray wonders, “Can we treat neurodegenerative disorders by administering therapies directly to the bloodstream?” Examples would be drugs that inhibit the action of “bad for the brain” substances in blood, or other drugs that mimic or enhance the action of blood-borne “good for the brain” substances.

By now it has perhaps occurred to you that the next thing you ought to do is dance on down to the local blood bank and ask if they’ve got any young blood for you. No dice. Blood products, like pharmaceutical drugs, are regulated by the Food and Drug Administration, which demands evidence of efficacy — something they won’t have anytime soon. So even if you were willing to jump from a mouse study to the conclusion that you should go for an infusion, you can’t get one.

Meanwhile, Wyss-Coray and his team are examining what happens to the brain’s regenerative capacity when they block eotaxin. They’re exploring any possible connection between levels of eotaxin and other pro-inflammatory immune-signaling molecules to Alzheimer’s. And they’re expanding their blood-borne substance screen from the original 66 chemicals to more than 500 of them, hoping to reel in factors with rejuvenating potential. Having come so close to the Fountain of Youth, why stop? You could say it’s gotten into their blood.

“We’re all Transylvanians now,” says Villeda. **SM**

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## THAT, TO ME, IS JUST WILD.”

another, communicated through a hole in the wall separating their parents’ homes — eotaxin passing through the peripheral blood system may trip receptors on endothelial cells, triggering some further reaction on the brainy side of the divide.

Other blood-borne factors besides eotaxin undoubtedly contribute to age-related declines in brain function. One of the six substances the Wyss-Coray group fingered as likely culprits was a signaling protein called MCP-1, which like eotaxin is a pro-inflammatory molecule, stoking the immune system’s inflammatory fires by attracting immune cells called macrophages. MCP-1 was previously linked to the reduction of the brain’s ability to produce new nerve cells by another lab at the medical school, led by associate professor of neurosurgery Theo Palmer, PhD.

Palmer showed this in a dish, not in the living brain, so the blood-brain barrier wasn’t tested here. He also made no attempt to tie his findings to age. However, the Wyss-Coray lab’s observation that MCP-1 levels increase with age in mice and humans — and the well-established observation that the older we get, the more our systemic inflammatory apparatus tends to get stuck in overdrive — suggests a striking conclusion: Chronic, age-related elevation in pro-inflammatory molecules in our blood may translate into a decline in our brain’s ability to



# drawn together

ARTIST AND SURGEON CONVEY THE BODY'S SECRETS

By Tracie White

Photograph by Leslie Williamson

*"I counsel you not to cumber yourself with words unless you are speaking to the blind. ... How in words can you describe this heart without filling a whole book? Yet the more you write concerning it, the more you will confuse the mind of the hearer!"*

— LEONARDO DA VINCI

Every other week on Monday afternoons, a container of colored pencils is placed prominently on the coffee table in the surgeon's office. Nearby is a sketchpad. Such simple old-fashioned instruments, the pencil and paper. Then the surgeon and the artist enter the room, and the recipe is complete.

Even with the advent of all kinds of advanced technological illustrative and imaging devices, these are still the tools that medical illustrator Chris Galapp and surgeon Robert Jackler, MD, use to illustrate some of the most technical of microsurgical techniques — hypoglossal-facial anastomosis, middle fossa craniotomy and stapedotomy, among others. Page after page of their drawings already comprise such tomes as Jackler's *Atlas of Skull Base Surgery and Neurotology*, which explains the "how-tos" of surgeries deep inside the skull.

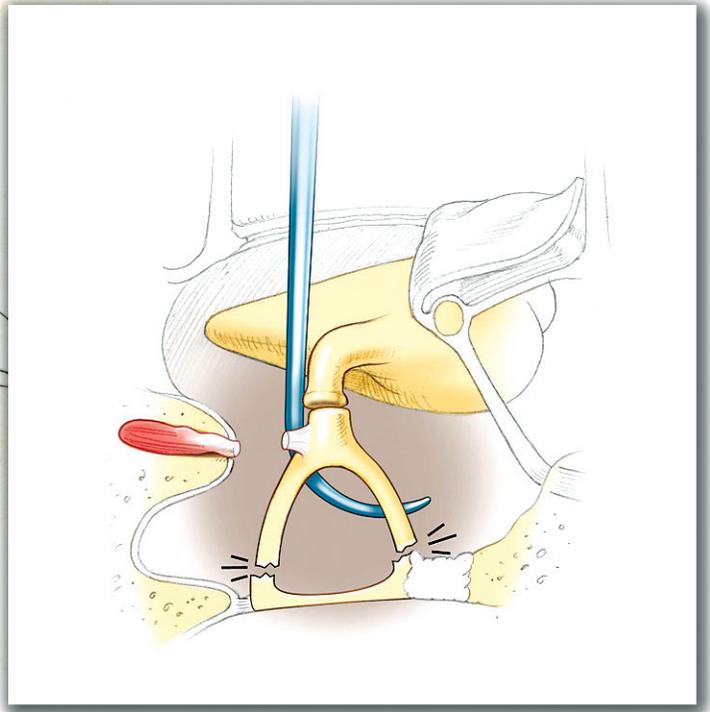
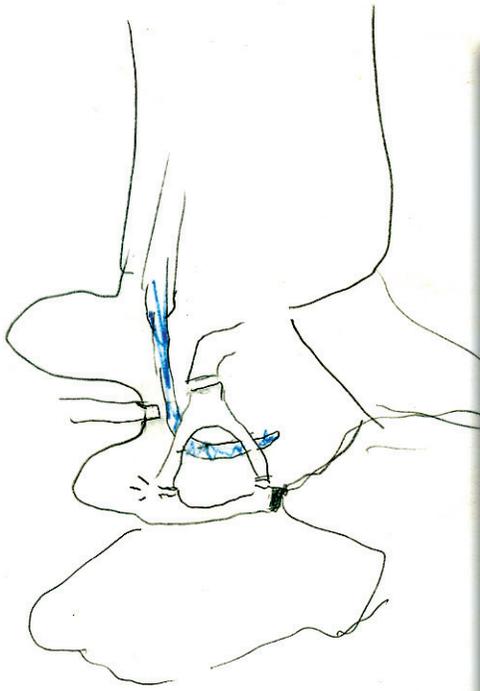
And it all begins with a crude pencil sketch.

"I'm a terrible drawer," says Jackler, professor and chair of otolaryngology, who for years has arrived fresh from surgery — removing tumors found in the base of the skull, restoring hearing, repairing eardrums and other problems — and begun describing in vivid detail to Galapp exactly what he has done inside his patients' heads. Often he scribbles on paper to help convey his thoughts. "I make my messy sketches," he says, "and she brings them to life."

Jackler, together with Galapp, who has a master's degree in medical illustration, has published three illustrated books on skull base surgery, and they are now working on a fourth, an exploration of middle ear surgery. The works are also available online, and the pair is going virtual. With help from Nikolas Blevins, MD, associate professor of otolaryngology, and colleagues in computer science, they're creating enhanced 3-D videos that will allow users to feel the images when they touch them.

Their work is inspired by the famous medical illustrators throughout history — Leonardo da Vinci, Andreas Vesalius, Max Brödel — who have used art to describe the structure of the human body and to elucidate medical procedures. "It's really a natural marriage, this combining of art and science," says Galapp, who strives to follow in the footsteps of her heroes — the Renaissance artists who melded scientific under-

ARTIST CHRIS GALAPP AND SURGEON ROBERT JACKLER HAVE COLLABORATED FOR THE PAST 20 YEARS ON ILLUSTRATIONS THAT DEPICT DELICATE SURGERIES OF THE INNER EAR AND PLACES DEEP WITHIN THE SKULL.



standing of anatomy with artistic skill. “Both work to explain the world.”

Jackler has found that, for him, the use of art is simply the best way to communicate his wealth of experience that few others have. “We’ve spent more than 20 years drawing things that have never been drawn before,” he says.

On a recent Monday, Jackler’s shirtsleeves are pushed up. Gralapp’s long hair is pulled back in a headband, a sketchpad in hand. The surgeon and the artist are reworking the third drawing of what will eventually be about 50 or 60 in a series used to illustrate a single micro-surgical procedure, which takes place in an area the size of the head of a pin. Called a stapedotomy, this surgery is the only way to fix abnormal growth or hardening of the middle ear bone — the stapes — which leads to progressive hearing loss. The procedure involves removal of the arch of the stapes bone, the smallest and lightest bone in the human body, and replacement with a teeny-tiny piston. First performed in 1956 and steadily refined since, it’s surgery on a minute scale.

This particular surgery has been illustrated in other books, but it’s Jackler’s surgical techniques developed over years of fixing problems that will be newly drawn. Just how does the surgeon deal with a slipped crimp? What does the surgeon do if the prosthesis is too long? It’s Jackler’s rare expertise at revision surgery — he’s the guy who gets called in to repair complex surgeries that went wrong — combined

**The collaboration**  
 ROBERT JACKLER’S SKETCH (LEFT)  
 OF THE REMOVAL OF THE TINY STAPES  
 BONE INSIDE THE EAR IS THE BASIS  
 FOR CHRIS GRALAPP’S  
 FINAL ILLUSTRATION (RIGHT).

with Gralapp’s artistic talent, that create books that fellow surgeons swear by.

“The pictures are so clean they help you walk through the operations mentally before you operate,” says Richard Gurgel, MD, a neurotology fellow at Stanford who specializes in surgeries on tumors of the ear and skull base. He studies Gralapp’s illustrations in the version of *Atlas of Skull Base Surgery and Neurotology* on Stanford’s website the night before his surgeries, often the removal of benign tumors from cranial nerves.

Other surgeons use the images right inside the operating room. “Before the book went online, surgeons often called from operating rooms and said, ‘I’m looking at your book. Can you clarify a bit?’” Jackler says. Now most study them on the computer, but he still gets the calls.

Gralapp’s goal is to clarify the complex. “As an illustrator I eliminate the unnecessary,” she says.

For the stapes procedure, she’s imagined she’s a nano-sized munchkin who is sitting inside a human ear, and she is drawing the illustrations from that point of view. “It’s a different perspective than what the surgeon sees peering into the ear when he does the surgery,” she says. “But you can’t always see clearly the concept of the surgery from the surgeon’s

# "We've spent more than 20 years

DRAWING THINGS THAT HAVE NEVER BEEN DRAWN BEFORE."

point of view. This perspective is much easier for people to understand."

There will always be a role for the artist in science, Galapp says, as long as there are medical websites out there that need art, as long as there is the complex that needs to be clarified. "We communicate better, far better, through art," she says.

On this Monday afternoon, Jackler guides her through the stapedotomy.

"This type of microsurgery can be devilishly tricky at times," Jackler says, looking down at Galapp's sketch-in-progress laid out on the coffee table.

"This minuscule bone," he says, pointing out the stirrup-shaped middle ear bone in Galapp's illustration, "the stapes, should be able to move, like a piston." He uses his hands to show the movement of a piston, a fist pumping against an open palm.

The surgeon's hands are his greatest tool, and Jackler uses them often when he talks. Galapp understands what he's describing almost before he describes it.

**Jackler's obvious excitement about the collaborative process reveals an interest in art beyond the hobbyist.** His wife, Laurie, is an artist. Prints of the earless Vincent van Gogh self-portrait have remained prominent at his desk for years. He decorates his walls with 18th- and 19th-century medical illustrations. "We stand on the shoulders of giants," he says.

Twenty-four years ago, when they first started working together, meeting up at UC-San Francisco — Jackler, a youngish surgeon, and Galapp, a youngish illustrator — the

artist would occasionally join the surgeon in the operating room. But after a few years she stopped coming to watch. They developed their own creative process, and it is one that works best for them here in the quiet of the office with the sketchbook and the pencils.

The two share their own visual language using colors and simple shapes to illustrate surgeries often microscopic in scale. They speak in colors and symbols and the intricacies of difficult-to-get-to anatomical spaces that few in the world have seen up close and personal.

"I think blue would describe this better," Jackler says. And, "When I think of the tympanic membrane I think of clouds. It's almost all water."

Years of practice have honed Galapp's interpretation skills, and she quickly brings his words to life. "I've been a bit impressionistic here," she says.

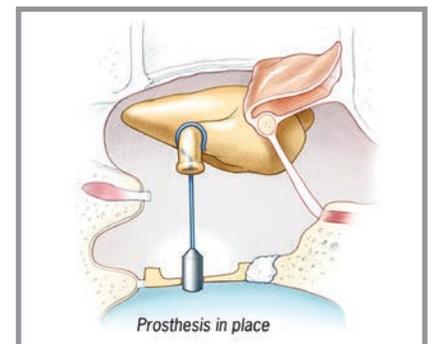
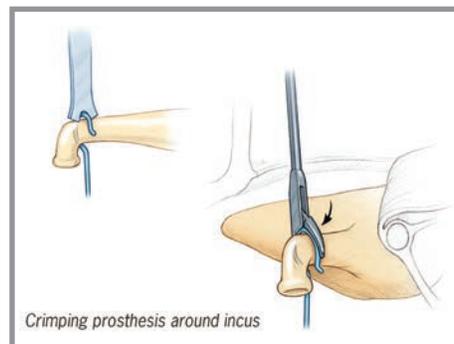
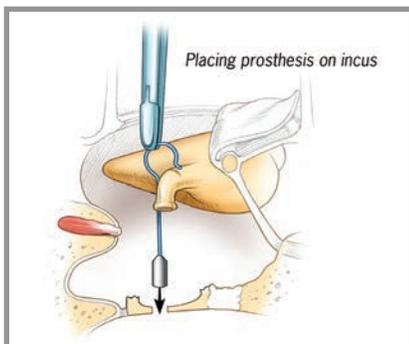
He nods. "That's beautiful," he says. Then makes a few more suggestions.

A little more shading, a little bit more shaping, and they're one step closer to the truth. **SM**

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## The final view

THESE ILLUSTRATIONS SHOW A FEW OF THE STEPS INVOLVED IN PLACING A TINY PISTON IN THE EAR AFTER THE REMOVAL OF THE STAPES.



## FEATURE

The unexpected

C O N T I N U E D F R O M P A G E 2 1

“Initially it was, lose her; then, lose both of them; or then it was, we have to choose,” he says. “And then we were OK, and then I was going to lose her again.”

*A few weeks later, when Minnie’s hold on life seemed especially tenuous, the Narths decided to have Kieron baptized at Stanford Hospital.*

Minnie is Catholic and Paul, Hindu. They plan to expose Kieron to both faiths. “I asked the social worker if she could schedule a baptism while I could still hold him,” Minnie says. Together with a Catholic priest, a nurse, a few friends and Minnie’s sister, the Narths celebrated their tiny son’s baptism in one of the hospital’s gardens.

The next several months were a blur: powerful systemic chemotherapy that got rid of the tumors in Minnie’s body, then, to target the brain tumor, surgery to implant a port that would deliver chemo directly to it. Soon after surgery, a terrifying 45-minute seizure. Then more chemo. Then, Minnie’s doctors determined that the chemo wasn’t eliminating the brain tumor, so she had 13 rounds of whole-brain radiation.

Throughout this time, Paul kept a very close watch on his wife. An engineering manager at Hewlett-Packard, he often worked from her hospital bedside — the connection to his job helped the medical odyssey feel more normal, he says. At home, he watched for signs that she might be going downhill. During one ER visit, Paul rattled off a string of Minnie’s recent lab results to the medical resident attending to them.

“Are you a doctor?” the resident said, startled. The Narths laugh about this now.

“My friend Anna Mae says, ‘Go, Paul!’” Minnie says. “He knew my history inside and out. I don’t think I would have survived anything without him.”

As Minnie lay with her head immobilized in a mesh mask to receive her whole-brain radiation, she calmed herself by visualizing Paul and Kieron as superheroes, a strategy inspired by her husband’s heroics and Kieron’s tiny Superman costume. “During each session I would imagine them blasting away the tumors,” she says, raising one arm in a streamlined superhero salute.

Minnie’s continued treatment left her with almost no energy for Kieron. “It was a little heartbreaking for me because I couldn’t take care of him,” she says. During periods in the fall of 2009 when Minnie was well enough to be home, the two nannies who took turns caring for the baby would put him to sleep and then bring him to Minnie so they could nap together. She was too exhausted for much else. “Kieron was

very close to his nannies,” she says. “It’s hard that they saw his milestones, and I only got them secondhand. But there was no choice.”

“I don’t think you missed a huge amount,” Paul says gently to his wife. “It was better that he was so young.”

Today, 2-year-old Kieron obviously has a strong bond with both parents. He has the bright eyes and wide, baby-toothed grin of a happy little boy, and a sharp interest in gadgets, too. “Don’t type, Kieron!” both parents say when he gets dangerously close to an open laptop.

Paul and Minnie are keeping an eye out not just for mischief but also for possible aftereffects of the chemo. They had a scare when a friend suggested Kieron’s speech was delayed, but a formal assessment reassured them that his language development is on track. And they’re comforted by the news that, in general, babies who get chemotherapy in the womb seem to do well. The first baby in Theriault’s case series is now a healthy 22-year-old, and a group in Mexico City that has followed “chemo babies” even longer than Theriault has documented that these young people can have healthy children of their own.

### EPILOGUE:

*After Minnie’s radiation treatments put her brain tumor into remission, she received an autologous stem cell transplant February 2010*

*to lower the chance that her disease would relapse. In August of that year, the Narths threw a big party to celebrate Minnie’s good health, their second anniversary and Kieron’s first birthday. Aziz remembers feeling overwhelming joy as she watched Minnie interacting with her family: “I kept thinking of the wonders of the medical therapy that enabled her to get to that point,” Aziz says. “And also, here was this sweet little boy who, during his gestation, had undergone such an amazing experience with his mother ... here he was beautiful, healthy and able to enjoy the love of his mother and father. It was the most wonderful celebration.”*

*Now in remission for more than a year, Minnie suffers some short-term memory problems but is otherwise healthy. She’s caring for Kieron and enjoying the ordinary fun that comes with being the mother of a toddler: playing together, listening to music and dancing, taking him to preschool. And she ran the San Francisco Nike Women’s Marathon in October. **SM***

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## FEATURE

After cancer's cured

CONTINUED FROM PAGE 26

diet — and do some sort of surveillance plan, my patients have the chance of living healthier, longer lives than their peers,” he explains. “It’s not all grim.”

And surviving cancer can drive patients to live more meaningful lives. Many of Spiegel’s patients tell him that in many ways life is better. “They trivialize the trivial,” he says. “Cancer teaches about what matters in life.”

As for Tom, she looks healthy and happy — no one who spotted us in the coffee shop that day could have detected any signs of past sickness or struggle. If given the choice, Tom wouldn’t have asked to battle cancer four times, but she acknowledges that her experience has helped shape her. “It’s given me my life’s work,” she explains.

And, through life-coaching of people with cancer and volunteer work with patient groups, she is determined to make survivorship easier, to help patients emerge from the “shadow of cancer.” She wants to ensure that those who pass through their own sliding doors aren’t lost on the other side. **SM**

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## FEATURE

Make your own cancer diagnostic test

CONTINUED FROM PAGE 27

professor Rob Tibshirani, PhD, developed SAM, a free Excel plug-in that makes it easy. So download SAM, open Excel and click on the SAM ribbon. Choose “two class unpaired” as the response type, select “unlogged” (if any of the values are in hundreds or thousands) or “logged” (if they’re not) and click OK for a chart of the results. Set the delta value that corresponds to 5 percent false discovery rate, click “list significant genes” and then you’ll see them: Genes

that are over-expressed in tumors compared with normal samples will be red. These are the ones to choose from. Pick those with the highest fold change (greater than 2 is best) and the lowest false discovery rate.

Now check whether each of the finalists is over-expressed in tumor tissue in the majority of the experiments. Rule out those that appear in just a few. Those that remain are your contenders for the diagnostic test.

**Resource:** SAM (<http://www-stat.stanford.edu/~tibs/SAM/>)

**Cost:** Free

**Time needed:** Maximum 24 hours

### IS IT SPECIFIC FOR DISEASE?

Since you’re developing a diagnostic that tests for tumors, you want to make sure the gene is not produced elsewhere in the body. Go to gene portal BioGPS, type each mRNA ID into the search box and look at the result across body tissues. Ideally, your gene is not made elsewhere, showing a level close to zero.

**Resource:** [biogps.com](http://biogps.com)

**Cost:** Free

**Time needed:** Five minutes or less

### REALITY CHECK

You’ll need blood samples from 10 cancer patients and from 10 healthy patients for comparison. You can order these online. Two reliable companies are Conversant Bio and US Biomax.

**Resources:** [conversantbio.com](http://conversantbio.com) or [usbio-max.com](http://usbio-max.com) or other tissue provider

**Cost:** About \$50 each, total \$1,000

**Time needed:** A week or two for delivery

Then ship the samples to a contract lab to assay them using an ELISA test based on your top mRNA pick. Two reliable companies are Assay Depot and Science Exchange.

**Resources:** [scienceexchange.com](http://scienceexchange.com), [assaydepot.com](http://assaydepot.com) or other contract lab

**Cost:** \$2,000 to \$3,000 per gene

**Time needed:** Four to six weeks’ wait

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If the assays find the protein in the cancer patients’ blood samples and not in the others’, you have found yourself a biomarker — the basis for a diagnostic test. Now, you can get out the word by publishing your results. A peer-reviewed journal is best, though competitive. Try a publication related to the type of cancer you’ve singled out, or a general open-access journal like *PLoS One*. **SM**

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# high-dose drama

RECONSIDERING A CONTROVERSIAL CANCER TREATMENT

**Breast cancer is always a scary diagnosis**, but metastatic breast cancer — in which the cancer has spread beyond the breast — is among the scariest. Fewer than one in 20 of these patients are alive 10 years later. And new treatments during the past decade have added only a few months of life for most with this diagnosis. • So Stanford's Judith Shizuru, MD, PhD; Antonia Müller, MD; and their colleagues found reason for hope when they followed up on 22 metastatic breast cancer patients who had received an unusual treatment more than 10 years ago and discovered five were still alive, all but one with no signs of disease. The women, who had enrolled in the study between 1996 and 1998, had received chemotherapy at a much higher dosage than was standard — then had their decimated blood cell population replenished with their own purified blood stem cells. • Such positive results, albeit from a small study, might seem promising. But the reaction among many breast cancer researchers has been restrained, to say the least. The study reopens a painful episode in medical history — one that a large part of the medical community considers a closed case.



JUDITH SHIZURU WANTS TO SEE IF THE GOOD RESULTS OF A TINY STUDY FOR METASTATIC BREAST CANCER HOLD UP IN A LARGE ONE.

professor of blood and bone marrow transplantation. Adding to the confusion and angst of the era, one of the trials turned out to be a fraud.

By the late 1990s, the first reputable clinical trial results were showing that high-dose chemotherapy worked no better than standard treatment. There was one important difference between these trials and the Stanford study, however: In the other trials, the stem cells were not purified, but were a mixture of cells from the blood and bone marrow, which likely contained cancer cells.

"We know that in metastatic breast cancer, about 40 percent of bone marrow and mobilized blood samples are contaminated with cancer cells, so it's not surprising that unmanipulated grafts might contribute to breast cancer recurrence," Shizuru says.

Those negative results came just when the Stanford group was ramping up its trial using purified stem cells. "Our trial was small because referrals just stopped coming," she says.

Now, the Stanford trial's tantalizing long-term results are prompting Shizuru and colleagues to call for further investigation with a larger, randomized study using cancer-free blood cells. "This is not a miracle cure, but it's possibly a start, or at least a restart, on this issue," says Shizuru. — CHRISTOPHER VAUGHAN

In the 1980s and 1990s, high-dose chemotherapy for metastatic breast cancer followed by transplants of the patients' own blood stem cells had many enthusiastic backers, despite the fact that the therapy had life-threatening side effects and was unproven. Women with slight odds of surviving pushed for it, sometimes going to court against insurance companies that balked at paying. At the same time, private clinics sprang up to offer the therapy, and few were testing whether it worked.

"There were probably only about 720 women who were enrolled in trials that underwent transplant, out of the thousands who were treated outside of trials," says Shizuru, associate

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## Canoodling with cavemen

THANKS FOR THE GENES

FOR A FEW YEARS NOW, SCIENTISTS HAVE KNOWN THAT HUMANS AND THEIR EVOLUTIONARY COUSINS HAD SOME CASUAL FLINGS, but now it appears that these liaisons led to a more meaningful relationship. • Sex with Neanderthals and another close relative — the recently discovered Denisovans — has endowed some human gene pools with beneficial versions of immune system genes. • Although modern humans, Neanderthals and Denisovans share a common ancestor in Africa, the groups split into separate, distinct populations approximately 400,000 years ago. The Neanderthal lineage migrated north and northwestward into West Asia and Europe, and the Denisovan lineage moved northeastward into East Asia. The ancestors of modern man stayed in Africa until 65,000 years or so ago, when they expanded into Eurasia and then encountered the other human-like groups. • Last year, a partial genome sequence of Neanderthals, who died out approximately 30,000 years ago, revealed the trysts left as much as 4 percent Neanderthal DNA in the genetic blueprint of some present-day humans. Last December, the genome of another human cousin, the extinct Denisovans, made clear that up to 6 percent of some people's genomes are Denisovan in origin.



Now, a team of researchers led by Peter Parham, PhD, professor of structural biology and of microbiology and immunology, has found that these matings had a positive effect on modern human fitness. "The cross breeding wasn't just a random event that happened; it gave something useful to the gene pool of the modern

human," says Parham, who is the senior author of the study, which was published Aug. 25 in *Science Express*.

The useful gift was the introduction of new variants of immune system genes called the HLA class-1 genes, which are critical for our body's ability to recognize and destroy invading viruses and bacteria. HLA genes are some of the most variable and adaptable genes in our genome, in part because the rapid evolution of viruses demands flexibility on the part of our immune system.

"We are finding frequencies in Asia and Europe that are far greater than whole-genome estimates of archaic DNA in modern human genomes, which is 1 to 6 percent," says Parham. Within one class of HLA gene, the researchers estimate that Europeans owe half of their variants to interbreeding with Neanderthals and Denisovans, Asians owe up to 80 percent and Papua New Guineans, up to 95 percent. — SUSAN L. YOUNG

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