trailblazing treatment reboot

Years after a rocky start, a pioneering immunotherapy drug gets a fresh analysis

BY RUTHANN RICHTER

PHOTOGRAPHY BY TIMOTHY ARCHIBALD

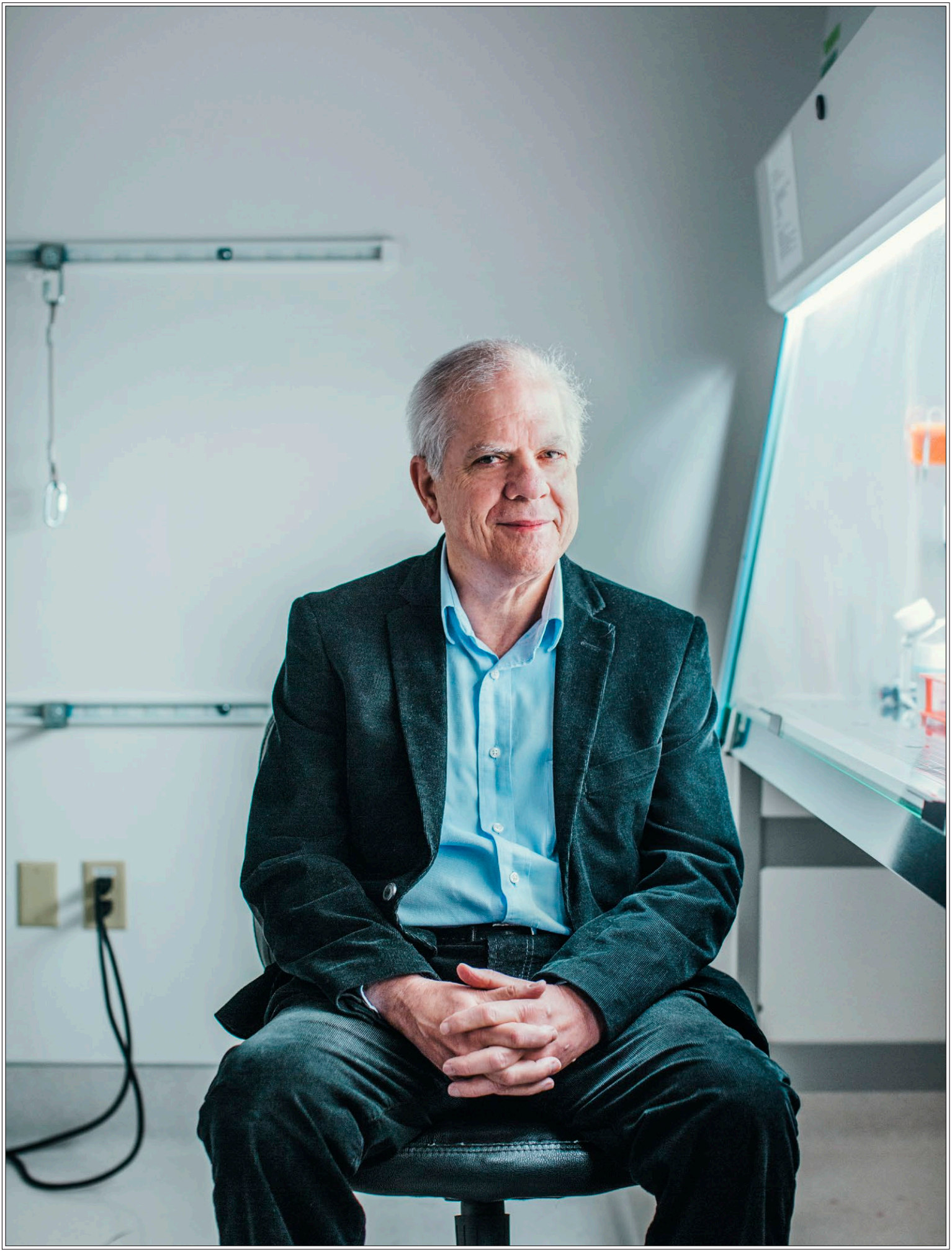
WHEN RICHARD CARDONI WAS DIAGNOSED WITH PROSTATE CANCER 20 YEARS AGO, his doctors chose a conventional treatment route: hormone therapy, followed by radiation. That worked beautifully for nearly 10 years, Cardoni said, until tests showed his tumor had rebounded.

This time, his Stanford oncologist, Sandy Srinivas, MD, decided to try an experimental drug that used a radically new approach to attack the disease. Cardoni's cancer had spread beyond the prostate to nearby lymph nodes, so he qualified for the treatment, which at the time was available only to men with metastatic disease.

"I had this cancer that was coming back. I wanted to try anything that would stop it," said Cardoni, a retired San Jose surgeon who asked that his real name not be used in this article.

The new treatment, known as Provenge, capitalizes on the body's own powers to combat cancer. It helped set the stage for a revolution in cancer treatment when in 2010 it became the first immunotherapy drug the federal Food and Drug Administration approved for use in patients — in this case, for those with advanced disease.

EDGAR ENGLEMAN NEVER LOST FAITH IN PROVENGE, A DRUG THAT HAD ORIGINS DECADES AGO IN HIS LAB AT STANFORD.



"In 2010, people thought this would just open the floodgates," said Srinivas, professor of urologic oncology at Stanford. "Every patient would get Provenge, and this would be the wonder drug."

However, the treatment was perhaps ahead of its time: It was a completely new concept, somewhat alien to patients and physicians, which may have made it more difficult to accept. During the next several years, its path proved to be a rocky one. Its manufacturer faced marketing challenges and was forced to declare bankruptcy. The company's assets then changed hands twice.

But Provenge is enjoying a revival, in part because of a new, large-scale trial to see if it stalls cancer progression in patients with early stage disease. Some clinicians believe patients are more likely to benefit from the drug if they take it before the disease has a chance to advance.

Throughout the ups and downs of Provenge, Edgar Engleman, MD, never lost faith in the drug, which had its origins decades ago in his lab at Stanford.

In his initial days at the Stanford Blood Center, in the 1980s, Engleman began wondering how he might take advantage of the unusual capabilities of a white blood cell known as the dendritic cell. These unique immune system cells have fingerlike projections that help them interact with the environment. In 1973, Ralph Steinman, MD, at Rockefeller University, identified and named the cell, winning a Nobel Prize for the work.

But there was still much to be learned about the cell, and the blood center, which Engleman directs, was an ideal place to begin. White cells were routinely discarded from blood donations because they might cause harm if given to patients with compromised immune systems, so Engleman's lab had a plentiful supply for study. In 1989, his group succeeded in isolating the dendritic cell in humans, a first step in understanding its role as one of the body's defenders.

"Dendritic cells are uniquely capable of educating the immune system to see new things. There aren't a lot of cells that do that," said Larry Fong, MD, leader of the Cancer Immunotherapy Program at UCSF who worked with Engleman as an oncology fellow at Stanford. "So being able to isolate them was an important first step."

Engleman then began to consider what some thought was an impossible challenge: What if he could extract dendritic cells from cancer patients, removing the cells from the tumor environment, and then somehow educate them to attack the cancer? It was contrary to traditional thinking — the immune system typically doesn't attack cells it views as "self," and tumor cells are seen as self.

"This was the 1990s, when the concept of immunotherapy was completely foreign and there was great skepticism," said Engleman, a cellular immunologist and professor of pathology and of medicine. "Nobody thought this was feasible."

'In 2010, people thought this would just open the floodgates. Every patient would get Provenge, and this would be the wonder drug.'

But Engleman wasn't deterred. He began working with Ronald Levy, MD, a professor of oncology at Stanford, who was then testing methods of vaccinating patients against their own tumors using a different mechanism. The scientists were fortunate, Engleman said, in finding antigens — proteins unique to a tumor — that could prime the dendritic cell to target the tumor.

They began testing the therapy in four lymphoma patients, all of whom developed measurable responses; in one patient, the tumor was completely suppressed, they reported in a 1996 paper in *Nature Medicine*. They conducted a larger trial with 35 patients with B-cell lymphoma, again with promising results that were published in *Blood* in 2002.

In 1992, Engleman started a company, Activated Cell Therapy Inc. in Mountain View, California, teaming up with Samuel Strober, MD, a professor of medicine who was interested in immune suppression in organ transplantation and autoimmune disease. Within a few years, the company was renamed Dendreon and later moved to Seattle. At that point, the two Stanford scientists severed their financial ties.

The company decided to test the therapy, under the generic name sipuleucel-T, as a treatment for metastatic pros-

tate cancer among patients who had failed all other therapies, including hormone therapy. Prostate cancer is the most common form of non-lung cancer among American men. This year, more than 174,000 men are expected to be diagnosed and more than 31,000 will die of the disease, according to the American Cancer Society. When the company was launching its trial, patients with metastatic disease had no options other than palliative care, Engleman said.

"At the time there was very little hope for these patients, and the bar for treatment success was low," he said. "I felt it was likely to be extremely safe because these were cells from the patient, not foreign cells. … It was hard for me to imagine toxicity from that. So I felt the downside risk was very minimal. And indeed, it was found to be very well tolerated."

The company ultimately published results of a trial involving 512 participants with metastatic disease. Half received an infusion of the drug, while the other half received a placebo infusion. The findings, published in 2010 in *The New England Journal of Medicine*, showed the chance of survival over a three-year period to be 31.7% among the treated patients, compared with 23% in the placebo group. Among patients receiving the drug, the average increase in survival was four months.

On the basis of the trial, the FDA approved the drug the same year to much fanfare and outsized expectations. The company, marketing the drug under the name Provenge, initially enjoyed great success. The drug has since been prescribed to more than 30,000 patients in the United States, according to company figures.

"There was a big uptake, as it was very sexy, a new approach. You are stimulating your own body to do all the magic," said Srinivas, the Stanford oncologist.

Immunotherapy was still a relatively new concept. But the field soon exploded, with the introduction of other, FDA-approved immunotherapy drugs that work through a different mechanism than Provenge does. Immunotherapy soon became the hottest area of cancer treatment and research.

But Dendreon struggled to market the drug, in part because it was complicated to administer, Srinivas said. For instance, when Cardoni was taking the medication, he had to drive to a company-contracted lab in Oakland, California, and undergo leukapheresis, in which his blood cells were removed, and the red cells, platelets and plasma were returned to his body. The white blood cells were sent to a laboratory in Seattle, where the dendritic cells were exposed to the tumor antigen, thus priming them for action. Cardoni returned to Stanford several days later for an infusion of the treated cells. He had to repeat the process three times.

Cardoni, who wasn't deterred by going to such lengths for the treatment, said he had no side effects. Most patients have only mild effects, such as chills, fever and headache during the infusion, though there is a 2% risk of stroke, Srinivas said.

On the downside, the drug was relatively expensive, $93,000 for a full treatment, which seemed a fortune at the time (immunotherapy drugs now cost at least $250,000 a year). Moreover, it was hard to quantify the impact of Provenge because there is no biomarker to measure its effects.

Unlike other prostate treatments, the drug does not necessarily affect PSA, or prostate specific antigen, an imperfect marker that is used to gauge the progress of disease. That was off-putting to some clinicians and patients.

"I know there are still physicians who don't believe in Provenge and don't use it," said Russell Pachynski, MD, assistant professor of oncology at Washington University in St. Louis, who began using the drug as an oncology fellow at Stanford. "I think to some extent, they might not understand how it works. It doesn't work like traditional chemotherapy. It's not a targeted pill. Now we have worked out more of the mechanism of the drug, but when it was approved, there were a lot of questions about exactly how it was working — and oncologists like to know precise mechanisms of action, especially for a novel, first-in-class therapy. We know these immune cells are stimulated and activated, but what exactly happens when they are put into the patient?

"The other thing the patient and the oncologist see is PSA, and the PSA went down in fewer than 3% of patients in the trial that led to Provenge's approval. So people think it doesn't work because your PSA doesn't go down, and that's the metric by which they are gauging response. However, PSA is only one way to assess response, and there are drugs that lower the PSA very nicely, but don't improve overall survival. So, there is a lot of education that has to happen," said Pachynski, who is a strong believer in the value of the drug.

Because of these questions, it became a bit of a conundrum for prescribing physicians, Srinivas said. "It was a little labor-intensive to give the drug and, for all of this, the return seemed like it was very little," she said. "Patients would say,

CONTINUES ON PAGE 44

est impact," Galvin said. "With her help, we made YouTube videos advertising the program and sent student representatives — trained by her — to each science classroom to answer students' questions about the program."

Rivera was motivated "by the impact that science and engineering could have on people's lives — both for those who practice it and those who benefit from its advances," Galvin said.

"I just remember feeling like a different, more mature version of myself came out of doing the program my senior year," Rivera said.

Still, she faced some challenges while she was in the program, as do many other students. In her case, family health difficulties made it hard to attend every session in her senior year, and she missed quite a bit of school. But she said FAST helped her stay on track academically, while coaching from mentors and the scientific process itself both taught her resilience.

"I didn't know that most of the time in science, research is like 99% failure," Rivera said, "And now, I think that's kind of what makes science so interesting for me. The fact that it is a trial-and-error process."

Galvin said having a space for ambitious effort and for spectacular failure is essential in learning, and mentors at any level can play a part in making that happen.

"We need safe opportunities to fail and be celebrated for trying really hard," Galvin said. "The potential of graduate students and all sorts of professional scientists to inspire the public to engage in science, follow curiosities, get messy — no matter age, race, socioeconomic status — is sorely untapped because many feel that is the job of professors and 'professional' educators."

In February 2019, Lloyd Minor, MD, dean of the School of Medicine, hosted a lunch for the FAST founders and several of its graduate student leaders. "I'm proud of them for shaping the next generation of thinkers and thankful for their strong dedication to our community," Minor said.

Galvin and Liu are sharing their training materials and guidance with student organizations within Stanford. Their team has also begun meeting with people throughout the Bay Area who are seeking to start their own chapters of FAST or incorporate the lessons FAST has learned in its four years of operations and monitoring of student progress.

They plan to expand the academic scope of FAST into social sciences, including psychology and sociology, and into the arts. They're also considering how to make FAST's learning environment more inclusive of students from immigrant backgrounds.

"One idea is to have a dual-language option for students to have Spanish-speaking mentors who will work with them in Spanish half of the days during brainstorming and experimenting and English for proposal writing and practicing presenting," Galvin said. "In this new twist on FAST, the students who are native Spanish speakers can feel empowered while still learning to navigate our English-speaking science community."

As a Mexican American woman in bioengineering, Rivera is still outnumbered, just as she once was in her honors biology class. But discovering her passion for science and having women mentors to inspire and support her has made it easier for her to persevere.

"Though it's not completely apparent," she said, "you do always still feel the fact that you're not necessarily taken seriously. But I remember, during the FAST program, when I felt like all of a sudden that feeling didn't matter anymore. I just knew what I wanted to do, and I was so excited about it." **SM**

— Contact Julie Greicius at jgreicius@stanford.edu

FEATURE

Trailblazing treatment reboot

CONTINUED FROM PAGE 37

'I go through all of this, did it really work?' We physicians had to put up our arms and say, 'We have no idea.' We know the PSA doesn't go down. Eventually people live longer, and patients ask by how much, and we say four months. But patients themselves are not that impressed."

Cardoni said he believes the drug helped bolster his immunity to fight the cancer, but he can't say for sure because he was taking another treatment — an anti-androgen drug — at the same time.

Those kinds of issues finally overwhelmed the company, and in 2014 it declared bankruptcy. Valeant Pharmaceuticals Inc. acquired its assets in 2015, then sold it to a Chinese company, Sanpower Group Co. Ltd., in 2017.

Around the time of Sanpower's acquisition, the company CEO and about 10 other company officials visited Engleman at Stanford, sitting around a conference table at the blood center and peppering him with questions about the history of the drug. They told Engleman they intended to expand the market into Asia while maintaining U.S. operations. Engleman said they had done their homework, as they understood the drug and the market well.

One of Sanpower's first actions was to launch a clinical trial that will test the drug in patients with early stage disease. In the 1980s and 1990s, patients with slow-growing cancers would undergo immediate treatment with surgery and/or radiation, but the trend in the past decade has been to avoid over-treatment and opt instead for active surveillance.

At least 30% of men diagnosed with low-risk disease now choose that option, which includes regular monitoring to make sure the cancer has not progressed.

The trial, which recently got underway, will include 450 men at 50 sites around the United States. Half will get the drug and half will simply be monitored. The goal is to see if the drug prevents them from slipping from a somewhat benign to a more serious disease.

"This is a drug we should be using earlier," said UCSF's Fong, who long ago proposed that the company take this approach. "When you have a patient progressing with cancer that's behaving aggressively, this might not be the right treatment, but if you have a patient with a very slow-growing cancer, that's where this type of treatment could work the best. That patient's immune system will be in better shape, which is what you need for a treatment like Provenge. You need a runway for the immune system to kick in."

He and others have continued to study the drug to better understand its underlying mode of action and to determine how it might be most useful. For instance, Fong and his colleagues examined tissues from Provenge-treated patients who had their prostates removed and found that the drug activates T cells to attack the tumor.

Others are testing Provenge in combination with other therapies, including hormone therapies and some of the newer immunotherapy medications, to see if a two-pronged approach is more effective.

"I think the biggest attribute of Provenge is its ability to be combined with other things," Srinivas said. "That is the direction in which immunotherapy is going. There are a lot of drugs that by themselves may not be good, but they might be a great partner with other things."

Engleman, meanwhile, has continued his research in immunotherapy, particularly with an eye toward making a dendritic-cell approach that is easier to administer. The goal is to deliver molecules directly to patients, activating the dendritic cells inside the tumors, rather than through a series of infusions of these cells. In 2015, he and his colleagues published a paper in *Nature* showing in a mouse model how this could be done.

Engleman has since formed Bolt Biotherapeutics Inc., in Redwood City, California, to pursue the approach. The company is developing anti-tumor antibodies that are linked with dendritic cell stimulators to deliver an immune punch to cancer. He described these modified antibodies as "guided missiles" that directly target their payload to cancer cells. He hopes to begin human trials later this year, he said.

"I still believe in the approach of taking advantage of these powerful cells,"

Engleman said. "So we can rev up the immune system, knock down cancer and ultimately win."

That would be a win, too, for patients like Cardoni, whose cancer remains in check two decades after his initial diagnosis. He said he's benefited from having a wide range of treatments available, including experimental medications like Provenge.

"That's why, I believe, I'm alive after 20 years," he said. **SM**

— Contact Ruthann Richter at medmag@stanford.edu

PLUS

A legacy of trauma

CONTINUED FROM PAGE 39

the Mount Sinai School of Medicine, offered an intriguing new idea: that children of traumatized parents are at risk for similar problems because of epigenetic changes that occurred in the biology of their traumatized parents. Epigenetics refers to how PTSD may possibly alter the way genes express themselves in a trauma survivor and how such alterations can then be inherited by children on a cellular level and later their neurons, brain molecules, neuroanatomy and genes. These epigenetic changes are transmitted to children by a process called "intergenerational transmission" by having a negative impact on the parents' sperm or egg quality or impacting the mother while she is pregnant.

How can one disentangle the effects of environment from genetic and molecular factors, especially when parents and their children often share the same living environment and are exposed to the same social and psychological stressors? By focusing on the stress hormone cortisol, researchers have ventured into these murky waters and emerged with enticing new insights.

After trauma, the brain's central coordinator of our response to stress, the hypothalamic-pituitary-adrenal axis, mounts a chemical and hormonal reaction. The HPA axis directs a cascade of complex chemical reactions, and one of the end products, cortisol, appears to be crucial in helping the traumatized brain recover. The scientific community predicted that cortisol levels would be high in PTSD sufferers, yet over the last two decades, study after study has shown that patients with PTSD actually have lower-than-average cortisol levels than those who have been exposed to trauma but do not have PTSD and healthy controls. Indeed, the story of cortisol and PTSD has turned out to be complicated, moving beyond cortisol to encompass metabolites of cortisol, glucocorticoid receptors in the brain, and the genes and proteins involved in regulating the activity and sensitivity of those receptors.

WEB EXTRA

Shaili Jain discusses her new book, https://stan.md/2PZkGRS

To study the epigenetics of PTSD, Yehuda examined the impact of trauma exposure on the salivary cortisol of pregnant women. Researchers collected salivary cortisol samples from 38 mothers who were pregnant when they evacuated the World Trade Center on 9/11 and from their 1-year-old babies. When compared with mothers who did not develop PTSD after 9/11, lower cortisol levels were observed in both the mothers who did develop PTSD after 9/11 and their babies. Mothers who were in their third trimester during 9/11 had the lowest cortisol levels.

This trimester effect may have been related to the traumatic stress altering the expression of a specific enzyme in the placenta. This enzyme, which becomes active in the placenta only late in the second trimester, is supposed to break down cortisol into an inactive form. If the activity of the enzyme is altered, elevated levels of maternal cortisol hormones circulating in the placenta could have had a negative effect on the fetus' cortisol hormones.

When I asked Yehuda what the take-home message from the study was, she said:

"The message is simple: Mothers who are traumatized during pregnancy can transmit defects to their offspring, in utero, because the offspring accommodates somehow to the level of stress hormone. … The offspring do not need to have actual (traumatic) experiences in their life for this to be true. We do not think about pregnancy as the very important developmental event that it really is. Otherwise, we would take much better care of traumatized pregnant women than we do."

Other studies showing that pregnant women with PTSD are more likely to have impaired uterine blood flow, low-birth-weight babies and premature babies underscore the crucial relevance of in utero exposures to PTSD on the biology of the developing baby.

These novel ideas linking traumatic stress, epigenetics and intergenerational transmission now come to my mind every time I meet a patient who comes from a community that has survived a group trauma. I can't help but wonder about how much of his or her suffering today is rooted in historical events and if what I am witnessing is, in part, the brunt of a much broader and deeper injury. Are traumatic echoes of massive group-based oppression, forced relocation or political subjugation also present in the room with us? Are these collective sorrows now carried in the blood of future generations? If future generations don't recognize these collective sorrows for what they are, will they become curses that permanently wound their souls?

Though the science of epigenetics remains in its infancy, what seems to be clear is that we humans are an accumulation of our traumatic experiences, that each trauma contributes to our biology and that this biology determines, to some extent, how we respond to further traumatic events as they emerge in our lives. **SM**

Editor:
ROSANNE SPECTOR
Associate Editor:
PATRICIA HANNON
Art/Design Direction:
DAVID ARMARIO DESIGN
Director of Print and Web Communication:
SUSAN IPAKTCHIAN
Senior Communications Strategist:
PAUL COSTELLO
Senior Director, Content Strategy:
MICHELLE BRANDT
Writers:
HANAE ARMITAGE
NATHAN COLLINS
KRISTA CONGER
MELISSA DE WITTE
ERIN DIGITALE
BRUCE GOLDMAN
JULIE GREICIUS
RUTHANN RICHTER
Copy Editor:
MANDY ERICKSON
Circulation Manager:
ALISON PETERSON

Stanford Medicine is published four times a year by the Stanford University School of Medicine Office of Communication & Public Affairs as part of an ongoing program of public information and education.

Stanford MEDICINE

Letters to the editor, subscriptions, address changes and correspondence for permission to copy or reprint should be addressed to *Stanford Medicine* magazine, Office of Communication & Public Affairs, 455 Broadway, 4th floor, MC 5471, Redwood City, CA 94063.
We can be reached by phone at (650) 723-6911, by fax at (650) 723-7172 and by email at medmag@stanford.edu.

To read the online version of *Stanford Medicine* and to get more news about Stanford University School of Medicine visit http://med.stanford.edu. For information from the Stanford University Medical Center Alumni Association visit http://med.stanford.edu/alumni/.