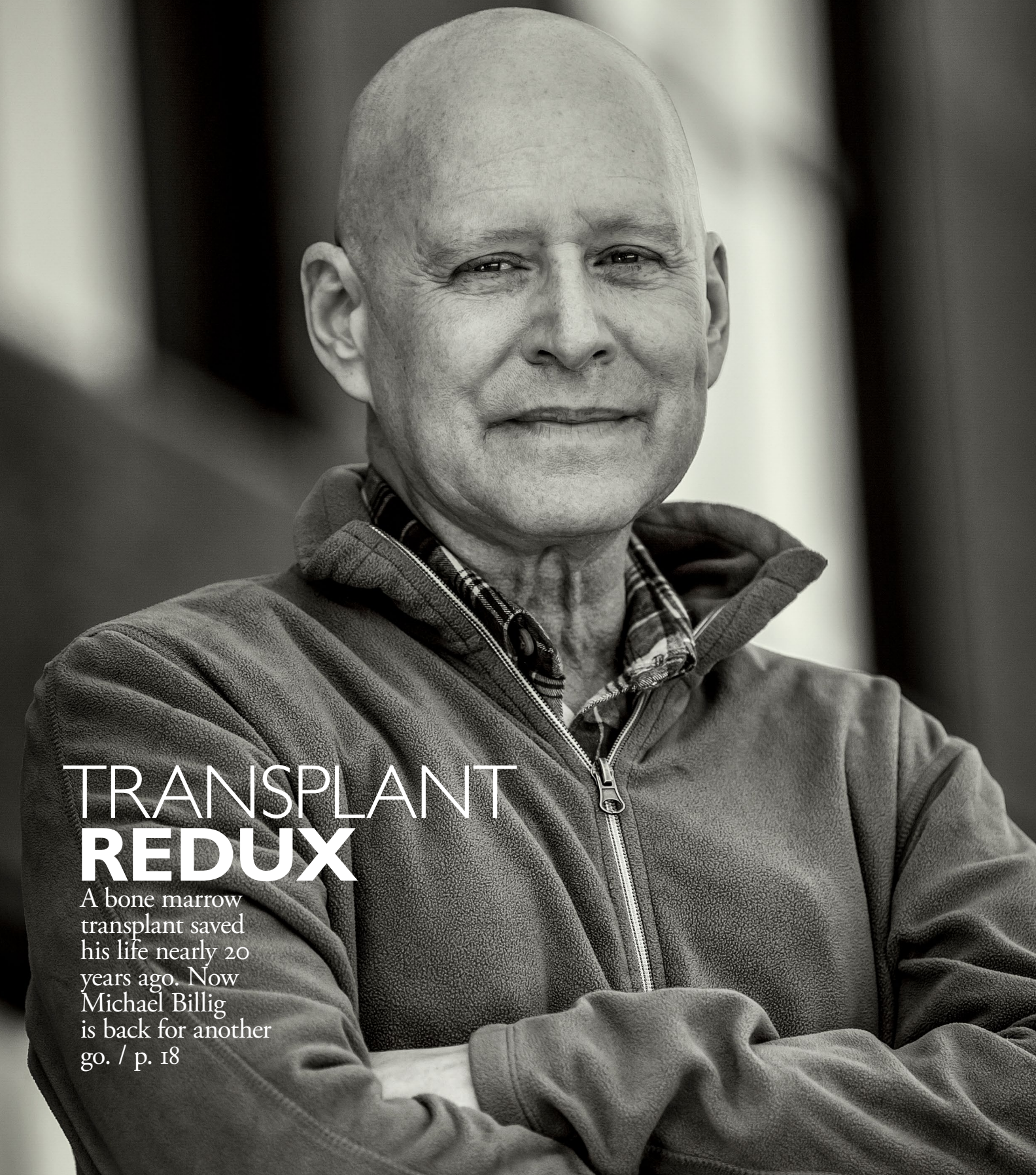
FALL 2018

HOPKINS MEDICINE



TRANSPLANT REDUX

A bone marrow transplant saved his life nearly 20 years ago. Now Michael Billig is back for another go. / p. 18

BACK TO THE BRINK

Nearly 20 years after a pioneering bone marrow transplant saved his life, Michael Billig found himself back at Johns Hopkins, once again putting his trust in a team of "hematological masters of the universe."

BY **BILL GLOVIN**
PHOTOGRAPHY BY **HOWARD KORN**

Michael Billig and wife, Heidi, share a stroll on the eve of his second bone marrow transplant here last February.

To borrow an expression from the late baseball great Yogi Berra, it's deja vu all over again when I arrive on a Sunday afternoon in late March at The Johns Hopkins Hospital. I am here to visit my cousin Michael Billig, who is in the middle of a bone marrow transplant in the Kimmel Cancer Center's IPOP (inpatient/outpatient) unit. The hospital campus appears to have been on steroids since I visited in 1999 to track Michael's experience for "To Hell and Back with My Cousin Michael," a cover story for this magazine about the experience of his first transplant, which was aimed at curing him of chronic lymphocytic leukemia (CLL).

At that time, Michael was in his early 40s and among the first 50 patients in a pioneering IPOP program aimed at reducing the chance of infection by having patients live in a nearby apartment outside the hospital. The program today does about 250 outpatient transplants a year and can take pride in the fact that similar outpatient programs exist in more than 50 hospitals throughout the country.

Michael and I are now in our early 60s, and we have a long history. Our mothers were sisters, and my childhood was filled with Sunday drives from New Jersey to Rockaway, Queens, where his family and our mutual grandmother lived. Just a grade apart, Michael and I were inseparable on those visits. As teens, we had extended sleepovers at each other's houses, worked side by side as dishwashers in a summer camp and learned the same Phil Ochs songs on our acoustic guitars. Later, there would be weekly squash matches, bar and bat mitzvahs, weddings, the birth of daughters and careers in academia: Michael as an anthropology professor at Franklin & Marshall College, and I as an editor at Rutgers University.

The 12 weeks Michael spent at Johns Hopkins the first time around had been an ordeal, to be sure, but in the end, Michael emerged "cancer-free." Five years later, I updated readers on Michael's condition and happily reported that while he still had four more years of checkups, the last of his bone marrow biopsies at Johns Hopkins confirmed that his bone marrow and blood cell counts were completely normal—and that he had been able to complete a book, buy a house and see his daughters go off to college.

I also told readers that Michael, through his outreach efforts for the Leukemia & Lymphoma Society's First Connection Program, found the article useful in detailing his transplant experience in occasional speaking engagements. But as the years passed, Michael gradually backed away from outreach, feeling that new and ever-expanding Johns Hopkins facilities and improving medical advances had made his experience obsolete.

Early last fall, Michael learned that it all was about to become way too relevant again, and we talked about a second article that might again prove useful. Michael's determination and positivity the first time around had been inspiring and made me proud. I wondered if he would be able to bring that energy and attitude to his new ordeal again.

SOMETHING'S NOT RIGHT

While vacationing in Maine in early July 2017, Michael felt increasingly lethargic and lightheaded. He initially thought he had a virus, but lab tests showed hemoglobin and platelet blood counts that had mysteriously dropped since his last physical, less than a year earlier.

A follow-up test a few weeks later indicated another drop to "dangerous levels." A bone marrow biopsy was ordered, and the results showed that 18 percent of Michael's marrow consisted of malignant, nonfunctional blast cells—a certain indicator that Michael's symptoms were the result of a myelodysplastic syndrome (MDS), a rare form of leukemia. He more specifically had a subset of MDS known as therapy-related myeloid neoplasm, likely a long-term consequence of his first transplant for CLL.

"MDS can be managed by medicine and transfusions (red cells and platelets) but only cured by a bone marrow transplant involving a relative or a donor from a registry," Michael emailed. "This is quite different from my previous transplant, where I was able to use my own bone marrow cells."

Michael knew firsthand the considerable physical and mental toll and the risks involved in another transplant: possible death from infection because of a compromised immune system or the required catheter, as well as a failure to engraft. But with the options of only a short-term remission and chemotherapy for the rest of his life, Michael never hesitated in applying for entrance into Johns Hopkins'

Left: Daughter Monica Billig, on leave from her job in Denver, donates her stem cells—which Michael receives the following day via infusion.

much-evolved Bone Marrow Transplant Program.

"I have my first appointment on Friday," Michael emailed me. "Hopkins now has a center for bone marrow failure that consists of a team of hematological masters of the universe. Nineteen years ago, two people received their stem cells on the same day. One was me; the other was a nice woman who had MDS and was getting cells from her brother. She was a 'failure to engraft,' meaning that the doc had to tell her that she was going to die in about 30 days, which she did. I still light a candle for her at the Relay for Life."

GEARING UP

In Michael's formative years, he had been the type to immerse himself in a new passion a few times a year and eagerly devour all there was to know about it. That trait followed him into adulthood; he is a walking encyclopedia on Wagner operas, fishing, the Amish, his precious Phillies and race walking. When Michael got sick the first time, CLL became his focus, and he went about learning all he could about treatment methods, ongoing clinical trials and new drug therapies.

He took the same approach to MDS. "The treatment for MDS has come a long way since 1999, so my plan is to fight hard and live normally," he told me. "I will teach my classes, write, etc., until I go in for the transplant … I hope to know my grandchildren and watch my daughters—and yours—grow into real adults. That said, this disease is potentially fatal, and that is just the way it is."

From the start, the program requires that patients who live more than an hour from the hospital stay with a full-time caregiver in the Hackerman-Patz Patient and Family Pavilion, which sits just across the street from the Kimmel Cancer Center's Harry and Jeanette Weinberg Building. Once trained, the caregiver administers meds, maintains the catheter, serves as head cheerleader, and manages diet, laundry, transportation and shopping. The caregiver is also trained to alert the nursing staff to unexpected developments in a patient's condition.

Michael had the advantage of Heidi Wolf, his pediatrician wife, who took a four-month leave of absence from her position at Penn State Health Milton S. Hershey Medical Center to fill the caregiver role. Heidi was no stranger to cancer; she had previously battled Hodgkin lymphoma, and her parents were both cancer survivors. "When I was a resident, cancer was not a specialized part of pediatrics, so it was something we were trained to treat," she pointed out.

The pair had met online in 2013 after Michael's marriage had dissolved. Coincidentally, Heidi had been practicing at Johns Hopkins at the time. In summer 2014, the couple had married in the shadow of a Maine lighthouse, enjoying the area so much that they had returned every summer since. They had bought a second home and were going through the closing when Michael began to feel the first symptoms of MDS.

Michael and Heidi arrived at Johns Hopkins in late October for an early morning consult with oncologist **EPHRAIM FUCHS**, a key member of the bone marrow transplant team since 1994. Michael's primary physician from his first transplant had since left Johns Hopkins, but a few of the long-tenured nurses still remembered him.

"Dr. Fuchs basically spelled it out for us," Michael reported. "There are many things that could go wrong, but most of these are manageable nowadays. The odds of bad things (even the worst thing) happening are not insignificant, but by and large, he expects that I will be able to 'graduate' to the transplant and that the transplant will—after a long ordeal—have successful results." Michael added that after that conversation with Fuchs, he could see the stress lifting from Heidi's brow.

The transplant would involve extracting healthy stem cells from a bone marrow donor and infusing them into Michael's

depleted marrow. For the transplant to be successful, Michael's body would need to accept the donor stem cells. This would allow him to reform red cells, white cells and platelets that had been depleted by chemotherapy and total-body irradiation. The process would include daily blood draws, frequent red cell and platelet transfusion, and injections of a medication that stimulates the production of white cells. He would also need anti-rejection, antibiotic, antiviral and anti-fungal drugs, as well as other drugs that addressed several of the side effects he would likely experience. Best case scenario, the entire IPOP process would unfold over about nine weeks.

From October to early January, Michael scaled down his professorial office hours and social interactions to avoid infection during the four rounds of chemotherapy treatments he needed to kill the cancer cells in his bone marrow. During this time, he met several times with Johns Hopkins oncologist/hematologist **JONATHAN WEBSTER**, who oversaw his treatment and directed the chemotherapy treatments, which were administered through a Mediport surgically implanted in Michael's chest.

By late February, Michael's immune system had sufficiently recovered from the chemo, and he was ready to begin the bone marrow program.

Now it was on. Both of Michael's 30-something daughters had volunteered to donate their stem cells: Shira in Los Angeles, and her younger sister, Monica, in Denver. In early November, they had received their kits and taken the steps needed to sequence DNA and determine their match potential. Monica proved the better choice, which was fortuitous since Shira announced she was pregnant a few months later. This promised to make Michael a grandfather for the first time.

SHOWTIME

After some unexpected delays, Michael, with his shaved head, Heidi and personal items they couldn't live without arrived at Johns Hopkins to stay, on Feb. 21. The next day, Michael had a double-lumen catheter implanted. This would be vital for moving medicines and transfusions in and out of his body. Before his CLL transplant 19 years ago, the catheter implantation had required full anesthesia by a surgeon. This time, a physician assistant implanted the catheter while Michael was sedated but conscious.

A few weeks later, Monica took a leave of absence from her job as a yoga instructor for kids in Denver and came east to donate her stem cells. In Lancaster, she injected herself in the belly twice a day for five days in order to stimulate stem cell growth. As she undertook her final injection, she had a panic attack. "I was leaving for Baltimore in the morning and was overcome with worry and concern," she recalled. "Just being a donor requires an awful lot, but I realized it was just a fraction of what my dad was about to go through. It also gave me enormous admiration for those on the registry who donate to people they don't know."

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MONICA BILLIG

The following day, Feb. 28, with Michael, Heidi and her mother by her side at Johns Hopkins, Monica laid perfectly still for four hours as 14 million stem cells and blood were extracted and filtered intravenously from her left arm, with the blood returned through her right arm.

One day later, Michael received Monica's cells via infusion through his catheter—and the battle between graft and host began.

As Michael began to receive frequent transfusions of red blood cells and platelets and a load of medication, he came to realize that the nurses played a much more active role in evaluating his progress and deciding on treatment strategies than during his first transplant.

Fuchs was but one of a team of four transplant team physicians who met each morning with the four nurse practitioners. It was the nurse practitioners' job to manage the teams responsible for evaluating and providing care to the eight to 15 inpatients and 20 to 30 outpatients who are on the bone marrow transplant ward at any given time. Many of the outpatients develop complications and are required to spend days, or even weeks, as inpatients. Thankfully, while Michael would go on to have his own set of complications (nosebleeds, rashes and fevers) and spend many long days feeling like he'd been hit by a ton of bricks, he was never required to stay in the unit overnight.

As the long weeks on the IPOP unit unfolded, Michael discovered less camaraderie with fellow patients than he'd experienced before. "Previously, transplant patients got most of their treatments in a large, open room filled with patients and nurses (and an occasional doctor)," said Michael. "This created a wonderful communal spirit with a lot of gallows humor (nonpatients were called 'hairies'). We all got to know each other well." This time around, Michael received his treatments in a curtained-off private space, with a nurse coming in and out several times an hour.

He found he preferred the communal approach: "The sociability of the older way made it a lot easier to get through such a shared ordeal."

DOWN THE STRETCH

On a cool day in mid-March, Heidi met me at the elevator outside the IPOP unit, handing me a mask to cover my mouth and ushering me to Michael, who was sitting up in bed as bags of platelets dripped intravenously into his left arm. Every 15 minutes or so, a nurse slid through the curtain to check Michael's vital signs, change out a bag or provide medication. Michael's nurse practitioner, **AUDRA SHEDECK**, looked in on him every day and made most of the treatment decisions. "My white cell counts were around 50 for a long time and are now 160," Michael boasted, as I took a seat beside him.

As we caught up, Heidi went off to do laundry, shop for groceries and visit the couple's dog, Sophie, who was staying nearby with friends. When Heidi returned, we began the 10-minute hike to the Hackerman-Patz apartments. Michael walked slowly and was annoyed that he already had to stop at a bathroom to urinate. The constant transfusions meant excess water weight of some 25 pounds and the need to visit the bathroom as many as a half-dozen times on any given night, a common and persistent symptom of this second transplant.

At the apartment, Heidi and I went off to pick up a pizza and wings, and then we all headed to a large common kitchen and dining area, which we had all to ourselves. Unfortunately, Michael didn't have an appetite for much more than a wing or two. As during the first transplant, his taste buds had deadened.

At that point, taste buds were the least of it. Michael told me that he has found this second transplant to be much more difficult than the first; his immune system's battle to accept even a biological daughter's stem cells had led to symptoms he had never experienced the first time: unexpected nosebleeds, blood in his urine and that excessive weight gain from fluids. He also was considerably more tired and woozy.

"For most patients, advances have made both donor (allogeneic) and nondonor (autologous) transplants more tolerable," Fuchs explained to me the next day at his office. "But in Michael's case, he's 20 years older, plus he's been through it before, so his body is weaker."

Over the past two decades, Fuchs and colleagues at Johns Hopkins had pioneered advances—many made possible through clinical trials here—in gentler drugs for bone marrow transplant. Some are now used in place of the heavy doses of chemo and radiation to prevent the rejection of the donor's stem cells. Other new drugs have been introduced to help fight the kind of annoying symptoms Michael was experiencing.

Perhaps just as important: The Johns Hopkins team has worked to minimize the toxicities of bone marrow transplants from donors who are less than perfect matches, including half-matched, or "haplo," donors such as parents or children.

DRAMATIC ADVANCES SINCE 1999

When Michael Billig underwent his first bone marrow transplant (BMT) at Johns Hopkins back in 1999, the odds that he wouldn't survive the procedure were about 20 to 40 percent—largely due to the toxic effects of graft-versus-host disease (GVHD). In effect, the body's immune system would frequently fight off—and ultimately vanquish—the newly transplanted blood cells.

Today, it's rare to lose a patient to BMT, says oncologist **MARK LEVIS**, program leader of the Bone Marrow Transplant Program at the Johns Hopkins Kimmel Cancer Center. "Between 2013 and 2015, our latest available three-year data, we transplanted 97 consecutive patients with acute myeloid leukemia without a single mortality," he says.

The biggest game-changer? A post-transplant protocol developed by Johns Hopkins oncologists **LEO LUZNICK** and **EPHRAIM FUCHS**, now used widely by doctors around the world, who refer to it as "the Hopkins protocol." In the early 2000s, the two scientists found that giving patients high doses of cyclophosphamide—a drug derived from nitrogen mustard and used to treat blood cancers—three days after bone marrow transplant successfully thwarts acute and chronic GVHD. Johns Hopkins physicians also found that post-transplant cyclophosphamide enabled safe administration of new, half-matched ("haplo") bone marrow transplants—which now makes the procedure accessible to virtually everyone, Levis says.

Advances in genetic testing have also been key to improving outcomes. Among blood cancer patients, "every patient has a different mutation," explains Levis. The practice at Johns Hopkins now is to tailor therapy (both pre-transplant chemotherapy and post-transplant remission maintenance therapy) to the individual mutation. "Each treatment is targeted to the individual," says Levis.

Taken together, all of these advances now make it possible for Johns Hopkins oncologists to offer bone marrow transplants to increasingly older patients. "Twenty years ago, we rarely offered transplants to patients over 60," says Levis. "Now that's commonplace. In fact, we recently admitted a 75-year-old to the program. When I entered the field in the early 1990s, we would have sent him to hospice and he would have had four months to live. Now he's on track for a transplant with high odds of a good outcome." ■

By mid-summer, Billig is back at home in Lancaster with Heidi, feeling stronger every day and preparing to teach his fall classes at Franklin & Marshall.

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EPHRAIM FUCHS

As a result of their efforts, nearly all patients in need of a stem cell transplant can find a donor from within the family or from registries of healthy volunteers (see p.23).

ROLLER COASTER RIDE

Two indicators for successful engraftment are white blood count (WBC) and absolute neutrophil count (ANC). Throughout the weeks following Michael's transplant, these numbers fluctuated wildly, putting him, Heidi, his daughters, his two older sisters and others on an emotional roller coaster.

On St. Patrick's Day, he wrote about his positive WBC and ANC numbers, concluding that "failure to engraft can now be dispelled." But a month later, he wrote: "It seems that I will NOT be discharged this week as expected. Next week is possible, but no guarantees. This procedure is so frustrating. As soon as one begins to extrapolate one's progress linearly, one gets smacked down with some other unanticipated bodily weirdness. This time, I have BK virus, which is a common infection typically in immunosuppressed people (like me)."

The setback represented just another bump in a long road for Heidi, who described herself as "a crier who needs to keep that somewhat under control." At times, both Heidi and Michael kept quiet for fear that what they were thinking and feeling might be too much of a burden for the other. Despite Heidi's medical training, she found certain nursing aspects—especially dressing and cleaning the catheter—to be challenging.

Then there was the emotional toll. "The focus is on the patient, so the caregiver can feel left out and unappreciated at times," she told me. "Time management skills are essential, and there are demands on your sleep, your social life and pretty much everything you could possibly think of. Sometimes I've had to nag Michael to drink and eat and walk more. Then there are the friends and family members who want regular updates."

On May 7, some nine weeks after he had received his daughter's stem cells, Michael was discharged from Johns Hopkins with a congratulatory certificate of completion. The following day, he had his catheter removed, buoyed by the fact that Monica's cells seemed well on their way to working inside him.

Michael and Heidi, anxious to return to normality, gave up their Hackerman-Patz apartment and returned to Lancaster, content to make the 90-minute drive to Baltimore several times each week for Michael's required follow-up visits.

But the roller coaster ride continued into the summer. On the plus side, Michael's BK virus had disappeared, he'd lost 25 pounds of water weight and he was exercising again. He had felt strong enough to participate in graduation ceremonies at Franklin & Marshall and make two brief trips to the couple's new house in Maine.

And then, a seemingly crushing setback: In mid-May, Michael's lab work indicted that only 8 percent of his T cells—a subtype of white blood cells—were Monica's. "Heidi and I were completely freaked out," reported Michael. "Dr. Fuchs told me that T cell numbers rarely reverse themselves and that, most unfortunately, the transplant may have been a failure."

But the following week, Michael's phone rang at 9 p.m. on Friday evening. It was Fuchs on the line to say that a follow-up test had showed a remarkable turnaround: 28 percent of Michael's T cells were now inexplicably Monica's. "I had never seen this situation before," Fuchs told me later. "Would I call it a miracle? Let's just say that I'm happy that it's happened, and it certainly opens up the possibility that we are back on track for a cure."

By June 28, more than 90 percent of Michael's T cells were Monica's.

So, Michael has cleared yet another hurdle and feels better week by week, though his struggle for a cure goes on. There were visits to Johns Hopkins in mid-July and late August, but Michael's plan was to spend the bulk of his summer in Maine, teach in the fall and complete his latest book on the Amish. He says he's eternally grateful to Heidi, Monica, and all the doctors, nurses and support staff at Johns Hopkins who helped him through this second, more difficult struggle.

For me and the people closest to Michael, his resolve was even more inspiring the second time around.

"There is a certain profundity in having one's child give life back to a parent, while another child is having your first grandchild," philosophized Michael. He will continue to monitor his counts and count his blessings, each and every day. ■