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A HEALING HELL

Bone-marrow transplantation may be the worst treatment in all of modern medicine – and the best.

BY JEROME GROOPMAN

Courtney Stevens was a high-school sophomore in Monroe, North Carolina, when she found out she had a disease that would probably kill her. The first signs were subtle—she had lost her usual edge and endurance in varsity tennis and track—but six months later the cause of her fatigue was identified. She had leukemia, a cancer of the bone marrow’s white blood cells, which causes the cells to proliferate wildly and fill the bone-marrow cavity. The result is to stop marrow from performing its normal function, a vital one: the manufacture of every component of our blood and our immune system.

“The doctors in Charlotte said that my only chance to live was a bone-marrow transplant,” Courtney told me not long ago, speaking in something between a lilt and a drawl. Destroying the leukemia would require radiation and chemotherapy at levels that would also destroy all of her remaining normal marrow cells. Essentially, Courtney had to be treated to the point of death. She would then be rescued with bone marrow taken from a healthy donor.

Courtney imagined that a graft meant taking a piece of bone with its gelatinous marrow and surgically implanting it in her body. Actually, a bone-marrow preparation is infused into a vein; once it’s in the bloodstream, the cells will home in on the marrow space. And what’s infused often isn’t bone marrow as such but a painstakingly separated component of bone marrow—its stem cells. Under a microscope, stem cells look undistinguished—they’re small and round with robin’s-egg-blue cytoplasm and a squat nucleus—but they can perform acts of biological resurrection. Unlike other cell types in the body, which die off after dividing a few dozen times, a single stem cell has the ability to reproduce itself indefinitely. Its progeny can also abjure immortality and turn into ordinary blood cells—red cells, white cells, and platelets. As a result, a relatively small population of stem cells can completely reconstitute a host’s blood and immune system. Indeed, in some laboratory experiments a single stem cell has spawned the half-trillion blood cells of an entire mouse.

A successful graft requires stem cells from a donor who is genetically compatible with the recipient. Unfortunately, nobody in Courtney’s family proved to be a good match, which significantly reduced the likelihood of a successful treatment. “My parents and I prayed on it real hard,” Courtney, a devout Baptist, went on to tell me. “And then we did a lot of research.” Both her mother and her father are health-insurance agents, and they concluded that her best chance would be at the Fred Hutchinson Cancer Research Center, in Seattle. There Courtney was cared for by the clinical director, Fred Appelbaum, who set about finding a donor from the National Marrow Donor Program. Some three million people now participate in the program, which means they have been genetically typed and have agreed to donate marrow if they are called

upon. It's no small commitment: you must typically undergo general anesthesia as the marrow-rich bones of your pelvis are repeatedly punctured by a large-bore trocar.

In late December, Courtney was "conditioned" to receive stem cells from an anonymous donor: her diseased marrow was destroyed by radiation applied to her whole body and by high doses of chemotherapy. Left without any immune defenses after this treatment, she was placed in what she calls a "bubble"—a special laminar airflow isolation room. "It was a complete nightmare," she recalled. "For days, I'd be on all fours and just retch and retch." Her skin was badly burned by the total-body radiation, and the drugs made her delirious. "I looked like a lobster, and thought I had bugs crawling on me. I'd hit myself and scream." The hardest part for her, though, was being removed from human contact. Visitors are strictly limited, and those who enter must wear special masks, gloves, and tight-fitting gowns. "I was in that sterile bubble, and forgot what skin against skin felt like. That was lost. I just wanted to hold on to my mom or dad, like a two-year-old, and I couldn't."

Other problems lay ahead. Though the anonymous donor's graft swiftly "took," the white blood cells spawned by the graft started to attack Courtney's own tissues. It was less that she was rejecting her graft than that the graft was rejecting her—an often fatal condition called graft-versus-host disease. Most of the damage occurs in the bowel, the liver, and the skin. "I had terrible diarrhea, a blistering rash all over my body, and jaundice," Courtney recounted. "I was the color of an egg yolk." Dr. Appelbaum gave her immunosuppressive medications, but he didn't want to restrain her newly spawned immune system completely, for the marauding immune cells were also likely to target any leukemic cells that might have survived.

Twenty-eight days after receiving the donor marrow, Courtney Stevens was discharged from the hospital. When she entered the hospital, she had been "in great shape" from her varsity athletics; now she couldn't mount a short flight of stairs. But she believed that she was going to survive. "I was the youngest of the twenty on my floor at the Fred Hutchinson Center," she told me, and then she paused. "I can tell you name after name that passed away. Only three made it."

In the almost three decades since a "war on cancer" was proclaimed, most of the advances in the field have been disappointingly incremental. Only recently has there been a sense that strides, and not just steps, are being made. For all the talk of "breakthroughs," however, the clinical realities continue to mock our dreams and adhere to a grim equation: the stronger the cancer, the more punishing the treatment.

Bone-marrow transplantation remains the most powerful weapon in the growing arsenal against cancer. In the past couple of decades, I have guided a great many patients through the procedure and seen results that appeared nearly miraculous. Nevertheless, I cannot regard it without a measure of horror. It is a treatment of last resort. Even when all goes well, it represents an experience beyond our ordinary imaginings—the ordeal of chemotherapy taken to a near-lethal extreme. I first performed the procedure in 1978, as a hematology-oncology fellow at the University of California at Los Angeles, where I spent four months a year on the transplant ward. U.C.L.A.'s marrow-transplantation program was then the second-largest in the nation, after the Hutchinson Center, and our success rates were enviable. But I quickly realized that it was the most devastating treatment that the human body could be subjected to. My memory is still haunted by my first patient, who was a cheerful young Japanese-American woman with

leukemia. After she underwent total-body radiation, I never saw her smile again. Her graft was slow in taking, and we were unable to sustain a healthy level of blood platelets, with the result that her blood wasn't able to clot properly. She hemorrhaged into her lungs, we couldn't stop the bleeding, and her protracted agony—a clinically induced one—ended in death.

These days, the bulk of my clinical practice involves patients with cancer and aids, and I suppose I am as battle-hardened as most people in those fields. Even so, the emotional demands of attending to marrow transplantation are simply of a different order. My third transplant patient this year was a close friend of mine; and it occurred to me that if she died from the procedure I might not have the emotional reserves to do another.

On an icy January morning of this year, Tamar Lowenstein, as I'll call her, flew, with her husband, from their home in Washington, D.C., to Boston, in order to meet with David Avigan, the director of bone-marrow transplantation at my hospital. Tamar was a thirty-nine-year-old corporate lawyer and the mother of three young children, and I'd known her for more than two decades. I sat beside her during the consultation both as a friend and as a physician who would help manage her treatment. For over a year, she'd been living with widely metastatic breast cancer, and had been evaluated at several first-rank medical centers. At each, she was told that in the normal course of things her condition was incurable. A statuesque woman with a no-nonsense manner, Tamar looked alert but drawn. She had been receiving chemotherapy every two or three weeks since the summer for the cancer, which had spread to her liver and her ribs, vertebrae, and skull. She was here because she knew that, given standard measures, she would very likely be dead within two years, and perhaps much sooner. If she submitted herself to the ordeal of bone-marrow transplantation there was a chance that she could be cured.

The technology of marrow transplantation was conceived mainly in a dog kennel in Cooperstown, New York, during the nineteen-fifties. A young Harvard-trained physician, E. Donnall Thomas, had retreated to a hospital there to work on a research problem that had eluded a generation of blood specialists. Although red blood cells could be successfully transfused from a compatible donor to a needy recipient, marrow cells could not: the body would identify them as foreign invaders and destroy them. Solving this problem wasn't merely an academic pursuit. In the wake of Hiroshima, the effects of intense radiation were a topic of urgent national interest, and it turned out that a primary reason the atomic bomb was so deadly was that its radiation destroyed the bone-marrow cells of its victims. As a result, the victims succumbed to hemorrhage from a lack of platelets or to infections from a lack of white cells. If new marrow could be supplied—and new blood cells produced—victims of radiation might be saved.

It was a more immediate wartime exigency—the need for doctors—that had led the government to subsidize medical education during the forties, and thus enabled Don Thomas, a poor kid from Texas, to attend Harvard Medical School. Then came a residency at the affiliated Brigham Hospital, where he watched helplessly as patient after patient, mostly children and young adults, succumbed to leukemia. In those days, there were only a few primitive chemotherapeutic agents, such as nitrogen mustard, which was derived from the mustard gas used in trench warfare. It quickly became apparent that although such drugs killed leukemic cells, they also killed normal marrow cells. Thomas believed that providing new, healthy bone marrow would prove essential to curing leukemia.

Thomas, who in 1990 received the Nobel Prize for his work, is a quiet man with deep-set eyes and a close-cropped white beard; he is now approaching his seventy-ninth birthday. When I spoke to him recently, he compared his move from Harvard to Cooperstown to the move his pioneer grandparents had made when they migrated in a covered wagon from the East to rural Texas: he says that he, too, was “looking for the freedom to set your own agenda.”

He wasn't the only scientist working on marrow transplantation in those days, but he may have been the most persistent. After testing various transplant techniques with dogs, he attempted transplants in human patients who had late-stage leukemia. Then, in 1959, when he'd put in four years of research at Cooperstown, he and his colleagues decided to stop human marrow transplantation except between identical twins. “Things were pretty grim,” Thomas concedes. Every one of his patients who had undergone transplantation for leukemia died during the procedure or shortly thereafter. Indeed, a review of the first two hundred attempts, in centers around the world, to transplant human marrow among nonidentical siblings found no successes. Only the fortunate few patients who had identical twins—and so could receive marrow that was perfectly genetically compatible—survived the procedure.

Eight years later, in 1967, Thomas, who was by then in Seattle, at the Fred Hutchinson Cancer Center and the University of Washington, decided to resume his attempts at transplants. During the preceding years, he had made important advances with his Cooperstown dogs. He had identified genetic markers on white blood cells—markers of “histocompatibility”—that permitted close matching of donor and recipient, and had observed consistently successful grafts among littermates in his kennel. Facing down a barrage of criticism from prominent scientists, he set about assembling a medical team that would be dedicated to the demanding care of patients undergoing transplantation. “I still believed there might be a cure for leukemia,” Thomas says. He was soon proved right.

It takes some two years for a new marrow graft to mature into a fully competent immune system. Eighteen months after leaving the hospital, Courtney Stevens fell ill with chicken pox. “I was really sick,” she recalls. “Just covered with it. My fevers were sky-high.” As a rule, people who had chicken pox as children still have the virus in their bodies; their immune systems have learned to keep it dormant. Once Courtney's original immune system was wiped out, she was vulnerable to a recurrence. It took high doses of antiviral drugs to subdue the infection.

If Courtney's bone-marrow transplant illustrates how many things can go wrong during the course of treatment, it illustrates, too, how successful medicine has become at coping with complications. Yet, even for those luckier than she was, transplantation is a long process, and patients generally spend a month or more in the hospital and then a hundred days closely monitored as outpatients. Courtney was determined to stay abreast of her studies during this time, and so was tutored in Seattle. After she returned home to North Carolina, she made the honor roll every semester.

Just a year after Courtney's transplant, she and her donor exchanged letters. (The National Marrow Donor Program stipulates that the identities of the donor and the recipient be kept from

each other for at least a year following the transplant.) Courtney learned that the donor was a registered pharmacist at a Seattle pediatric hospital.

At Courtney's graduation from Monroe High School, the graduates, in red academic gowns and mortarboards, sat with their families on a hot Carolina afternoon. When Courtney ascended the stage, the principal announced her name, and then stepped aside. Taking his place in front of Courtney was a petite woman in her thirties with chestnut hair and brown eyes. Courtney knew immediately who she was. So did the other graduates, and they tossed their mortarboards in the air as Courtney embraced her donor. Courtney, her classmates were well aware, had gone through a kind of hell; and now she was back.

Bone-marrow transplants that use the host's own marrow are categorized as "autologous." As a rule, autologous grafts aren't optimal for conditions such as leukemia—the conditions for which the transplant procedure was originally devised—because such a graft could simply reintroduce the disease. Some fifteen years ago, however, researchers started to explore the use of autologous grafts in the treatment of other kinds of cancers. Standard chemotherapy, they realized, was limited largely because of its destructive effects on the marrow. Marrow cells, like cancer cells, divide rapidly, and chemotherapy drugs generally target dividing cells. But if you had the ability to replenish the marrow, through autologous grafts, you could administer the drugs at levels that would otherwise prove lethal. Suddenly, the prospects for treating cancer changed dramatically: formerly incurable cancer—stubborn metastatic tumors that had resisted normal, survivable doses of chemotherapy or radiation—might succumb to extraordinary doses. Right now, that was Tamar Lowenstein's best chance for survival.

David Avigan, a wiry man with boyish black curls and a gentle mien, chose his words with practiced precision as he presented the hypothesis that reaching extreme levels of toxicity might overcome the cancer's known resistance to standard regimens, and reviewed with Tamar the available data. "Let's take the most conservative approach in assessing this outcome rather than presenting the best statistics," he told her. "Preliminary evidence indicates that some twenty per cent of women have a five-year disease-free survival. Are they truly cured, meaning the cancer will never come back? No one can say. Are there complications of the high doses of chemotherapy that can result in fatal diseases later in life? Yes." So there was a better than even chance that despite a prolonged and harrowing treatment she would die of cancer anyway. On the other hand, she knew that a standard regimen would retard the cancer's progression somewhat and that, in its final stages, a morphine drip would enable as easeful and pain-free a decline as was possible. Those were the alternatives.

Tamar listened intently, and occasionally jotted notes in her diary. Her husband, Daniel, stood up and paced, explaining that he was too tense to sit.

I had recused myself from the discussion. Tamar and Daniel both knew that I favored going ahead with the transplant, but I was afraid our friendship would impair my ability to present objectively what she faced. The complications of the treatment could not be easily controlled; its course could not be easily predicted; and there would be no turning back. Now Tamar, having listened carefully to Dr. Avigan, decided to go ahead with it.

Fortunately, we were able to spare her the usual procedure of boring into her pelvic bones to collect stem cells. Through the use of a new technique—"peripheral blood-stem-cell transplantation"—the cells were obtained from her circulating blood, having been coaxed out of the marrow by a special regimen of drugs. Forty litres of her circulating blood were then filtered through a machine that skimmed off stem cells. At the end, we had more than twenty million of them—more than enough. The stem cells would be stored in liquid nitrogen until we needed them.

Tamar kissed her children goodbye, explaining that she would be gone for a long while and then hoped to come back better. She arrived at the hospital believing that she had prepared herself for the procedure. She would soon learn what I had learned: that it is not a procedure for which anyone can be prepared.

We administered four days of chemotherapy at levels ten times as high as could be given in standard settings; only when the poison had cleared from her blood were her stem cells thawed and infused. I visited Tamar each morning and evening, and watched as she was brought as close to death as was clinically sustainable.

"It's getting worse every hour," she said miserably, several days after the last dose; the maximum impact of chemotherapy comes about a week after its administration. Her lips were so blistered that even speaking was painful. Her eyes were sunken, and her body trembled. She turned to the side of the bed, searching for what's politely called the emesis basin. I found it on her night table, and held it under her quivering chin. A fetid mix of bile and bloody tissue gushed forth. I reached over to help wipe her face. "Be careful," she said, in a small voice. Even the lightest touch was like a searing iron on her burned lips.

I swabbed the vomit first from her chin and from the area around her lips, avoiding the oozing blisters. I then applied a thin layer of Vaseline over her mouth; even through the latex of my gloves I could feel the heat.

Tamar had a raging fever, reaching 104° F. at times during the day. The extraordinary amounts of chemotherapy had produced a chemical burn throughout her gastrointestinal tract, from mouth to rectum. Then, taking advantage of her lack of immunity, a fungus began to grow in her macerated gut.

Carol, a nurse specialist on the transplant team, came into the room and told Tamar it was time for her Amphotericin infusion. Amphotericin is a potent antifungal, but it has toxic effects, too. Each infusion caused Tamar to shake with painful rigors and further raised her temperature.

Tamar closed her eyes as a sedative that the nurse had given her prior to the Amphotericin began to take effect. I gripped Tamar's hand and watched the Amphotericin run slowly into her vein.

In less than a minute, Tamar began to shake violently, her teeth audibly gnashing. I gripped her hand harder, but she had no strength for returning the gesture. The nurse gave her more of the sedative, and then began to bathe her skin with alcohol. This was an effort to stem the rising temperature, but it worsened the rigors, and Tamar began to moan.

“I wish I hadn’t done it,” she breathed. “It was a mistake.”

“You’ll get through this, Tamar,” I told her. “This will pass.”

“How long?”

I said I didn’t know exactly. Soon, I hoped.

Tamar went without eating for five weeks, because her mouth and stomach were so severely burned that she regurgitated even clear consommé and jello. Her weight dropped by forty-six pounds, and her form became skeletal. We had to feed her by infusing a rich mixture of proteins, sugars, and vitamins into a vein. Over the next two months, she began a slow, steady recovery.

Tamar kept a photograph of Daniel and her children on the table next to her bed. It was this picture that she turned to when she feared that the hell she entered had no end. “I told myself,” she said later, “that I must return to the kids.”

The process of returning to the world—a world of ordinary cares and burdens—can represent another kind of complication, particularly because bone-marrow transplantation is not only an extreme procedure but an extremely expensive one. Courtney Stevens, for example, has just completed four years of study at Liberty University, in Lynchburg, Virginia, but she could do so only because she received a scholarship: her family spent all their savings to pay for her transplant. Her parents sold both of their cars, and Courtney’s special college fund “went kaput,” in her words. Friends and neighbors had held community fund-raisers for her. The bone-marrow transplantation cost more than three hundred thousand dollars, and the family’s health-insurance policy would pay only seventy per cent of it.

Having paid steep insurance premiums ever since the transplant, Courtney has now passed the five-year mark with no sign of leukemia, and so is eligible for more standard rates. That’s fortunate, because she will soon need cataract surgery. “I have eyes like a seventy-five-year-old,” Courtney, who is twenty-three, says, and she laughs, apparently glad that she’s still around to have such problems. Cataracts are among the delayed complications of the procedure. Another of them is about a three-per-cent risk that she will develop a second malignancy, from the chemotherapy itself. But Courtney views such concerns with equanimity. “I’m not supposed to be here. And I thank God each day I am.”

For the poor, the financial exigencies are, of course, even more acute. Medicaid is a state-based program, and its level of support varies widely from region to region. Several years ago, the State of Oregon declared that it would no longer pay for marrow transplantation, and patients with leukemia crossed the border into Washington, racing to establish residency and qualify for Medicaid there before their disease killed them. Recently, Oregon relented somewhat, and created a priority list of therapies that would be available on a year-to-year basis, depending on the size of the state coffers. Within the category of marrow transplantation, some diseases have been ranked above others; if your particular type of leukemia failed to make the cut, you may be out of luck.

And when transplantation is applied in entirely novel ways to treat currently incurable maladies, even private insurance companies can simply refuse to pay. For example, the Hutchinson Center is exploring the use of marrow transplantation for scleroderma. An unusual and devastating disorder of the immune system, scleroderma is marked by relentless scarring and contraction of the skin, lungs, esophagus, and other organs, until the patient suffocates or starves to death. Because scleroderma is caused by a diseased immune system, the Seattle team reasoned that it might be beneficial to graft healthy donor stem cells that would spawn a new immune system. There is, as yet, no proof that this approach will succeed, but the alternative is grim: fifty per cent of advanced scleroderma patients die within three years of diagnosis. Even so, every one of a total of fourteen scleroderma patients eligible for the experimental treatment at the Hutchinson Center was denied support; three died while waiting for their appeals to be considered by their insurers.

“It’s unclear if bone-marrow transplantation could be developed today in the United States, in the face of managed care,” Fred Appelbaum told me soberly. What frustrates researchers and clinicians like Appelbaum is that no insurer seems willing to make the up-front investment in clinical research, although all insurers readily reap the financial benefits after it succeeds.

Today, nearly four out of five transplant patients who have leukemia and a genetically compatible family donor survive; more than half of those with a matched but unrelated donor, like Courtney, survive, too. And the prospects for patients with otherwise incurable cancers—patients such as Tamar—are improving all the time. In June of this year, a new clinical research building at the Fred Hutchinson Cancer Research Center was dedicated to E. Donnall Thomas. At the ceremony, sitting among the numerous assembled scientists, clinicians, philanthropists, and politicians, were a hundred patients and their families. At one point in the ceremony, they stood up en masse. On behalf of those who survived, and those who did not, they offered silent thanks to Dr. Thomas for persevering.

The astonishing successes of bone-marrow transplantation are, without question, among the most gratifying aspects of contemporary oncology. And yet for all the effort and resources we have devoted to mastering the technique, we can only hope that in another decade or so it will have become obsolete, because something more effective and less punishing has taken its place. In the meantime, we do what we can with what we have.

This September, Tamar Lowenstein returned to my hospital as an outpatient for X-rays and blood tests. The masses of cancer that once appeared as black nebulae on her bone scan had vanished. Her liver was normal, no longer distorted by metastatic deposits. And her strength and weight are gradually returning. As the physical devastation of the transplant begins to wane, so, oddly, do her memories of an ordeal that was in equal measures harrowing and miraculous. Still, it’s too early to say that she is truly cured—that her breast cancer will not eventually reëmerge, or that the treatment itself won’t someday produce cancer. “I can’t focus on either right now,” Tamar told me when we last spoke. She maintains that it’s enough to rebuild her life, day by day. “What I know is that I wanted the best shot, the only shot, at a cure,” she says. “And I’ve had it.”

(This is the first of two reports from the cancer wars.)