

## *Prologue: Patient One*

Henri Termeer sat behind the wheel of his car outside Boston's renowned Brigham and Women's Hospital, waiting to pick up a batch of placentas discarded from the delivery room. At Genzyme, the two-year-old start-up he had recently joined as President, they called his little Toyota hatchback the "placentamobile."

Genzyme was working furiously on a treatment for Gaucher disease, a debilitating, often deadly, disorder involving the buildup of fatty substances in the spleen or elsewhere in the body.

Gaucher was an "orphan" disease, a rare condition that was genetic in origin and affected a small number of people who had, medically speaking, no place to call home. A majority of the orphan disease patients were children. There were no therapies available for their disorders. There were also no patient support groups or social connectivity.

But worst of all, these forgotten souls and their families were desperate because few knew much about their condition and there was insufficient incentive to cure it. The affected patient populations were too small and R&D too costly and uncertain. There was little or no hope for a cure.

Genzyme was laboriously extracting the tiny amount of enzyme found in the placentas that could break down those fatty substances, but the number of placentas needed to produce enough enzyme was beyond daunting—around 22,000 human placentas per patient per year.

On the drive back to Genzyme's headquarters, Termeer thought of the patient who was being kept alive by his precious cargo. Four-year-old Brian Berman was responding well to treatment with a reconfigured enzyme the company would later call Ceredase. Administered through painfully long intravenous infusions, it was being tested in Berman's experimental trial at the National Institutes of Health (NIH) hospital outside Washington. Biochemist Roscoe Brady, MD, was his attending physician. To keep up production of the experimental drug, the placentamobile had to stay on the road.

Henri Termeer got out of his car and carefully removed the leakproof cooler. Genzyme had leased the 15th floor of an old building in the heart of

Boston's red-light district, known as the "Combat Zone." The sight of the 37-year-old Dutchman carrying a cooler packed with medical waste did not deter the local entrepreneurs—he was propositioned three times between his car and the office.

Discovering that the building's elevator was once again broken, Henri lugged the heavy cooler up the 15 flights of stairs to the lab, where the placentas were centrifuged. As the mighty machines rumbled, forcing the liquid from the tissue that contained the enzyme, work in the entire building would stop. The floors were vibrating too much.

Meanwhile, at NIH, a different form of disruption was taking place. Brian Berman was, for the first time in his life, playing like any other "normal" little boy. A few weeks earlier, Brian had been diagnosed with Gaucher disease, a diagnosis that carried a sentence of organ failure, loss of ambulation, and likely early death. Doctors had wanted to remove his spleen. Engorged by lipids, it had enlarged so dramatically that his belly had swelled to the size of a basketball. "It was pushing all his other organs out of the way," Termeer would later recall.

Brian's mother, known professionally as Dr. Robin A. Ely, was a family physician who had given up her practice after Brian was first diagnosed with Gaucher. Small, brown-haired, and a bundle of barely suppressed energy, she discovered that the most promising work anywhere on Gaucher was taking place just down the road from her home in Potomac, Maryland.

But first, Dr. Ely and her family were told there was no hope for Brian. "We were told he has a disease called Gaucher disease," Robin recalled. "There's no treatment and you'll have to bury your child very soon. It was awful."

Dr. Ely remembers a period of "grieving and freaking out." But then, her mother called to say she had spoken with the head of the Weizmann Institute of Science, an internationally famous research university in Israel.

"She called him and said, 'My grandchild was just diagnosed with Gaucher disease, can you help me?'" Robin remembers. "The guy said to her, 'You know what, you're very fortunate because the world's expert on Gaucher is ten minutes from where you live, and that man is Dr. Roscoe Brady.'"

"I called up his office and spoke to Dr. Brady on the phone, and I told him that I had a three-year-old son who was just diagnosed and given a

death prognosis. I said, ‘Do you have anything?’ He said to me, ‘If you knew what I had, you’d come running at my door.’

“That’s what he said to me. I said, ‘Well, then, here I am running at your door.’ I went for a meeting with him that week.

“I said, here’s what I want to do. I want to give up my practice and I want to work for you for nothing. Don’t pay me a dime.”

Looking back, Robin says she was acting like what is now called a “warrior mother.” There was nothing she would not try. No task she would shrink from doing.

“They said, ‘Okay, fine. If you think you can handle it, fine.’ I went to work for them, and meanwhile Brian was getting sicker and sicker by the day. He was just about to go into heart failure, and we were going to have to do an emergency splenectomy.”

She lobbied hard for her son to be included in the experimental enzyme-replacement protocol Brady was planning, pleading, “Give my child one last chance before we do this operation and remove his spleen.”

It was December 15, 1983. Roscoe Brady had told Robin, “We have this modified enzyme, and your son will be the first to try it.” Brian Berman was in a hospital bed and his “warrior mother” was by his side.

“We had a crash cart in the room. They didn’t know whether he was going to go anaphylactic. They didn’t have any idea what he was going to do.”

Robin recalled unforgettably, “They injected him with the enzyme—and everything went fine. We left, and that week he started perking up. It was quite amazing.”

The next week, Robin went in for a follow-up appointment and was told the doctors planned on giving Brian another injection in a month. A month? That seemed to Robin like an awfully long time.

“I don’t know where I got the chutzpah,” Robin recalls now, “but I said, ‘you know what, I have a very strong feeling that unless you give him one injection per week you’re not going to see what you’re looking for. You must give it to him once a week.’

“They are looking at me like, ‘who are you?’ But I said, ‘I am telling you, I am telling you this with all my heart. I am trying to tell you something.’”

Much to Dr. Ely’s amazement, “they listened to me.”

“In seven weeks his hemoglobin shot up, and his belly—it was like a balloon that somebody let the air out of. It just went ... like that. Everybody was like, ‘what?’ It was amazing.”

But after seven weeks, for the first but not last time, Genzyme ran out of enzyme. A massive amount of placentas was needed to keep the supply on line, more than even the most well-traveled placentamobile could provide.

“They ran out,” Dr. Ely says, “and they said ‘we are going to try and make as much more as we can, as fast as we can.’ But it was another seven weeks, and in those seven weeks he went all the way back down. It was horrible for us. It was a nightmare.”

Termeer recognized the little boy’s response, “When we ran out of enzyme, he would get worse pretty quick. He had a remarkably fast reaction to the enzyme.”

His mother saw it too, “When they got more, they injected him. He went right back up again. Just like he had before over those first seven weeks.”

To Henri Termeer, Brian Berman was “his own control.” He was also all the proof he needed. In search of a cure, Termeer thought to himself, “Wow, we’re there.”

Brian became Patient One. He was the first to benefit from a bold, innovative new treatment for Gaucher disease. But Berman was also the first beneficiary in what would, over the next three decades, become a new paradigm that has revolutionized the biotechnology and pharmaceutical industries, and indeed the world of medicine—a paradigm built around and for the treatment of the world’s rare disease patients.

Genzyme and its leader, Henri Termeer, would lead this transformation. “Our company became very purpose-driven. Other companies may be very strategy-driven... . We had a purpose,” said Termeer. “The purpose was the patient. Patients were what we talked about. Patients were the pictures that we showed to each other. Patients were how we reported success of what we were doing. This connection, this thinking about the patient as being the central focus... . It is remarkable how easy that translates, how cross-cultural that becomes.”

“In the rare disease world it is almost possible to know the name of every patient you are treating,” Genzyme’s chief medical officer Richard Moscicki, MD, once told *BioCentury* magazine.

“It becomes very personal. Patients would visit Genzyme. People had pictures of patients on their desks and in the hallways, so you knew that what you were doing was directly impacting patients you had met. That created a very different sense of mission.”

Today, there are roughly 7,000 rare diseases afflicting an estimated 30 million people in the United States—or one in ten Americans. A rare disease is defined as a serious, chronic condition, often life-threatening, that affects fewer than 200,000 people. A few of the more common are well known, such as cystic fibrosis and muscular dystrophy, but the names of most are known only to those who are afflicted by them.

Add the number of patient family members, caregivers, and significant others to this population and the rare disease community expands to at least 100 million people in the United States—and well more than 500 million worldwide. The depth of feeling and urgency surrounding rare disease is anything but rare.

Today, families living with rare disease become fierce patient advocates, boosters for scientific research, activists for increased funding, and allies for other families living through similar experiences. They quit their jobs and start foundations to help fund research. They move wherever necessary to participate in clinical trials. They share their story with friends, family members, and people they work and worship with. Dealing with a rare disease becomes an all-consuming, passionate pursuit that surpasses all others.

None of this would be happening if patient families felt there was no hope. And if hope in the rare disease community has a father, it is Henri Termeer.

Henri Termeer was among the first and most successful entrepreneurs of biotechnology. He was a member of a group of gifted leaders who led fledgling, disparate businesses built on recombinant DNA technology. He pioneered the development of therapies for ultrarare diseases that not only harnessed the newest genetic technologies but were fundamentally patient-centered. Termeer was the first of biotech's leaders to be patient-centric, long before the term was "cool." He helped forge biotech's public policy agenda and inspired a generation of like-minded entrepreneurs.

Termeer was not just present at the creation of the orphan drug revolution—he was in many ways its catalyst and instigator. He took the first steps on a journey that would lead to the approval of dozens of orphan drugs and the growth of a multibillion-dollar industry and would take Genzyme from a company with 17 full-time U.S. employees to a powerhouse with more than 14,000 employees in 50 offices and labs around the world.

At the beginning of this adventure, Henri Termeer might well have felt it was just him and Brian Berman taking an enormous chance. There is always a risk in going first in a clinical trial. There is no conventional wisdom, no standard operating procedure, and no history of trial and error. But for Brian Berman and his family, it was the ultimate leap of faith.

“I can tell you that of all the things that I remember from the 30 years that I was there,” Henri Termeer told an audience of business students, “those are the moments that I remember the most, and those motivated me forever the most—that moment of saying, ‘Wow. It works.’”

“I had so many detractors in those days, people who said you are out of your mind,” he said. “But I had seen this boy.”

Henri Termeer’s and Genzyme’s success would later be measured by the growth of Genzyme into a multibillion-dollar, Fortune 500 company and the development of a roster of innovative, life-saving treatments.

But to families of rare disease patients like Brian Berman, it all added up to one word—hope.

And, exclaiming in front of a gathering that had assembled to honor Henri Termeer, the grief-stricken father of a rare diseased daughter remembered his words the day he had learned of a therapy being developed by a Boston biotech company, “Hope was spelled Genzyme.”