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## For His Sick Kids, a Father Struggled to Develop a Cure

*Mr. Crowley Built a Biotech Firm, Ran Drug Program, but Still Faced Hurdles*

By GEETA ANAND | Staff Reporter of THE WALL STREET JOURNAL

PRINCETON, N.J. -- John Crowley had bad news for his 5-year-old daughter.

Ever since Megan could remember, her father was promising to bring her a "special medicine" to make her better. Megan suffers from a rare genetic disease that makes her so weak she can't walk, talk clearly or breathe on her own -- and it threatens to take her life.

Mr. Crowley had created and built an entire company devoted to finding a cure for the disease. In October 2002, he sat beside the dark-eyed, porcelain-skinned girl strapped into a wheelchair, the hum of her ventilator audible in the bright playroom. He had told her days earlier that the medicine was ready, and now he had to let her down. "Honey, I'm sorry, we're not going to be able to go to Florida to get your special medicine right now," he said softly.

Megan -- and her younger brother Patrick -- both have Pompe disease, a fatal illness that affects fewer than 10,000 people world-wide.



**John Crowley**

Seeking a treatment, Mr. Crowley, now 36 years old, quit his job as a financial consultant, met with legions of scientists and teamed up with one. He borrowed \$100,000 on his home and 401(k) plan to start a biotech company, then raised \$27 million in venture capital when the company developed an enzyme that showed early promise. When he thought he needed the muscle of a big company to get a drug into production and testing, he sold his company to Genzyme Corp., of Cambridge, Mass., for \$137.5 million -- one of the richest deals ever for a biotech drug untested in humans.

Yet even though Mr. Crowley had moved mountains on the scientific and business fronts to get the treatment into testing, he couldn't seem to speed the drug to his own rapidly weakening children. When he sold his company, he gave up control of the medicine they needed. The shortage of the drug, conflict-of-interest questions and Genzyme's own internal protocols rose up in his path. His personal goal -- getting the drug to his kids -- at times conflicted with the company's view of how to get the drug to market as soon as possible.

"It ripped me apart," he says. "Many times, I'd be talking aloud about programs and budgets, and at the back of my mind be thinking, 'Oh my God, this is not good for Megan and Patrick.' "

Genzyme, a public company with annual revenue of \$1.3 billion, had already made money developing drugs for obscure diseases. The 1983 Orphan Drug Act gives companies incentives to develop drugs for rare diseases. Genzyme has used the incentives to sell about \$619 million a year of an enzyme-replacement therapy for Gaucher Disease, another rare genetic disorder.

Henri Termeer, Genzyme's chief executive officer, says he thought a father's sense of urgency would be a powerful catalyst for the company's \$50 million-a-year program to find a treatment for Pompe disease. "I wanted him to come in here, make a lot of noise, shake every corner of the company and get things moving," Mr. Termeer says.

Under the 2001 deal, Mr. Crowley made \$6 million (most of the acquisition price went to venture capitalists) and took over Genzyme's Pompe-research program.



Najah Feanny Hicks

The Crowley family, from left to right: Aileen, Patrick, John Jr., John Sr. and Megan

But there was never a promise that Mr. Crowley's children would get treated first. To persuade Mr. Crowley's own venture-capital investors to go along with the Genzyme deal, says Marshall Smith, the investment banker at Morgan Stanley who worked on the sale, "it was important for him to demonstrate to shareholders and his board that he was negotiating the best deal for shareholders -- not just his children."

A Genzyme spokesman says it would have been impossible for the company to guarantee Mr. Crowley's children would be in the first clinical trials of any drug, because the Food and Drug Administration has the final say in approving how such trials are designed.

Still, Mr. Crowley felt confident his kids would get the drug quickly since he was in charge of its development. "It was never said, but there was a very tacit understanding that we needed to get

the drug as quickly as possible to everyone, including Megan and Patrick."

The son of a New Jersey policeman, Mr. Crowley never planned on a career in the health-care field. After graduating from Harvard Business School, he took a job consulting for financial institutions. He married his high-school sweetheart, Aileen, and their first child, John, arrived in 1994. Two years later, Megan was born, looking to all like another healthy baby.

But when 15-month-old Megan wasn't pulling herself up or standing, a neurologist ordered a series of tests. That led to a grim diagnosis and shocking prognosis on March 13, 1998: Her doctor didn't expect her to live beyond her second birthday. Her infant brother Patrick was just a week old at the time; later he was also diagnosed with the same disease.



**Aileen Crowley**

Pompe is caused by a defective or missing enzyme. Normally, that enzyme breaks down a substance in the body called glycogen. Without the enzyme, glycogen builds up in the muscles, and they degenerate, leading in virtually all cases to heart failure and death. To treat Pompe, researchers have been experimenting with making a version of the missing enzyme.

After he took the job at Genzyme, Mr. Crowley spent most weeknights at a hotel in Cambridge, while his family stayed in New Jersey to be close to relatives. With cash from the sale of his company, they bought an eight-bedroom house in Princeton. They installed an elevator for their two youngest children, who are both in wheelchairs, and had ramps built so the kids could get to the pool. The couple's oldest child, 8-year-old John, doesn't have Pompe.

While Mr. Crowley's job was to spearhead the Pompe program, he didn't have sole authority at the company over how tests would be set up. Shortly after arriving, he chose a team of a dozen people from throughout Genzyme who would make the decisions with him, including those with experience dealing with regulatory approvals. Many key people on the team didn't report directly to him. "I couldn't just order them to give the drug to Megan and Patrick,"

Mr. Crowley says.

That led to the first conflict. Most of Mr. Crowley's colleagues thought the fastest way of getting the drug approved was to test it on children younger than Mr. Crowley's.

Hal Landy, then-Genzyme's director of clinical development, and others on the team argued for testing in infants as the quickest route to FDA approval. Infants who exhibit Pompe symptoms often have a more severe form of the disease, and live only about eight months. Because of their shorter lifespan, the trial could be conducted more quickly. Mr. Crowley pressed for also testing the drug on older children.

By spring of 2002, Genzyme had gotten a drug ready for testing in humans. The drug -- an enzyme that has to be grown in live cells -- was difficult to make. While equipment to grow it in large quantities was being built, the company was making it in small batches, from ovary cells derived from Chinese hamsters. Supplies of the drug were scarce. The team decided on two trials -- but neither would include Mr. Crowley's children.

One trial would be for infants less than 6 months old, and the other for children up to age 3. There was no getting around the fact that bigger kids, who weigh more, would need more of the drug. Including older children would mean having to decrease the number of patients in an already tiny trial -- jeopardizing its chances of success.

Mr. Crowley signed off on the decision. Megan, then 5, and Patrick, 4, wouldn't qualify. "That was heart-wrenching," he says.

While those trials were being planned, Dr. Landy says he and others were trying to find a way of getting treatment to the Crowley children. They hit on a solution: The company said it needed to solve the mystery of why patients who had taken the enzyme responded very differently. They came up with what they called a "sibling trial" -- in which only Megan and Patrick would be enrolled. Though both children have the identical genetic mutation for Pompe, Patrick is much more severely affected.

Mr. Crowley was elated. He phoned his wife from his office, telling her that in a few months, by July or August 2002, the kids could be on the drug.

In August, as he vacationed with his family on the New Jersey shore, Mr. Crowley anxiously awaited word about whether Children's Hospital of Philadelphia had agreed to conduct the trial. Though drug companies pay for trials, hospitals have discretion over what trials they will host.

When nobody called, Mr. Crowley phoned one of the doctors at the hospital and learned officials had raised concerns about the study. The hospital questioned the fairness of a study that included only the children of a top executive of the company making the drug. That conflict of interest, the hospital feared, could skew the trial.

The hospital declined to be a site for the trial. "This was a very difficult decision for us," Judy Argon, the hospital's vice president of research administration, said in a statement.

Mr. Crowley couldn't sleep. Five months had elapsed since Dr. Landy told him he wanted to treat the children. They had grown palpably weaker during that time. Patrick, who had been able to sit up a year earlier, had lost much of his muscle strength. He could no longer hold up his head. Megan was going to kindergarten, accompanied by a nurse, but she couldn't hold her head up for long. "When they start losing that, it's like losing a final bit of dignity," Mr. Crowley says.

Increasingly desperate, Mr. Crowley considered just snatching some of the vials of the drug from Genzyme's storeroom and giving it to his kids. "I thought about it all the time," he says. But that wasn't possible. The drug has to be infused intravenously every two weeks, and Megan and Patrick, whose veins are particularly fragile, would require surgery to implant a special device so they could get intravenous medicine. That

meant the children would have to be hospitalized, and hospitals aren't allowed to administer experimental drugs without government permission.

Sometimes, very ill patients can be given unapproved drugs under an FDA-approved "compassionate use" program. But Genzyme hadn't applied for such permission for its drug because it didn't have enough of the medicine. It was barely making enough to supply its own clinical trials. The company was investing tens of millions to build new bioreactors to make more of the drug, but they wouldn't be up and running for at least another year.

It was a constant struggle to keep the children alive. Both needed respirators to breathe and stomach tubes for feeding. Megan caught a cold that turned into pneumonia and landed her in intensive care for six weeks. Patrick's ventilator stopped working when his parents were pushing him through a parking lot after attending a "Disney on Ice" performance. They revived him with difficulty on the pavement beside their minivan.

The Crowley home became a virtual hospital, with nurses and therapists coming and going round-the-clock. Mrs. Crowley separated herself from her husband's mission of finding them a treatment. "I'm just trying to keep them healthy," she would say over and over.

By fall of 2002, husband and wife were frantic. "I felt like a huge snowball was rolling down the hill and I wanted to get in front of it and stop it," Mr. Crowley says.

So he decided to take matters into his own hands. Without telling his team at Genzyme, he called a researcher at the University of Florida in Gainesville, whom he had worked with at his private company. He asked if that hospital might conduct the sibling trial. The researcher was enthusiastic, and they quickly wrote up a new trial plan, which they thought would avoid conflict-of-interest questions. This trial wasn't limited to the Crowley kids but designed for children who had the same unusual form of the disease -- that is, they didn't die as babies.

Within two weeks, the hospital board had approved the trial. Mr. Crowley returned home, told his wife they should prepare to move to Florida the next week and informed Megan that her "special medicine" was finally ready. (Patrick, the sicker of the two, is less able to communicate.)

Megan, then 5, overflowed with questions: What color was the medicine? Who else had gotten it? How did they do? She can't speak clearly but communicates well with a combination of sign language and spoken words.

Mr. Crowley's excitement was short-lived. Two days later, Dr. Landy called him furious that he and the team at Genzyme had been left out of the loop. He had only learned about the plan when the hospital called to arrange for delivery of the drug. "There were inaccuracies" in the trial design, Dr. Landy said, noting it suggested as many as six children could be enrolled when Genzyme had only enough drug on hand for two. Mr. Crowley says he thought other kids could be added to the test as more medicine became available.

In any case, numerous internal approvals were required at Genzyme before any plan could be submitted anywhere. Genzyme controlled distribution of the drug, not Mr. Crowley. And Genzyme paid for the costs of any trial. Dr. Landy said the Florida plan simply couldn't go forward.

Mr. Crowley appealed in vain to other top company officials who sympathized but wouldn't intervene. "Can you blame the guy for trying?" Mr. Termeer, Genzyme's CEO, says. "But in the end, we had the systems in place to rein him in."

At home, Mr. Crowley was also on the hot seat. His wife was angry he had raised and dashed the family's hopes so many times. She didn't want to hear about any more plans. "Just call me when you're ready to take the kids to the hospital," she said.

She left it to him to break the news to Megan, who had been eagerly awaiting the trip to Florida. The girl, interrupted in the middle of her Barbie Princess computer game, sat silently for a minute or two, chin in hand, and then returned to the keyboard.

Days later, Mr. Crowley had an assignment that made him even more upset. Genzyme had granted a request from top Spanish government officials to treat a Spanish Pompe patient on a compassionate-use basis. Mr. Crowley's job was to arrange to have the drug flown to a hospital in Spain immediately. Europe has looser rules for compassionate-use treatment; in the U.S., regulatory authorities require more testing before experimental drugs can be distributed. Genzyme had approved at least one such request from Europe before, hoping it would help the drug get approved there. Mr. Crowley had stoically made the arrangements.

It was more painful this time. He stared out the window, thinking, "What am I doing? In two phone calls, I can save a kid in Madrid I've never met, but I can't do it for my own kids," he says. He considered taking his children to Europe to get the treatment, but they were too weak to travel.

In November, a few days before Genzyme filed its application with the FDA to start the trials on infants and young children, Dr. Landy returned to Mr. Crowley with a surprise: a new proposal to treat his children. Dr. Landy later said he "felt badly it had taken so long" to get the Crowley kids on the drug, and he had tried to find a place close to Mr. Crowley's home that would treat them.

Genzyme had worked before with a geneticist at a small hospital in New Brunswick, N.J., called St. Peter's University Hospital. A Genzyme doctor had spoken with her. She thought her hospital would consent to treating the children because data gathered could help answer the scientific question of why some children responded better than others.

Mr. Crowley tried to keep his expectations in check. By this point, he worried that his presence at the company might even be hindering efforts to get the drug to his children. He told Genzyme he was leaving. On Dec. 19, he turned in his company identification and left the building.

On Christmas Eve, a card arrived at the Crowley home. It was from the geneticist at St. Peter's hospital. Inside, she had written: "You asked for something to place under your Christmas tree." She had enclosed a copy of the hospital's letter approving the trial.

Two weeks later, the Crowley children, dressed in matching blue hospital gowns decorated with pictures of red clowns, were ready for their first infusion. Mr. Crowley pressed the button on the intravenous tube to start the colorless liquid flowing into Megan's veins. Megan held her pink stuffed dog, Nosey, under one arm, and waved with her right hand.

While Patrick awaited his infusion, Mr. Crowley broke the tension by joking with the nurse hooking up the IV bag over his bed: "Be careful, don't drop that. It cost \$200 million." As Mrs. Crowley pressed the lever to start Patrick's treatment, the little boy trained his eyes on the Sponge Bob cartoon on the TV overhead.

The children went home the next day. They would receive four-hour infusions every two weeks. The first results wouldn't be known for 12 weeks.

In April, the geneticist, Debra-Lynn Day-Salvatore, took Mr. and Mrs. Crowley to a corner of the room in which the children were getting their infusions to report on their progress.

Megan's heart, she said, had shown a "dramatic reduction in size." Once swollen to almost double the normal weight, her heart was now down to a healthy size. Her liver, which had been so enlarged she had a Buddha belly, was much smaller. "She's developing a nice little waist," Dr. Day-Salvatore said.

Patrick, who is now five, showed far less improvement. She hadn't given up hope for Patrick, she said -- he had shown some response, and he may just be slower to improve. But his communication and interaction is limited. Dr. Day-Salvatore says she pretends to sneeze whenever she's around Patrick because it's one of the few things to which he responds, and he always says "bless you."

For the first time, the Crowleys faced the possibility that their children might be headed in different directions -- one might live and one might die.

The children continue to receive infusions. Dr. Day-Salvatore has set a new goal for Megan -- to try to wean her off of a ventilator, something rarely seen in patients who have used the machines for years. "This is very uncharted territory," Dr. Day-Salvatore says.

Genzyme says the trial for children age 6 months to 3 years is under way, though it's too early to talk about results. Still, Genzyme says it hopes to get FDA approval to market the drug in early 2005.

For now, Mr. Crowley is trying to make up for lost time with his children. In the spring, he accompanied Patrick to preschool some days and on others played nurse for Megan in kindergarten. When her dad is doing exercises, Megan often works out with him, curling two-pound barbells.

With 6-year-old Megan considerably stronger, he is discovering they can do new things together. He had never been able to take his daughter out alone for a drive because she would slump over. But on a warm July afternoon, he lifted her out of her wheelchair and into the front seat of his new green convertible. Then Mr. Crowley put Megan's portable respirator at her feet and her favorite Dixie Chicks song, "Ready to Run," in the CD player, and the two pulled out of the driveway.

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