

## **A Brief Synopsis of...**

# **“The Uncured: How one drug company shelved a Parkinson’s breakthrough”**

**By Nick Nelson**

Parkinson’s disease afflicts more than 3 million people worldwide, and there is no known cure. By the time its symptoms begin to emerge – the shaking, the freezing, the grim masking of the face – the disease already has choked off more than 70 percent of the dopamine that the brain needs for producing movement. There are dozens of Parkinson’s medications on the market today, and all of them have this in common: they do nothing to slow the advance of the disease. They might suppress its symptoms for a time, but the disease is unrelenting, and it advances at its normal rate. Existing treatments cannot stop Parkinson’s; they can’t even slow it down.

“The Uncured” is the true story of a drug that was truly different. When a young surgeon-inventor pumped GDNF into the brains of Parkinson’s patients, he witnessed the seemingly impossible. In the face of a disease characterized by its progressive worsening, the patients on GDNF got better. They could walk, talk, smile, smell and make love again. Clinical trial volunteers in England, Kentucky, New York and Chicago reported marked and sustained improvement. It was an “Awakenings” of sorts for the patients, some of whom had lived with Parkinson’s for more than 30 years.

In September of 2004, Amgen Inc. halted all human testing of the drug abruptly and indefinitely. Amgen officials said new safety concerns made GDNF too risky, but many of the patients suspected it was really just about money. They fought – and continue to fight today – for access to a drug they describe as miraculous.

“The Uncured” follows the experiences of six patients who volunteered to have holes drilled into their skulls, tubes threaded beneath their skin and hockey puck-sized pumps implanted in their bellies, all in the hopes that GDNF would provide the relief that no existing treatment could. Investigative reporter Nick Nelson conducted more than 100 interviews in the United States, Canada and Europe for the book. The 65,000-word manuscript weaves a David-and-Goliath tale of a meager group of determined patients who take on the world’s largest biotechnology company for the right to live.

## **Excerpt from “The Uncured”**

### **Introduction – Case No. 1: Stephen Waite**

It was a brisk, overcast winter morning in 2001 when Stephen and Margaret Waite drove to downtown Chippenham, a town between Bristol and Swindon in southwest England. Stephen parked his car in front of the five-story, steel and glass St. Paul office building, and he held the door open for Margaret and they both entered. The couple stood in line for half an hour before a pretty young woman from the Social Security Department asked them to follow her to a small, boxy room, empty except for a

desk and three chairs. Most entered that room hoping to plead or cajole their way into new social security benefits. There was a conspicuous red call button on the desk that threatened to bring security guards running if one wouldn't take no for an answer.

The young woman looked bewildered when she heard Stephen's request. The man had just handed her a stack of government disability checks – payment slips he could have exchanged for cash. He was returning them, the man explained with an impish grin. He didn't need them any more.

Since she began working at the Social Security Department, she told Stephen, she had never seen a person hand them back before. This was highly irregular.

Stephen explained that Parkinson's disease had once left him unable to work and, 10 years prior, had forced him to apply for benefits. But now an experimental drug was curing him. He now had plenty of work and felt guilty accepting government aid. She looked incredulous and said, If you take a turn for the worse, you can come straight back.

Stephen thanked her and left the room smiling. He was 27 when a doctor said to him, "Stephen, you have an incurable disease called Parkinson's." Stephen was a draftsman and an architect at the time, and he had just started work near his hometown of Chippenham. He was married with two daughters, a toddler and an infant. Margaret first saw Stephen in a crowded malt shop when she was 14. Stephen was 17 and looking brilliant in a white and navy Sea Cadet uniform. She turned to a friend and whispered, "I think I might marry him." Five years later, she did.

The couple decided not to tell family or friends about the disease because they worried it would jeopardize Stephen's employment, so they kept the secret for 20 years. Stephen blamed his erratic movements on back problems, but the cover story grew suspect as his condition worsened. In 1990, when he and several coworkers were laid off, it seemed a fitting time to confirm what most people close to him already had guessed.

Parkinson's had spared him the use of his hands, so he could take on small drafting projects. But his legs had become wobbly and unreliable. He got around with the aid of a wooden cane, but often it was

impossible for him to visit a job site, and his work suffered for it. In 1992 he began collecting disability benefits from the government.

By the year 2000, Stephen had lived with Parkinson's for nearly 30 years. He would start his day by heaving himself from his bed to the floor, where he would begin an elbow-splitting crawl to the kitchen for his pills. He would swallow 30 of them by the end of the day, but by that time their effect was diminishing. He finally asked his neurologist about brain surgery, and he was referred to a neurosurgeon in Bristol who happened to be looking for five patients for an experimental drug trial.

It is a testament to the misery of late-stage Parkinson's that Stephen didn't balk at what the trial would demand. Two pumps, weighing more than a pound apiece, would be sewn into his abdomen, and thin tubes would connect to the pumps and would be shimmied under his skin from belly to brain. A pair of holes, each the size of a U.S. nickel, would be drilled into the skull, and a tiny catheter would be passed through the hole, pushed deep into the brain and secured to the skull with screws. He would have to make a monthly trip to the clinic for an emptying and refilling of the pump, which would be done with a large needle through the skin of the stomach. All this for an unproven drug with no guarantees.

At that time GDNF had been tested in animals repeatedly with dramatic results. In humans the drug had been tested only twice and had failed as dramatically. Patients reported nausea, anorexia, vomiting, weight loss and abnormal sexual behavior, and they showed no significant improvement in their Parkinson's symptoms. But the surgeon in Bristol had designed a new method of getting the drug into the brain. It was possible this drug could relieve some of Stephen's symptoms. It might even reverse the disease.

It was a pleasant thought, but Steven had no real hope of this. By the time he learned of the trial he had lived longer with the disease than without it and had accepted Parkinson's as his companion until death. By participating in the trial, Stephen was donating his body to science in a way. If the drug proved safe and he improved, science had taken one step closer to a new treatment or cure. If it failed, science knew to look elsewhere.

“You may not believe,” he said of his mindset of the time, “That I had gotten in such a state that I was thinking more about other people than I was for myself. If it would not have been successful, I still would have felt good about it.”

Stephen and four other men became the first humans to have GDNF pumped into their brains. It was a phase I clinical trial – a safety trial whose main objective was to prove that the treatment was safe.

Within three months of the first dose, Stephen was more mobile and had better balance than he had in years. “I could walk from the bedroom to the kitchen... It was amazing – for years I had been falling out of bed and crawling to the kitchen. It was almost immediate, and it was improving.”

If GDNF had simply slowed the march of the disease, it would have been a breakthrough. No current drug used to treat Parkinson’s can do that much. But the patients reported, and the clinical data confirmed, that the downhill slide had not only halted, it had reversed. After one year the patients showed an average *improvement* of 39 percent on the Unified Parkinson’s Disease Rating Scale, the gold standard for gauging the severity of Parkinson’s symptoms.

The improvements rippled through Stephen’s life in remarkable ways. By the end of the first year, he had stopped using the cane, had cancelled the disability benefits and had bought a Jaguar XJ-6. He could drive alone to the store and shop for trousers, trying them on in the fitting room before buying them, rather than buying them first and trying them on at home, as before. After one year his other medication had been cut in half. The improvements continued into a second and third year.<sup>1</sup>

At that time Stephen knew little about Amgen, the California-based company that owned the rights to GDNF. Amgen had provided the drug for the Bristol trial but had little involvement otherwise and almost no interaction with the patients. In June of 2004, however, Amgen called on Stephen and asked him to share his experience with a roomful of drug developers at a conference on GDNF at the Marriott Grand Hotel Flora in Rome. Amgen was preparing a strategy for bringing GDNF to market, and the

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<sup>1</sup> See Gill, Steven S. et al., “Direct Brain Infusion of Glial Cell-Line-Derived Neurotrophic Factor [GDNF] in Parkinson’s Disease,” *Nature Medicine*, May 2003, 589 and also Patel, Nikunj K. et al., “Intrapatamenal Infusion of [GDNF] in PD: A Two-Year Outcome Study,” *Annals of Neurology*, February 2005, 298.

purpose of the meeting in Rome was to bring Amgen employees and partners to discuss how GDNF should be launched globally.

Reading from prepared remarks, Stephen told the group, “Three years on from the surgery there have been rough periods but they are insignificant when compared with the ways I have improved. I can work at my drawing board at any time...I also take very little in the way of accompanying drugs, compared to the vast amounts I used before... Life is good and I feel very special to be part of this research.”

Stephen returned from the conference and resumed his busy life. His drafting business was thriving, and he was barely keeping up with demand. Parkinson’s was still a part of his life, but the disease had retreated enough for him to have a life again. Each month, he would go to Frenchay Hospital to have his pumps refilled. After three years, it had become part of his routine.

Three months after Amgen’s conference in Rome, Stephen went as usual to Frenchay for a refilling. But on that day, in early September of 2004, a nurse told Stephen he would not receive any more GDNF. Amgen was halting the trials immediately out of safety concerns. He would need to have his pumps switched off and removed.

Stephen said he would sign anything, he would assume whatever risk, if Amgen would allow him to continue on the drug. He learned that nearly 50 other patients had been receiving GDNF before it was taken away and that many of the patients, like him, were desperate to recover it. When Amgen refused, some of the American patients sued the company in federal court and demanded access to the drug. The process was slow, and Stephen did not know what came of the lawsuit. One year passed and then 18 months.

I met Stephen in late July of 2006, nearly two years after he lost GDNF. He had asked that we meet at a pub near Chippenham because he had moved recently into a smaller home and boxes were piled everywhere. Stephen and Margaret arrived in a small van – they had sold the Jaguar – and when he climbed out, Stephen walked with a wooden cane. He wore a green and white checkered shirt and gray

slacks. Margaret walked beside him with a steadying hand on his arm. We sat at a wooden picnic table on the pub's hedge-rimmed lawn under a sagging green and red umbrella.

Stephen is about five-foot-ten, has a stocky build, a ruddy complexion, squinting eyes and a wry sense of humor. He talks in a sing-song way with the rich, Welsh-tinged accent of the region. He told me that the relapse had not been immediate, as he had feared it would be. There was no abrupt onset of symptoms in the days and weeks after GDNF was withdrawn. Parkinson's crept back into his life in undetectable ways. The symptoms reemerged more gradually than they had disappeared during the trial. Yet certain milestones marked his descent.

The cane was one. He had started using it on bad days a year or so after the trials ended. Now it went with him everywhere, as before. The disability benefits were another. A few months before I met him, Stephen had reapplied for the checks he had triumphantly returned three years earlier. Selling the car, selling the house – these were other indicators.

Stephen seemed to be a naturally cheerful person, much more at ease cracking a salty joke than griping about his declining health. He looked uncomfortable with the somber subject of our conversation and attempted often to steer it toward lighter topics. After circling for a while, he finally spoke of losing the drug.

“Having had the illness for so long – for 30-odd years – when they gave me the GDNF, I relaxed too much, possibly. When they took it away from me I had no fight in me any more. I was close to a nervous breakdown. I was in an awful state. Fortunately, I think now I'm putting myself together.” He seemed to answer my other questions cautiously, and he chose his words deliberately as if tiptoeing around deep wells of emotion.

At the end of that first interview, he uttered a sentence that reflected the sad simplicity with which he regarded the past five years. Far away in America, scientists had debated the ethics of Amgen's decision, lawyers had challenged its legality in federal court and patients had condemned it in the press as unconscionable. Removed as he was from these conversations, Stephen did not know what forces took

GDNF away from him or what kept it out of his reach. He knew that he once had it, and that it was wonderful, and that it was gone.

“Amgen took away my Parkinson's,” he said. “And then they gave it back to me.”



Stephen and Margaret Waite. Cold Ashton, August 2006

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