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From M.S. Patients, Outcry for Unproved Treatment

By DENISE GRADY

For her first appointment with Dr. Daniel Simon, Neelima Raval showed up with a rolling file cabinet full of documents. She had downloaded every word written by or about Dr. Paolo Zamboni, a vascular surgeon from Italy with a most unorthodox theory about multiple sclerosis.

Dr. Zamboni believes that the disease, which damages the nervous system, may be caused by narrowed veins in the neck and chest that block the drainage of blood from the brain. He has reported in medical journals that opening those veins with the kind of balloons used to treat blocked heart arteries—an experimental treatment he calls the “liberation procedure”— can relieve symptoms.

The idea is a radical departure from the conventional belief that multiple sclerosis is caused by a malfunctioning immune system and inflammation.

The new theory has taken off on the Internet, inspiring hope among patients, interest from some researchers and scorn from others. Supporters consider it an outside-the-box idea that could transform the treatment of the disease. Critics call it an outlandish notion that will probably waste time and money, and may harm patients.

These critics warn that multiple sclerosis has unpredictable attacks and remissions that make it devilishly hard to know whether treatments are working — leaving patients vulnerable to purported “cures” that do not work.

The controversy has exposed the deep frustration of many people with this incurable, disabling disease, who feel that research has let them down. It is a case study in the power of the Internet to inform and unite angry patients—which may be a double-edged sword. Pressure from activists helped persuade the Multiple Sclerosis Society to pay for studies of Dr. Zamboni’s theory, but the Internet buzz has also created an avid market for a therapy that is still unproved.

“It’s eye-opening the way this group of patients has grabbed hold of the social-networking technology,” said Dr. Simon, an interventional radiologist at JFK Medical Center in Edison, N.J. “They’ve taken this to a level I’ve not seen in other patients. Patients used to read an article or two. Now, they’re actually seeing procedures on YouTube. Is this the future of medicine?”

Scientifically, the jury is out: Dr. Zamboni’s hypothesis is being studied. It is not known whether narrowed veins are more common in people with multiple sclerosis than in others, and even if they are, whether the narrowings are a cause, or an effect, of the disease. There is no solid proof that opening the veins can help. There have been no studies with control groups — the only way to find out whether a treatment works.

“In my view the evidence is quite scanty and the biological plausibility is low,” said Dr. Stephen L. Hauser, the chairman of neurology at the University of California, San Francisco. Many neurologists agree. Dr. Hauser said there was much stronger evidence that the disease arose from genetic variations affecting the immune system.

But Dr. Adnan H. Siddiqui, part of a team at the University at Buffalo that has been studying Dr. Zamboni’s theory, said that it made sense and that the data from Italy was encouraging. Still, he emphasized that more study was needed, and that patients should not be treated until the research was done.

In Demand

Despite the lack of proof, many patients are captivated by the idea that multiple sclerosis might turn out to be a vascular disease. They want to believe it can be fixed with a relatively simple procedure, and they want to be tested and treated. Now.

These patients say they cannot afford to wait for research results because they will wind up in wheelchairs before the studies are done. Their only option so far has been a lifelong course of drugs with limited benefits and harsh side effects. To some, balloon treatment seems no riskier than those drugs.

Dr. Zamboni himself has said that the procedure should not yet be done outside of studies. He said in an interview that he was conducting research only and had turned down thousands of requests from people wanting to go to his clinic at the University of Ferrara.

But other doctors have set up shop. A clinic in India with a toll-free American phone number has an online advertisement for a “liberation package.” Patients are posting testimonial videos and trading tips on clinics in Bulgaria, Poland and Jordan.

In the United States, where many hospitals forbid experimental treatments outside of studies, a “back alley” network of doctors willing to perform the procedure has begun to develop, said Dr. Salvatore J. A. Sclafani, chairman of radiology at Downstate Medical Center in Brooklyn. He said he knew of about a dozen. The doctors try to stay under the radar, and patients quietly pass their names to one another.

“It reminds me of abortion in 1968,” Dr. Sclafani said.

He said he had treated about 20 patients at Kings County Hospital before the hospital ordered him to stop in early April. He said he had a waiting list of 300 to 400 patients..

Meanwhile, researchers are trying to answer basic questions. On June 29, the team in Buffalo is to begin the first treatment study to include a control group. The controls will be given a sham procedure, and compared with others who get the real thing. Initially, 30 patients — only those with an early form of the disease — will be enrolled. Thousands of people applied.

The Multiple Sclerosis Societies in the United States and Canada will spend \$2.4 million over the next two years on studies at seven centers. Researchers will study veins in patients with different stages of multiple sclerosis, in healthy people and in those with other neurological diseases. The studies will not test the balloon treatment, but are meant only to find out if the narrowings really exist, if they are related to the disease and if they are a cause or an effect.

Some patients complain that the society has been too slow to consider the new idea. A splinter group — the Reformed Multiple Sclerosis Society — has formed to increase the availability of the vein treatment.

Joyce Nelson, the president of the Multiple Sclerosis Society in the United States, said, “I wasn’t aware how thin the veneer was and how close to the surface the frustration was.”

“ ‘We can’t wait’ has resounded,” Ms. Nelson said. But she added, “There isn’t a way to rush the work that needs to be done.”

As the procedure has caught on in some places, few serious complications have been reported. But at Stanford University, a woman, 50, treated with stents (wire-mesh tubes used to hold blood vessels open) and blood-thinning drugs, died of a brain hemorrhage after returning home, and another patient needed heart surgery after a stent placed in a neck vein came loose and was swept into the heart. The procedures were stopped.

Dr. Michael Dake, who treated the patients, declined several requests for an interview, but said by e-mail that he hoped to discuss “a number of exciting developments” about the procedure “in the near future.”

Dr. Philip Pizzo, the dean of Stanford's medical school, said the vein theory "deserves to be explored" — but only in studies. A study with a control group is being planned.

About 400,000 people in the United States have multiple sclerosis; worldwide, there are 2.1 million. (The disease is more common in temperate zones than in the tropics, and affects more women than men and more Caucasians than members of other groups.) It usually begins in young adults, with fatigue, vision problems, numbness, bladder trouble and difficulty with walking, balance and coordination. The disease eats away a fatty substance, myelin, that coats nerves, and gradually scars the nerves. The damage is thought to occur because the immune system, for unknown reasons, mistakenly attacks myelin.

Most patients, 85 percent, start out with a form called relapsing-remitting. In about half of those the disease becomes progressive, harder to treat and more disabling. Ms. Raval, who is 38 and has had multiple sclerosis for 13 years, implored Dr. Simon to test her for narrowed veins and, if he found any, to open them.

Dr. Simon regularly uses balloons and stents to open bile ducts and blood vessels. He was impressed with Ms. Raval's determination, her trove of information and her background. She has a degree in toxicology and works for a drug company. But he was also familiar with Dr. Zamboni's work—and deeply skeptical of it.

"My initial take was, it doesn't make any sense," Dr. Simon said.

But Ms. Raval had high hopes. She said she believed that the balloon treatment would be "the next best thing to a cure." The usual drugs have not worked for her. Her 5-year-old son is eagerly awaiting the day when she can run with him, but she is finding it harder and harder even to walk. **Theory Born of Experience**

Dr. Zamboni, 53, (no relation to the inventor of the ice-rink machine) began studying the medical literature on multiple sclerosis in 1995 when his wife learned she had the disease.

"What I found was like a detective story," he said.

He discovered reports of vein abnormalities and of brain lesions forming around veins. But the research had been abandoned. Vein disorders are his specialty; he has been studying them for 25 years. He began using ultrasound and other imaging techniques to examine veins, and found narrowings in the neck and chest veins in people with the disease, but not in healthy ones. He suspected that abnormal blood flow and pressure in the veins— not just narrowing alone — might cause minute amounts of bleeding in the brain, leading to an immune reaction and inflammation that damaged myelin and nerves.

Iron deposits could also form, and add to the damage. He wondered if opening the narrowed areas might help.

In 2006 he began using balloons to treat patients, including his wife, whose symptoms went away and, he says, have not come back. Other patients who, like his wife, had relapsing-remitting disease, also recovered fully, he said; but some did not respond at all. In those with progressive disease, fatigue improved, but not mobility problems, according to a pilot study he published in December in *The Journal of Vascular Surgery*. And in half the treated patients, the neck veins closed up again. The study did not have a control group, and the patients were also taking drugs to treat multiple sclerosis. More rigorous trials will start in Italy this summer, Dr. Zamboni said.

Another doctor, Marian Simka, who has been performing the procedure in Pszczyna, Poland, has reported that it has made symptoms worse in some patients..

Researchers in Buffalo have confirmed (but not yet published) that narrowed veins and abnormal blood flow are more common in people with multiple sclerosis. But, while Dr. Zamboni found them in all patients and no healthy people, the Buffalo team found them in about 60 percent of patients and 15 percent of healthy controls.

Granting a Patient's Wish

Dr. Simon sensed that Ms. Raval would have no peace unless she could learn whether she had narrowed veins, and he wanted to help her.

So he offered to perform a test to find out, a venogram. It involves passing a tube into a vein in the groin and up to the neck and chest, and then injecting dye to take X-rays of the veins. He felt sure there would be no blockages.

“And then she would be able to stop obsessing over this and move on with her life and get some kind of conventional treatment,” he said.

But he was stunned to find narrowings, right where Dr. Zamboni's theory predicted: in the jugular vein in the neck, and the azygous, a vein in the right side of the chest.

Ms. Raval was elated. She felt certain that opening up those veins would solve her problems. Dr. Simon agreed to try.

Although it was, technically, an experimental procedure, Dr. Simon said he did not have to ask his hospital for permission to perform it. The details were similar to other procedures that interventional radiologists do every day. It is not uncommon for them to take a device approved for one purpose and use it for another, like putting a bile-duct stent into a blood vessel — a practice called “off-label” use, which the Food and Drug

Administration allows. Interventional radiology, Dr. Simon said, is an “off-label specialty” that depends on innovation and adaptability.

On March 24, as Ms. Raval lay on a padded table in a treatment room, Dr. Simon passed balloons to the pinched spots in her right jugular and azygous, and dilated them.

The procedure took less than an hour. In the recovery room, Ms. Raval said she felt better already.

Over the next days and weeks, she noticed remarkable improvements. Her fatigue went away. She walked and climbed stairs more easily, and the color in her face brightened. Her husband and co-workers saw the changes, too, she said.

Was it real, or just one giant, communal placebo effect? Ms. Raval posted exuberant Facebook messages naming her “most amazing doctor.” Other patients began calling Dr. Simon.

Within a month, Ms. Raval again had trouble walking. She felt sure her veins had closed again. Another venogram showed they had. Dr. Simon reopened them.

Ms. Raval felt better — and then deteriorated again. On June 18, another venogram, her fourth invasive procedure in three months, suggested that the narrowings had recurred. She struggled over what to do. She could not keep having balloon procedures again and again. Dr. Simon consulted Dr. Dake, his former mentor, who recommended stents.

Initially, Ms. Raval and Dr. Simon had thought stents too risky. Unlike balloons, which are inserted briefly and removed, stents are permanent. They can migrate to somewhere they do not belong, like the heart, as occurred in Dr. Dake’s patient. Or tissue growth can clog them.

But Dr. Simon and Ms. Raval could see no other option. On June 23, he implanted a stent in her two jugular veins.

“I really have a good feeling on this one,” Ms. Raval said a few hours after the procedure. “I think this is the resolution, long-term. Let’s wait and see.”

In the meantime, Dr. Simon had conducted venograms on about 20 other patients with multiple sclerosis. He found narrowed veins in all but one. He said he was going to ask the hospital’s ethics panel for permission to perform balloon procedures in those patients. But the hospital would have to figure out how to get paid: insurance might cover venograms, but not an experimental treatment. The total charge for the procedure, including both hospital and doctor fees, would be about \$10,000, Dr. Simon said.

He and his partner, Dr. Noam Eshkar, said they knew many researchers thought patients should not be given unproven treatments outside of clinical trials. They said they did not disagree. But they also sympathized with patients who had progressive diseases and who felt they did not have the time to wait. "In the real world," Dr. Eshkar said, "things happen at the edge of scientific proof."