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### Researcher's labour of love leads to MS breakthrough

By André Picard and Avis Favaro  
From Saturday's Globe and Mail

*New way of thinking about debilitating disease has yielded stunning new treatments - but MS societies urge sufferers to be cautious before experimenting*

Elena Ravalli was a seemingly healthy 37-year-old when she began to experience strange attacks of vertigo, numbness, temporary vision loss and crushing fatigue. They were classic signs of multiple sclerosis, a potentially debilitating neurological disease.

It was 1995 and her husband, Paolo Zamboni, a professor of medicine at the University of Ferrara in Italy, set out to help. He was determined to solve the mystery of MS - an illness that strikes people in the prime of their lives but whose causes are unknown and whose effective treatments are few.

What he learned in his medical detective work, scouring dusty old books and using ultra-modern imaging techniques, could well turn what we know about MS on its head: Dr. Zamboni's research suggests that MS is not, as widely believed, an autoimmune condition, but a vascular disease.

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More radical still, the experimental surgery he performed on his wife offers hope that MS, which afflicts 2.5 million people worldwide, can be cured and even largely prevented.

"I am confident that this could be a revolution for the research and diagnosis of multiple sclerosis," Dr. Zamboni said in an interview.

Not everyone is so bullish: Skeptics warn the evidence is too scant and speculative to start rewriting medical textbooks. Even those intrigued by the theory caution that MS sufferers should not rush off to get the surgery - nicknamed the "liberation procedure" - until more research is done.

U.S. and Canadian researchers are trying to test Dr. Zamboni's premise.

For the Italian professor, however, the quest was both personal and professional and the results were stunning.

Fighting for his wife's health, Dr. Zamboni looked for answers in the medical literature. He found repeated references, dating back a century, to excess iron as a possible cause of MS. The heavy metal can cause inflammation and cell death, hallmarks of the disease. The vascular surgeon was intrigued - coincidentally, he had been researching how iron buildup damages blood vessels in the legs, and wondered if there could be a similar problem in the blood vessels of the brain.

Using ultrasound to examine the vessels leading in and out of the brain, Dr. Zamboni made a startling find: In more than 90 per cent of people with multiple sclerosis, including his spouse, the veins draining blood from the brain were malformed or blocked. In people without MS, they were not.

He hypothesized that iron was damaging the blood vessels and allowing the heavy metal, along with other unwelcome cells, to cross the crucial brain-blood barrier. (The barrier keeps blood and cerebrospinal fluid separate. In MS, immune cells cross the blood-brain barrier, where they destroy myelin, a crucial sheathing on nerves.)

More striking still was that, when Dr. Zamboni performed a simple operation to unclog veins and get blood flowing normally again, many of the symptoms of MS disappeared. The procedure is similar to angioplasty, in which a catheter is threaded into the groin and up into the arteries, where a balloon is inflated to clear the blockages. His wife, who had the surgery three years ago, has not had an attack since.

The researcher's theory is simple: that the underlying cause of MS is a condition he has dubbed "chronic cerebrospinal venous insufficiency." If you tackle CCSVI by repairing the drainage problems from the brain, you can successfully treat, or better still prevent, the disease.

"If this is proven correct, it will be a very, very big discovery because we'll completely change the way we think about MS, and how we'll treat it," said Bianca Weinstock-Guttman, an associate professor of neurology at the State University of New York at Buffalo.

The initial studies done in Italy were small but the outcomes were dramatic. In a group of 65 patients with relapsing-remitting MS (the most common form) who underwent surgery, the number of active lesions in the brain fell sharply, to 12 per cent from 50 per cent; in the two years after surgery, 73 per cent of patients had no symptoms.

I am confident that this could be a revolution for the research and diagnosis of multiple sclerosis Dr. Paolo Zamboni

Augusto Zeppi, a 40-year-old resident of the northern Italian city of Ferrara, was one of those patients. Diagnosed with MS nine years ago, he suffered severe attacks every four months that lasted weeks at a time - leaving him unable to use his arms and legs and with debilitating fatigue. "Everything I was dreaming for my future adult life, it was game over," he said.

Scans showed that his two jugular veins were blocked, 60 and 80 per cent respectively. In 2007, he was one of the first to undergo the experimental surgery to unblock the veins. He had a second operation a year later, when one of his jugular veins was blocked anew.

After the procedures, Mr. Zeppi said he was reborn. "I don't remember what it's like to have MS," he said. "It gave me a second life."

Buffalo researchers are now recruiting 1,700 adults and children from the United States and Canada. They plan to test MS sufferers and non-sufferers alike and, using ultrasound and magnetic resonance imaging, do detailed analyses of blood flow in and out of the brain and examine iron deposits.

Another researcher, Mark Haacke, an adjunct professor at McMaster University in Hamilton, is urging patients to send him MRI scans of their heads and necks so he can probe the Zamboni theory further. Dr. Haacke is a world-renowned expert in imaging who has developed a method of measuring iron buildup in the brain.

"Patients need to speak up and say they want something like this investigated ... to see if there's credence to the theory," he said.

MS societies in Canada and the United States, however, have reacted far more cautiously to Dr. Zamboni's conclusion. "Many questions remain about how and when this phenomenon might play a role in nervous system damage seen in MS, and at the present time there is insufficient evidence to suggest that this phenomenon is the cause of MS," said the Multiple Sclerosis Society of Canada.

The U.S. society goes further, discouraging patients from getting tested or seeking surgical treatment. Rather, it continues to promote drug treatments used to alleviate symptoms, which include corticosteroids, chemotherapy agents and pain medication.

Many people with multiple sclerosis, though, are impatient for results. Chatter about CCSVI is frequent in online MS support groups, and patients are scrambling to be part of the research, particularly when they hear the testimonials.

Kevin Lipp, a 49-year-old resident of Buffalo, was diagnosed with MS a decade ago and has suffered increasingly severe attacks, especially in the heat. (Heat sensitivity is a common symptom of MS.) His symptoms were so bad that he was unable to work and closed his ice-cream shop.

Mr. Lipp was tested and doctors discovered blockages in both his jugular and azygos veins. In January of this year, he travelled to Italy for surgery, which cleared five blockages, and he began to feel better almost immediately.

"I felt good. I felt totally normal. I felt like I did years ago," he said. He has not had an attack since.

As part of the research project, Mr. Lipp's siblings have also been tested. His two sisters, both of whom have MS, have significant blockages and iron deposits, while his brother, who does not have MS, has neither iron buildup nor blocked arteries.

While it has long been known that there is a genetic component to multiple sclerosis, the new theory is that it is CCSVI that is hereditary - that people are born with malformed valves and strictures in the large veins of the neck and brain. These problems lead to poor blood drainage and even reversal of blood flow direction that can cause inflammation, iron buildup and the brain lesions characteristic of multiple sclerosis.

It is well-established that the symptoms of MS are caused by a breakdown of myelin, a fatty substance that coats nerve cells and plays a crucial role in transmitting messages to the central nervous system. When those messages are blurred, nerves malfunction, causing all manner of woes, including blurred eyesight, loss of sensation in the limbs and even paralysis.

However, it is unclear what triggers the breakdown of myelin. There are various theories, including exposure to a virus in childhood, vitamin D deficiency, hormones - and now, buildup of iron in the brain because of poor blood flow.

While he is convinced of the significance of his discovery, Dr. Zamboni recognizes that medicine is slow to accept new theories and even slower to act on them. Regardless, he can take satisfaction in knowing that the woman who inspired the quest, and perhaps a dramatic breakthrough, has benefited tremendously.

Dr. Zamboni's wife, Elena, has undergone a battery of scans and neurological tests and her multiple sclerosis is, for all intents and purposes, gone.

"This is probably the best prize of the research," he said.

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*With reports from Elizabeth St. Philip, CTV News*

## **W5 DOCUMENTARY**

Watch W5's documentary on the groundbreaking new treatment for multiple sclerosis, which includes the first time the "liberation" surgery was filmed.

It is available on the Web at [www.W5.ctv.ca](http://www.W5.ctv.ca), and will be replayed Sunday on CTV Newschannel.

## **MS IN CANADA**

An estimated 55,000-75,000 Canadians have multiple sclerosis, and every day three more people in Canada are diagnosed with the disease. Canada has one of the highest rates of MS in the world. MS is the most common neurological disease affecting young adults in Canada.

- Women are more than three times as likely as men to develop MS.

- MS can cause loss of balance, heat sensitivity, impaired speech, extreme fatigue, double vision and paralysis. The disease is characterized by lesions on the brain, a result of the breakdown of myelin, the protective covering wrapped around the nerves of the central nervous system.
- The most common treatment for MS is corticosteroids. Steroids reduce inflammation at the site of new demyelination, lessening symptoms.
- MS was first identified and described by French neurologist Jean-Martin Charcot in 1868.
- MS is widely believed to be an autoimmune disorder, but the cause or causes are unknown. There are a number of theories about what might trigger the disease, including exposure to a virus in childhood; exposure to tobacco smoke; lack of the female sex hormone prolactin, which plays a role in the development of myelin; and vitamin D deficiency. Vitamin D may play a role in MS because it helps to construct the interior layer of blood vessels.
- Despite the long-held assumption that MS is an autoimmune disorder, new research suggests it is actually a vascular disease triggered by a buildup of iron in the brain due to problems in blood flow.

*Source: MS Society of Canada*

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