

## On the Trail of Autism

A Scientist and a CEO Collaborate to Find Answers

by Sharon Lindenburger

When David Patchell-Evans' daughter Kilee was diagnosed with autism at the age of 2½, he did what every parent faced with this diagnosis would seek to do. He set out on an impassioned search for ways to help his child. He read every book he could get his hands on, talked to medical and scientific experts, sought out a behavioural treatment program for his daughter, and communicated with other parents going through the same emotionally devastating circumstances.

Autism is a devastating brain condition that globally has reached enormous proportions. Affecting one in every 150 children, autism manifests in language difficulties, repetitive behaviour, social isolation, fixating upon objects, and lack of social skills. Autism is actually a spectrum of brain disorders ranging from Asperger Syndrome (in which the child may have good verbal facility but may lack the ability to understand non-verbal communication or to interpret emotional cues) to "classic" autistic disorder (which manifests in combinations of symptoms and behaviours consistent with autism spectrum disorders) to pervasive developmental disorder (also known as atypical autism). So little is understood about ASDs; so much is speculation and trial and error.

David Patchell-Evans is known as Patch to his friends and colleagues. His quest to find the cause and eventual cure for autism is remarkable. It shows how one

person from outside the medical profession can set into motion a process that has recently resulted in a significant medical research breakthrough.

Always a problem-solver, he decided that the key to addressing the mystery of autism lies in the realm of medical research. Patch's burning desire was to find a way to turn speculation into solid research findings. Four years ago, a serendipitous connection came into his life. He was introduced to neuroscientist Dr. Derrick MacFabe whose previous work with children with special needs had led him to begin researching autistic spectrum disorders. Both men realized they shared a deep desire to find the cause and eventual cure for autism. Dr. MacFabe, a scientist willing to follow a clinical suspicion he had, presented his fledgling research idea to Patch. Inspired by the commitment of the scientist, Patch has to date provided \$2.5 million toward the research from his own personal resources.

Using this money, the Kilee Patchell-Evans Autism Research Group has grown to a multi-disciplinary team, established at London Ontario's University of Western Ontario, under the directorship of Dr. MacFabe involving senior researchers and faculty, graduate students, post-doctoral fellows and research technologists.

Can "bugs" in your digestive system affect your brain? Breakthrough research by Dr. MacFabe's team has found strong evidence of a possible gut-bug-brain link in autism. A compound produced by bacteria found in the gastro-intestinal tract may have significant implications in autism. Dr. MacFabe's research has isolated a prime candidate for being a "culprit"—propionic acid—and the finding is creating waves in the international scientific community.

Speculation has been rampant for some time both among scientists and parents desperate for an explanation about the possible cause of this puzzling condition—that it has a link with something happening in the gut. It's well known that frequent digestive upsets are common in autistic children and that their behaviour often worsens after eating certain types of foods, particularly wheat or dairy products. But what is it exactly that's going on in autistic kids' guts? Are their stomach symptoms merely coincidental or do they perhaps point to something more significant in why and how autism happens?

"It's not uncommon for many parents of autistic children to report that their children would eat certain foods and that the behavioural symptoms would get worse," Dr. MacFabe says. "Digestive upsets would also appear to get worse as well, even though at the same time the child would be craving the food. Then the families would remove certain food products, such as foods with



Dr. Derrick  
MacFabe



David  
Patchell-Evans

gluten or casein and would report their child's behaviour improved. But was it only gluten or casein? Or could it be something else there in the gut, something that we were just not seeing yet?"

Dr. MacFabe began to suspect that this "something else" in the digestive system might be directly linked to brain function. "As we know, autism is a very complex condition and scientists are investigating it from all kind of perspectives—the genetics, immune function, behavioural effects, brain metabolism, environmental factors, and so forth. I began to wonder if there was something in common that could produce or exacerbate the plethora of effects being found in autism research from this diverse perspective," Dr. MacFabe says.

He found what appears to be a significant link in the bacterial compound propionic acid (PPA) which inhabits the gut. Many bacteria, particularly those which occur after long-term antibiotic exposure, produce propionic acid after using dietary carbohydrates from the food we eat. There is evidence that PPA can produce symptoms of hyperactivity, repetitive motions, and social impairment, similar to behaviours seen in autism. Repeated exposure to PPA appears to increase the severity and the duration of these symptoms. There are also indicators that PPA can have permanent effects on the brain, including the development of a unique neuroinflammatory response similar to that found in a Johns Hopkins study of the brains of autistic patients.

Propionic acid in itself is quite benign. Indeed it's natural. We all have it in our digestive system. It's part of a family of compounds called short chain fatty acids, important in normal gut and brain development and function. And it's also a common preservative in processed wheat and dairy foods. So what could be making it go awry and possibly reach the brain in high amounts to affect behaviour in such a dramatic way? That's the nature of Dr. MacFabe's quest.

His research has been published in peer-reviewed journals such as *Behavioral Brain Research*, the *American Journal of Biochemistry and Biotechnology*, and *Neuropharmacology*. The story of how this research got started is unique in the Canadian scientific community. Dr. MacFabe recalls the moment when Patch, after hearing about Dr. MacFabe's research ideas, looked at him for a long moment and then said, 'What do you really want to do?'

"To me, it was like a miracle—a wonderful example of a philanthropic person going beyond his own personal heartbreak over his child and getting behind a major multi-disciplinary project that could have the potential to affect millions of lives," Dr. MacFabe reflects. "Patch was willing to act on my hunch. Without him, we would certainly not have the results we have today."

For his part Patch says "I have chosen to support this research because I want to do something that will eventually alleviate the suffering of these families, because believe me, as a parent of an autistic child, I know how hard it is. I want autism to become a thing of the past."

In 2007 Patch received the Canadian Medical Association's Medal of Honour for his personal contribution to the advancement of medical research in Canada. The National Science and Engineering Research Council of Canada named Dr. MacFabe's UWO team and the research as among the top 50 scientific discoveries in Canada in 2007.

The research has attracted the attention of major international centres, including the Brain Development and Disorders Project at the Massachusetts Institute of Technology (MIT), George Washington University, and Sweden's Karolinska Institute and the Nobel Institute. Dr. MacFabe has been invited to speak as a keynote at major autism symposia across North America and Europe.

Dr. MacFabe has found possible links with other branches of autism science. He has found that PPA affects electrical activity in the brain relating to the

underappreciated presence of seizures in the disorder. It can also turn certain genes on and off—genes associated with brain development, learning and behaviour. It leads to impairment in brain-fat metabolism, known as “oxidative stress” which can damage proteins and lipids. It interferes with glutathione, the brain’s “cleaner-upper”. If glutathione doesn’t function normally, a person could possibly become over-sensitive to a variety of environmental toxins and metals. PPA also appears to put a “wrench” in mitochondrial metabolism, leading to increased production of toxic compounds called free radicals. This has major implications for neuron damage and the way the body uses dietary fats as fuel. PPA also can shut down the brain’s gap junctions (microscopic tubes which connect cell to cell), important in digestive system motility and brain development. It has an effect on cytokines in the gut, bloodstream and central nervous system, possibly leading to inflammation.

Now Dr. MacFabe is looking for the clue as to why this PPA-digestive system connection appears to happen to some children and not to others, and more importantly, why is the incidence of autism still rising?

“We suspect it’s about the balance of bugs in the gut,” MacFabe says. “There’s a normal level of bacteria we need in order to be healthy—our ‘good bugs’. But when things get out of balance and the normal bacterial level is disturbed, you can get the overgrowth of certain types of bugs. Over-use of antibiotics, both in patients with autism and in the general population may be one of the major factors here. Bacterial compounds may then have a profound effect on the brain and behaviour, particularly in early childhood or perhaps even in the fetus in the womb.”

Some children are exposed to antibiotics early in life if they have a history of throat or ear infections. Some women may have increased exposure to antibiotics if they had to take them just before or during pregnancy. One of the effects of widespread antibiotic use is that certain types of bacteria are becoming anti-biotic resistant (the so-called “super bugs”). Of particular concern is a gut bacteria known as clostridia which has been much in the news recently as becoming a major health problem affecting hospitals.

Why is MacFabe zeroing in on clostridia as a possible piece of the PPA puzzle? “There is research showing that clostridia, and not just foods alone, actually make PPA after breaking down dietary carbohydrates,” Dr. MacFabe explains.

Researcher Dr. Sydney Finegold of the UCLA School of Medicine recently published a paper flagging clostridia. He found a higher incidence of clostridia spores in autistic children than in children who do not have autism. He too noted a connection between propionic acid and clostridia, citing MacFabe’s research in his article and noting that “propionic acid is produced as a metabolic product by a number of intestinal bacteria, including some clostridia.”

Is this combination of PPA and clostridia a “smoking gun” in autism? “We need to be very cautious and not jump to premature conclusions. Autism is complex and many factors come into play. An important part of the puzzle appears to be the fact that some children genetically are better than others at breaking down this compound, providing a potential link to genetics and environment in the risk of a child developing autism. Our findings certainly merit further investigation,” MacFabe says. “I believe this is a promising and very important new direction for autism research.”

One thing is certain—this story of the scientist and the CEO, working together to change despair into hope, will continue to unfold.

Visit Dr. MacFabe’s website: <http://psychology.uwo.ca/autism.htm>

