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REVIEW AND COMMENTARY:

CBC – The Nature of Things with David Suzuki: Autism Enigma

Abstract

The purpose of this article is to introduce readers to a CBC documentary about a topical new research direction in autism – namely the possibility of a relationship between autism and bacteria in the gut. Key topics and controversies covered in the documentary are highlighted. Relevant background information, commentary, and references have been included to permit a critical perspective.

Autism has quickly changed from being a somewhat rare disorder to the most commonly identified developmental disability in the industrialized world. Since 1990, we have seen in North America an increase of about 600 per cent in children identified with autism (Hertz-Picciotto & Delwich, 2009; Suzuki, 2012). As of 2013, there are no accurate statistics on the prevalence of autism in Canada, though epidemiological research studies are underway (National Epidemiologic Database for the Study of Autism in Canada, 2012). In 2012, the prevalence in the United States was reported to be 1 in 88 based upon data collected between 2000–2008 (Centers for Disease Control and Prevention [CDC], 2012). A new National Interview Survey from the United States based on parent interviews is suggestive that the rate may be as high as 2% or 1 in 50 for children between 6 and 17 years of age, with boys being about four times as likely to be affected as girls (Blumberg et al., 2013). It has been argued that much of the prevalence increase since 2007 has been the result of diagnoses of children with previously unrecognized disorder (Blumberg et al., 2013). Nevertheless, the finding of a rapid rise of autism diagnoses, particularly in certain populations of new immigrants in certain geographical regions, strengthens the suspicion that there may be environmental causes (Barnevik-Olsson, Gillberg, & Fernell, 2010; Gruner & MacFabe, n.d.; Keen, Reid, & Arnone, 2010).

Autism is a general term that is more correctly described as a spectrum of disorders (i.e., autism spectrum disorders, ASDs). Three disorders – autistic disorder, Asperger syndrome, and pervasive developmental disorder – not otherwise specified (PPD-NOS), are usually considered part of the spectrum, but childhood disintegrative disorder and Rett syndrome sometimes also are included (Perry et al., 2011). What these disorders have in common are: qualitative impairments in social skills, qualitative impairments in verbal and non-verbal communication, as well as restricted and repetitive interests or behaviours and sometimes cognitive impairments (Perry et al., 2011). Traditionally, autism has

been considered a disorder only of the brain, but it is recognized that abnormal function of the gastrointestinal tract, as well as of the immune, hepatic, and endocrine systems also can occur in those affected (Herbert, 2005).

Current research is now providing a new perspective – the "Bacterial Theory." On *The Nature of Things*, hosted by David Suzuki, the episode *Autism Enigma* (Suzuki, 2012) discusses the possibility of a relationship between autism and bacteria in the gut. Although autism has previously been considered a permanent condition, it is possible that new research into gut bacteria might not only provide an explanation for autism, but also suggest a focus for viable treatments.

The human gut is populated by a large array of microbes that outnumber host cells more than 10 to 1, and that contain a total amount of genetic material that is 150 times the amount in the human body. These microbes are referred to as the *microbiome.* There is increasing recognition that the composition of the microbiome can be altered by changing factors in the environment. Changes in the composition and waste products of the microbiome are now suspected to play a role in the development of such conditions as obesity, diabetes, and allergies, as well as brain disorders such as depression, anxiety, and other mood disorders. The microbiome may also play a role in the development of autism (MacFabe, 2012). Of interest is that evolutionary biologists are considering the possibility that certain gut microbes may have evolved to "control" the host's behaviour or well-being in order to ensure both their and our mutual survival (Costandi, 2012).

One example of this symbiotic relationship is the colonization of the human gut by *Bacteroidetes* bacteria (e.g., *Bacteroides fragilis*). As explained by Wexler:

> The bacteria maintain a complex and generally beneficial relationship with the host when retained in the gut [they thrive in the nutrient rich environment of the gut and help to maintain proper physiological function of the host], but when they escape this environment they can cause significant pathology, including bacterium and abscess formation in multiple body sites. (Wexler, 2011, p. 260)

A second example of a symbiotic relationship between microbes and host is infection of cats with *Toxoplasma gondii*, a single-celled parasitic protozoan that also affects other warm-blooded animals, including humans (CDC, 2013). The parasite reproduces in the intestines of cats – their primary hosts. Infected cats release eggs of toxoplasma, which are then inadvertently consumed by intermediate hosts such as mice (Lee, n.d.). Once the mice are infected, they become attracted to cats. "Once a cat inevitably consumes the doomed creature, the parasite can complete its life cycle inside its new host" (Costandi, 2012, p. 33). The primary host (cat) benefits, as its prey is much easier to catch. As well, the microbes are assured of their transmission and, consequently, their existence. Presently under evaluation are effects of toxoplasma infection on human behaviour (Lee, n.d.).

Autism Enigma introduces viewers to the possibility that the high carbohydrate Western diet and long-term use of antibiotics could be environmental culprits that alter the nature of bacteria in the gut. By way of evidence to support this notion, several species of bacteria isolated from the stools of children with autism produce a waste product. Administration of this waste product into the brains of rats results in behavioural changes reminiscent of those in persons with ASD. This initial research lends early credence to the Bacterial Theory of autism – the view that there is at least some causal relationship between the microbiome and the development of autism.

In the past, a number of hypotheses have been proposed as possible causes of autism (detached mothering, watching television, pollution, drinking while pregnant, food allergies, and vaccination). These putative factors are mentioned in the documentary, although it is made clear in the documentary that there is no evidence that such factors are causal (Suzuki, 2012). In an interview with Christopher Sumpton, Professor Jeremy Nicholson raises the possibility that antibiotic use may be a trigger for autism. He says that "autism was only recorded as a disease in 1944 by Kanner," which is approximately when antibiotic use began (Sumpton & Nicholson, n.d.). Nicholson believes that antibiotics can alter the microbial balance in the microbiome, particularly in infants. This could cause effects in other

parts of the body, including the developing brain (Douglas-Escobar, Elliott, & Neu, 2013; Sumpton & Nicholson, n.d.).

Limited treatment options for ASD exist. Currently, early intensive behavioural intervention is most commonly recommended as an intervention in autism (Freeman & Perry, 2010). A recent meta-analysis has indicated that this approach "resulted in some improvements in cognitive performance, language skills, and adaptive behavior skills in some young children with ASDs, although the literature is limited by methodologic concerns" (Warren et al., 2011, p1). As mentioned in the documentary, autism is a spectrum disorder, so there is no typical case, and thus there is no single best way to structure interventions for all people.

The *Autism Enigma* documentary begins by showing the daily struggles of two families who have children with autism. One family has four children, two of whom are diagnosed with autism. The family immigrated to Toronto from Somalia. At a young age, it appeared that one of the sons was developing along a typical trajectory, but he began to exhibit symptoms of autism (such as isolation, lack of communication, and odd movements) after taking several courses of antibiotics for ear and chest infections. He also had many digestive problems, including severe diarrhea, suggesting a possible link between antibiotic use and these health issues. It was unclear from the documentary whether or not these problems had been present prior to the antibiotic use. Feeling desperate, the mother went to the annual AutismOne Conference. Through following this mother's experience, we learn that at this conference scientists, clinicians, and parents meet to learn about the most recent trends in scientific research into autism, as well as both established and unconventional treatments. There are usually no official protocols available to follow (Suzuki, 2012), which can be frustrating for parents and clinicians who want to use science-based treatments and therapies. The mother of this family returned from the conference with a few practical suggestions for helping her affected child.

The *Autism Enigma* documentary points out that the majority of recent research has been devoted to searching for a link between genes and autism. The documentary mentions that [as of 2007], the Autism Genome Project at the Hospital for Sick Children (SickKids) had identified 6 genes out of approximately 100 that are thought to contribute to the development of autism (Cecil, 2007). (As of 2013, up to 20% of autism cases have been found to be associated with a genetic mutation (Carter & Scherer, 2013).) The documentary also mentions that it is known from other studies that environmental factors could alter how genes function (e.g., environmental factors may result in genes to be turned "on" or "off" like a light switch), a process known as epigenetics (Kinney, Barch, Chayka, Napoleon, & Munir, 2010), as well as changes in gene expression (Latham, Sapienza, & Engel, 2012). The documentary points out that experiments could be carried out to test factors affecting how target genes replicate and turn on and off (Suzuki, 2012).

Dr. Derrick F. MacFabe, featured in the documentary, is a leading proponent of the Bacterial Theory of autism. He believes that the gastrointestinal problems of many people with autism could be significant to their condition. In a recent paper, he explained that the food that people eat can have major effects on "metabolism, immune function, and gene expression in many organ systems, including the CNS [central nervous system]" (MacFabe, 2012, p. 2). MacFabe's laboratory has been examining "the neurobiological effects of microbiota-produced short-chain fatty acids (SCFAs), such as *propionic acid* (PPA)" (MacFabe, 2012, p. 3). PPA is a fermentation product of many bacteria, including the intestinal species *Clostridia*, *Desulfovibrio*, and *Bacteroidetes*. Stool samples from patients with ASD have shown over-expressed populations of these species, as well as higher levels of PPA. These observations led MacFabe to propose that PPA is an environmental trigger of ASD. Brief infusions of PPA and related SCFAs into the brain ventricles (fluid-filled spaces in the brain) of rodents indeed produced "many behavioural, electrographic, neuropathological, and biochemical changes, consistent with an animal model of ASD" (MacFabe, 2012, p. 3).

With respect to treatment of autism, the *Autism Enigma* discusses vancomycin, an antibiotic used to treat infections caused by bacteria (Finegold, 2011a). Ellen Bolte's son Andrew, who has ASD, was featured. Her son's symp-

toms seemed to begin inexplicably around the age of 18 months. This form of ASD is called regressive autism because early developmental milestones are met, but children then regress to a state of withdrawal. Andrew appeared healthy, except for his gastrointestinal symptoms. "His stool was foamy, mucousy, [and] bulky" (Suzuki, 2012). He refused to eat solid foods, instead eating non-edibles such as tissues and ashes from the fireplace (Suzuki, 2012). The only difference that Bolte found between Andrew and her other children was Andrew's strong antibiotic use (six courses in just a few months) to treat what was initially believed to be an ear infection. It subsequently was determined that Andrew had a milk allergy, which is known to predispose to ear infections (Juntti et al.,1999). Because the use of antibiotics can impact bowel flora (Suzuki, 2012), Bolte concluded that autism could be due to a bacterial infection. She believed that an organism grows in the gut and produces a toxin; this toxin travels to the nervous system and causes the disorder. She asked her doctor to treat her son with oral vancomycin, which is not readily absorbed when taken orally (WebMD, 2013). Because this antibiotic remains in the gut longer than some other antibiotics, Bolte hoped that it would be able to effectively fight the microbes that she believed were causing autism.

Dr. Sydney Finegold, in an interview with Marion Gruner, said that Bolte's son:

> had a dramatic improvement, starting within a few days and persisting for six weeks while he was still on the drug. This involved improvement in language skills. He actually had no language beforehand, but he picked up a few words, and even began to string together tiny sentences towards the end… He would listen to people and respond. He would look at them, which was quite different from his usual behaviour. He didn't have any fits of anger and generally was a much more, nearly normal child. (Gruner & Finegold, n.d.)

Unfortunately, once the treatment with vancomycin stopped, the child's condition worsened, and many symptoms of autism returned. According to the documentary, once the use of antibiotic ceased, the child regressed. It was postulated that regression resulted because with antibiotic treatment, the bacteria had formed spores, and with antibiotic withdrawal, bacterial proliferation resumed. However, a special diet and probiotics helped to maintain reduced symptoms to some degree. Subsequently, vancomycin was found to improve function in 8 out of 10 children with regressive-onset autism who were studied, though beneficial effects faded after treatment stopped (Sandler et al., 2000).

A logical question related to the Bacterial Theory is: If ASD is really related to bacteria in the gut, might it be possible for persons with autism to undergo a procedure (e.g., taking probiotics or having a fecal transplant) to populate the gut with "good bacteria" to compete with the offending microbes**?** The documentary does touch upon this. We learn from an interview with Dr. Emma Allen-Vercoe, that an important goal of her research is to identify the thousands of bacteria in the gut that may play very important roles in human health (including ASD), and to develop a suitable mixture of bacteria for gut re-population (Allen-Vercoe & Petrof, in press; Petrof, Claud, Gloor, & Allen-Vercoe, 2013). Dr. Allen-Vercoe's experiments are being done in a special culture system that has been dubbed the "Robogut."

Certain other questions arising from the Bacterial Theory were left unconsidered in the documentary. For example, if autism is associated with bacteria in the gut, might autism be a contagious disorder and spread to infect other people? Can the Bacterial Theory explain autism as a spectrum disorder – the varied forms of the disease being due to involvement of different types of bugs or different SCFAs? If gut bacteria create spores when subjected to hostile conditions, could an ideal environment be temporarily created in the gut to prevent spores from forming, and then quick action taken against the exposed bacteria? Might persons with autism have a genetic metabolic problem that leaves them unable to properly metabolize potentially toxic SCFAs (including PPA)? In this case, rather than targeting specific gut bacteria, might it be possible to neutralize or destroy PPA or other toxic substances before they reach other parts of the body (i.e., the brain) and cause serious effects? Might it be possible to develop vaccines against toxic gut bacteria? (Since the airing of *Autism Enigma*, papers relevant to certain of these questions

have appeared. Refer to Frye, Melnyk, & MacFabe, 2013, for information about genetic metabolic disorders and conditions that might affected the metabolism of PPA. For progress about the development of a vaccine against *Clostridium boltae*, an autism-associated bacteria identified in 2003, please see Pequegnat et al., 2013.)

The idea that microbes on various areas of the body have a role in human health and disease is gaining recognition by the medical and research communities. The National Institute of Health's Common Fund Human Microbiome Project was recently established to study effects of such microbes "upon human development, physiology, immunity, and nutrition" (National Institutes of Health, 2012). Although this project is not currently being applied to investigate associations with ASD, investigation of the involvement of the microbiome in autism could possibly lead to the expansion of the project to explore this new concept. The recent insight article in the Toronto Star explained that Dr. MacFabe's research is bringing together two of the hottest topics in medical research (i.e., ASD and the function of microbes in the gut), but cautions: "A potential gut-autism connection is complex, controversial and not well understood. Many physicians are skeptical and caution that research is in the early stages" (Gordon, 2013). Hence, as previously articulated, documentary viewers – especially families and care providers of persons with autism – need to be aware that the Bacterial Theory is still in the hypothesis stage (Finegold, 2011b).

Despite these caveats, the *Autism Enigma* on *The Nature of Things* gives viewers information on some intriguing new ideas concerning ASD. The documentary follows specific patients and their families through treatments, and shows interviews with parents, to demonstrate the difficulties of the fight against autism. It was very successful in its main goal of offering information about the Bacterial Theory, as well as on advancements of current theories and projects, including the Autism Genome Project, rather than questioning the validity of the ideas. It did raise the possibility that modification of diet may help in some cases. However, voices of people with autism are missing from the documentary; others are always talking for them. It would have been helpful to hear from Ellen Bolte's son if he minded treatment with vancomycin, how he felt after being treated with this medicine, and if he felt better even for a while. Despite this deficiency, it is certainly a worthwhile experience to watch *Autism Enigma* to learn more about autism and the new Bacterial Theory.

Much is still unknown about autism. Research into causes and possible treatments for ASD should continue to be diverse in order to explore all possible avenues to understanding the nature of this complex condition (Chaste & Leboyer, 2012; Keen, Reid, & Arnone, 2010). Perhaps with another decade of multidisciplinary research, potential interactions between nature and nuture in the ASDs will be clearer and better understood.

Key Messages From This Article

Persons with ASD: It is important for your voice to be heard if you are invited to take part in a research study. It is important for you to say how you feel during a research study.

Professionals and careproviders: The ASDs are complex conditions. Please consider taking part in new research initiatives to further our understanding of the role of gut bacteria in these disorders.

Policymakers: New research into gut bacteria might not only provide a deeper understanding of all aspects of the ASDs, but also lead to feasible treatment strategies. Such research should be identified as high priority, and the level of funding for research in this area should be markedly increased.

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