

# Changing the course of autism: The science and intervention

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## Abstract

### Introduction

The international conference, “Changing the Course of Autism: the Science and Intervention”, organised by the UK charities Autism Treatment Trust (ATT) and Treating Autism (TA), provided a platform for a panel of international autism researchers and clinicians to present their latest research, current understanding of the pathologies associated with autism and interventions targeting these pathologies. The conference was held at the Royal College of Physicians of Edinburgh, in Scotland, on the 12<sup>th</sup> and 13<sup>th</sup> of June 2013.

### Meeting report

The central topics discussed were: dysfunction of the immune and gastrointestinal systems, the role played by the environment, importance of diet and nutrition, the health-comorbidity issues associated with the condition and the impact of environment and medical problems on the brain. Implications for diagnosis and intervention were also discussed.

### Discussion

Autism is a neurodevelopmental condition now affecting 1 child in 50 in the USA and 1 child in 66 in the UK. For the last two decades, the numbers of affected children have continued to rise world-wide, without any sign of reducing. Identifying the

environmental and genetic factors at play is essential to develop effective remedial and preventive intervention strategies. The condition is commonly associated with a range of health problems with the most commonly encountered affecting the immune and digestive systems as well as metabolism. These can be identified through appropriate biomedical testing and clinical investigations. Treating these abnormalities can lead to significant improvements in the child's health, development, social communication skills and behaviour. The current state of scientific and medical understanding of the condition enables to propose a convincing paradigm to explain the pathologies and developmental features of the condition.

### Conclusion

From the standpoint of public health and human rights, this framework makes it imperative to expand our understanding of how to choose the best treatment routes for affected individuals, and to implement these measures without delay.

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The authors have referenced some of their own studies in this meeting report. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

### The Science

Autism spectrum disorders (ASDs) are defined by impairments in social communication, the presence of repetitive and stereotyped behaviours and sensory integration dysfunction<sup>1</sup>, although these appear to be the tip of the iceberg of a much broader spectrum of problems that also span medical and physiological dimensions.

The prevalence of ASDs has continued to rise in the last two decades and autism is now affecting 1 child in 50 in the USA and 1 child in 58 in the UK<sup>2,3</sup>. It is estimated that 40-65% of this increase in prevalence cannot be attributed simply to greater awareness and recognition<sup>4,5</sup>. The Centres for Disease Control (CDC) in the USA has recognised that ASDs constitute a major public health concern, requiring ongoing public health surveillance and a coordinated response between federal, state and private partners to identify the risk factors at play<sup>6</sup>.

Dr Martha Herbert, from Harvard Medical School, USA, introduced the conference, calling for the redefinition of autism as a chronic dynamic state, as opposed to a fixed-trait disorder<sup>7,8</sup>. Evidence available today shows that

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autism is not a genetic-only, lifelong, hardwired brain disorder, but a dynamic condition that may be modulated throughout the life of affected individuals<sup>9,10</sup>. A study published by Fein et al. earlier this year demonstrated that overcoming the symptoms of autism is possible, a progression that the authors referred to as an “optimal outcome”<sup>11</sup>. Emergence from isolation and dependence to engagement in everyday life is a highly desirable outcome for affected people, even if full recovery remains elusive.

Dr. Herbert presented evidence that autism is not the fixed output of an abnormal, static developmental wiring programme, but the moment-to-moment expression of atypical patterns of brain function that arise as a consequence of impairment in physiologic mechanisms within cells and tissues that impair the ability of the brain to function at its full potential<sup>7</sup>. This makes it a whole-body disorder, wherein many aspects can be modulated that can in turn improve brain function. This novel paradigm suggests that there are many ways presently available to approach treatment and achieve improvement.

Dr Mady Hornig, Director of Translational Research in the Centre for Infection and Immunity and Associate Professor of Epidemiology at the Columbia University Mailman School of Public Health, USA, followed up on this framework, providing further evidence from animal studies that inflammation, infection and autoimmunity are implicated in the pathogenesis of ASDs<sup>12</sup>.

Environmental factors including toxicants and infective agents are thought to be central to the development of at least a subset of these disorders. For some of these agents, exposure is relatively rare; however, for many, the exposure is common. Explaining who gets sick, when and why, is especially challenging when exposure is ubiquitous in a given population.

Inflammatory and autoimmune parameters can be persistently altered in individuals with autism, leading to an array of behavioural and developmental dysfunction that is characteristic of ASDs. A “three strikes” model of causality is proposed, involving: (1) the timing of the exposure; (2) the combination of specific environmental factors; and (3) the genetic susceptibility of the individual. In this model, it is argued that the persistent abnormal expression of key immune factors compromises the integrity of the blood-brain barrier, allowing both exogenous (infectious, xenobiotic) and endogenous (autoantibodies, cytokines) substances to invade the central nervous system (CNS) and impair cognition.

Equally, the alteration of the microflora and healthy functioning of the gastrointestinal tract and other peripheral organs can contribute to immune and neurochemical disturbance in the blood, and thereby have a negative impact on the maturation and functioning of the CNS. Dr Hornig proposes that microflora-related dysregulation of brain-immune signalling is a critical component of the complex mechanisms leading to the development of autism and to the exacerbation of its clinical features<sup>12</sup>.

Professor Vera Stejskal, Associate Professor of Immunology at Stockholm University, Sweden, presented evidence of an overactive immune system and increased systemic inflammation in children with autism. Professor Stejskal proposes that these imbalances are caused by food allergies, especially to gluten and casein, as well as exposure to environmental pollutants such as nickel and mercury. With the help of an in vitro test MELISA<sup>®13</sup>, it is possible to identify the presence of allergen-specific memory T-cells in some autistic children.

Based on the results, treatment should follow the golden standard in allergology: avoidance of the relevant

allergen. This will result in reduction of inflammation and improved health.

Dr. Alex Richardson, Senior Research Fellow, University of Oxford and Founding Director of FAB Research, discussed in greater detail how human diets have changed dramatically over the last century, and their potential association with human disease. Abundant evidence now links modern, western-type diets – rich in highly processed, refined foods – not only to increased rates of ‘degenerative’ physical health problems such as cardiovascular disease, cancers, obesity and Type II diabetes, but also to a wide range of conditions affecting mental health, development and well-being<sup>14,15</sup>.

Nutrition affects the development and functioning of the brain as well as the body, and is now recognised as making a significant contribution to the most common and disabling mental health conditions, including depression, psychosis and dementia as well as childhood developmental conditions such as attention-deficit/hyperactivity disorder (AD/HD) and ASD<sup>16,17</sup>.

Brain development and function are inextricably linked with the health of the gut and the immune system, and industrialisation has changed the nutritional composition of human diets in many ways that are known to be pathological for both brain and body. These include: (1) dramatic increases in intake of sugars and other refined carbohydrates (and a corresponding lack of fibre and essential micronutrients) and (2) substantial changes in the type and balance of dietary fats – with a particular increase in the ratio of omega-6/omega-3 polyunsaturated fatty acids (PUFA). Conditions affecting mental health and well-being show high comorbidity with many physical health conditions, and increasing evidence supports the idea that dietary interventions can be helpful in the management of both.

Dr. Lorene Amet, Research Director, Autism Treatment Trust (ATT), reported that in a sample of 360 autistic children seen at the Trust, 59% presented with chronic clinical

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gastrointestinal (GI) complaints, characterised by abnormal bowel movements (74%), chronic constipation (31%) and/or diarrhoea (30%), abdominal bloating (30%) and abdominal pain (31%)<sup>18</sup>. Commonly, the children with affected digestive systems presented with abnormal body posturing (32%), such as leaning over furniture, to provide relief to pain arising from their lower abdomen. Children with autism also commonly present with severe chronic immune problems (observed in 65% of a group of 258 children with autism at the ATT clinic). These include eczema (24%), repetitive chronic and long-lasting infections (36%), food and/or inhalant allergies (37%) and asthma (7%).

These clinical signs and symptoms suggest the existence of comorbid health issues associated with ASD, as reported by the CDC in a large scale, epidemiologic study conducted in over 5000 children with developmental disability and 35,000 neuro-typical children<sup>19</sup>, and as recently reviewed by the two conference organising charities, ATT and TA<sup>20</sup>.

These health comorbidity issues were linked to abnormal behaviour. Indeed, children with chronic gut problems were more likely to present with hyperactivity ( $p = 0.002$ ); children with current GI problems were more than twice as likely to demonstrate hyperactivity than children without GI problems.

Sleep issues were also more prevalent in children with GI problems, with GI-affected children being nearly twice as likely as children without GI problems to also have sleep problems ( $p = 0.010$ ). Abnormal fits of crying spells, occurring suddenly and even at night time were also more likely in children with current GI problems than in those without such problems (odds ratio [OR] = 1.80,  $p = 0.024$ ). In addition, immune problems were tightly associated with self-injurious behaviour (OR = 1.85,  $p = 0.028$ ).

Developmentally, the children presenting with GI disturbances were also twice as likely to have experienced regressive autism, characterised by a loss of acquired skills in the areas of communication and socialisation, and also to present with novel, deviant, restricted and repetitive behaviours ( $p = .018$ ). In terms of biologic markers, 20% of children presenting with chronic GI issues presented with abnormal levels of faecal calprotectin, a surrogate marker of inflammatory bowel diseases that are characterised by pathological inflammation of the bowel wall. Our results also show that another surrogate marker for cell immunity, called neopterin, was found to be significantly correlated with isoprostane, a marker of oxidative stress ( $r = 0.547$ ,  $p$  (one-tailed)  $< .001$ , the  $R^2$  value of .299 indicates that the markers account for 30% of the variation in the levels of each other).

These findings indicate that the GI and immune problems encountered in autism are related to a range of behavioural and developmental abnormalities, and are associated with peripheral blood markers of inflammation, consistent with other reports<sup>21,22,23,24,25</sup>. Current scientific and medical knowledge regarding the clinical features and pathogenesis of ASDs calls for proper diagnosis and treatment<sup>20</sup>.

### Intervention

Professor Mike Snape (Autism Therapeutics Ltd.), speaking on behalf of Neuren Pharmaceuticals Ltd., talked about the current progress of the clinical trial conducted in Rett Syndrome with NNZ-2566, an analog of the terminal tripeptide of Insulin-Like Growth Factor 1 (IGF-1[1-3]), a molecule with anti-inflammatory effects. IGF-1, a naturally occurring growth factor functioning throughout the body and CNS, plays many roles in regulating growth and in preventing inflammation and cell death. NNZ-2566 is a novel, modified analog of IGF-1[1-3] that crosses the blood-brain barrier, is orally available and reduces neuroinflammation. NNZ-

2566 has a profile suitable for investigation in Rett and Fragile X Syndromes as well as in ASDs. MeCP2 and Fmr1 knockout (KO) mice are two preclinical models appropriate for assessment of putative drug treatments in Rett Syndrome and Fragile X Syndrome, respectively. MeCP2 KO mice have reduced life expectancy, behavioural abnormalities and cardiorespiratory irregularities. Fmr1 KO mice manifest phenotypic deficits similar to those seen in Fragile X Syndrome, including hyperactivity, short- and long-term memory deficits, learning and sociability impairments, reduced dendritic spine density and decreased phosphorylation of the signalling molecules, ERK and Akt.

Treatment with NNZ-2566 significantly ameliorates these aberrant features. NNZ-2566 significantly reverses these symptoms. Neuren is progressing with a clinical study of NNZ-2566 in Rett Syndrome (ClinicalTrials.gov Identifier: NCT01703533), ongoing at Baylor College of Medicine. This is a Phase IIa safety study in 60 adolescents and adults with Rett Syndrome. The study assesses the safety and tolerability of NNZ-2566 in Rett Syndrome along with effects on potential signals of efficacy, including EEG and measures of cardiorespiratory status and general function. The study has an estimated primary completion date of March 2014.

Dr. Nicola Antonucci from the Biomedical Centre for Autism Research and Treatment, Bari, Italy, presented his approach for clinical identification of the pathological processes at play in affected individuals and in treating the condition. The use of biomarkers in areas of inflammation, detoxification, oxidative stress, cellular energy production and metabolism can inform clinicians and researchers of the possible pathological mechanisms and guide medical interventions in a targeted and individualised manner.

Dr. Dario Siniscalco from the Second University of Naples, Italy, discussed the use of stem cell therapy in the treatment of ASDs. Central to this therapeutic approach is the restoration

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of immune and neural system regulation in ASDs. Several therapeutic processes are likely implicated in this therapy: (1) a stem cell self-renewal capacity (the ability to generate additional, identical stem cells), (2) a capacity to give rise to differentiated cells (with pluripotent, regenerative potential), (3) a paracrine regulatory capacity (the capacity to synthesize and secrete an array of key regulatory molecules) and (4) an immunomodulatory capacity (the ability to restore normal immune balance)<sup>26</sup>. Stem cell therapies in ASDs are, however, still in their infancy, and further clinical studies are needed to more clearly establish their safety as well as their therapeutic merits<sup>26,27,28</sup>.

Dr. Daniel Goyal, Neurosciences Department, University of Manchester, talked about comorbidity and the neuro-immunological approach to ASDs<sup>20</sup>. Dr. Goyal detailed the clinical symptoms associated with ASD, for example, the high prevalence of ear and throat infections, allergy problems and GI issues. Dr. Goyal explained how to address these problems clinically and the importance of developing strong liaisons with the child's medical practitioner to provide and monitor treatment. Dr. Goyal works in association with Angelette Muller (Nutrition Therapist) and Sue Simmons, Nutritional Therapist. Angelette Muller explained how to optimise the diet to promote healthier function and Sue Simons talked about the types of nutritional supplementation that can be used to address GI, immune and mitochondrial problems.

### Discussion

The societal, family and individual burden of autism is staggering. Conceptualising autism as a dynamic condition associated with treatable comorbidity - in which environmental exposures appear to play a key role -, rather than as a fixed-trait, purely genetic disorder, new paths that can lead to restoration and recovery may

be considered feasible. Central to autism pathogenesis are impairments of the immune, digestive and metabolic systems and their impact on the functioning of the CNS. A 'three-strikes' model of causality is proposed, in which timing of the exposure, the nature of the environmental factors and genetic vulnerability together determine the extent of developmental insult. Every effort must be made to provide an early diagnosis and to identify the specific interventions each ASD child needs. Every effort must be made to uncover the environmental factors that are implicated so that prevention and intervention programs can be targeted toward elimination of these agents, or mitigation of their effects.

Treatment options and lifestyle modifications such as diet are currently available and can make a large difference in the level of function for many individuals and in the quality of life for them and their families. More treatments are under development or being refined.

### Conclusion

It is therefore the view of the authors that many autism cases are likely to represent preventable and treatable conditions. From the standpoint of public health and human rights, this framework makes it imperative to expand our understanding of how to choose the best treatment routes for affected individuals, and to implement these measures without delay.

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