

The incidence of so-called autism spectrum disorders has increased dramatically over the past three decades. However, with modern biomedical therapy, such conditions are no longer regarded as incurable, as Richard A Collins explains in this report from the Asian Autism Conference held in Hong Kong.

Biomedical intervention and prospects for recovery from autism

There has been much controversy in recent years over the dramatic increase in the incidence of autism and autism spectrum disorders (ASD). The most controversial claim was the proposed link between the development of autism and the measles/mumps/rubella (MMR) vaccine.¹

In the USA, the prevalence of ASD is one in 166, a 15-fold increase since 1976.² Data from the UK indicate a similarly alarming rise. For example, the prevalence of 'autistic syndrome' in England and Wales in 1976 was four/five per 10,000.² Thirty years later, the prevalence of childhood autism in the South Thames region was 38.9 per 10,000.³ The phrase 'autism epidemic' has been used to describe this trend.⁴

Despite the apparent upsurge in ASD, there has been a major change in the response to diagnosis, as ASD no longer is considered untreatable and incurable.

'Reducing neuroinflammation by enhancing natural detoxification pathways may improve the clinical course of autism spectrum disorders'

'Autism is a pervasive developmental disorder defined by characteristic developmental and behavioural features that occur before the age of three years'

There is hope of recovery. This was the message from the Asian Autism Conference held in August at the Hong Kong Academy of Medicine.

The conference was organised by the Autism Parents Network Foundation (APNF), a Hong Kong-based parents' support group. It emphasised the paramount role of biomedical intervention and therapeutic approaches such as applied behaviour analysis in effecting recovery from ASD.

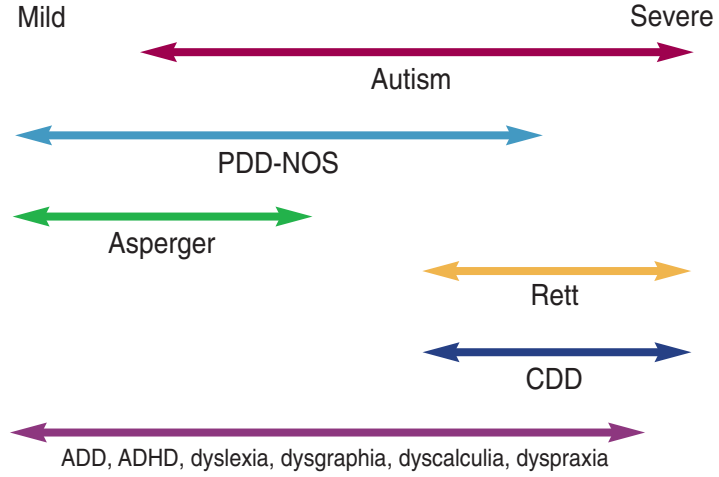
The conference attracted over 300 participants from Hong Kong and other parts of south-east Asia including Japan, South Korea, Philippines, India, Singapore, Malaysia, Macau, Taiwan and the People's Republic of China. One-third of participants were medical practitioners. Parents and professional groups including paramedics, therapists, clinical psychologists, academics and teachers of children with special needs comprised the remainder. The aim of the conference was to improve understanding of the advances in treatment methods, correct misconceptions about the cause and treatment options available, and strengthen frameworks for managing treatment strategies so that informed decisions can be made.

What is autism?

Autism is a pervasive developmental disorder defined by characteristic developmental and behavioural features that occur before the age of three years. These include: qualitative impairment in social interaction (eg marked impairment in the use of multiple non-verbal behaviour, such as eye-to-eye gaze); qualitative impairments in communication (eg delay in, or total lack of, the development of spoken language); and restricted, repetitive and stereotyped patterns of behaviour, interests and activities (eg inflexible adherence to specific, non-functional routines or rituals).⁵

Autism spectrum disorders include Asperger's syndrome (also known as high-functioning autism), Rett's disorder, childhood disintegrative disorder and pervasive developmental disorder not otherwise specified (PDD-NOS).⁵ The disorders vary greatly in their severity, and the boundaries between specific diagnoses are often blurred. Many practitioners in this field now consider attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD) and other specific language deficits (eg dyslexia) among the ASDs (Fig 1). The theories of the causes of

Fig 1. The range of autism spectrum disorders (ASD), which are a group of pervasive developmental disorders that vary greatly in the severity of their symptoms. Apart from classical autism, ASDs include pervasive developmental disorder not otherwise specified (PDD-NOS), Asperger's syndrome (also called high-functioning autism), Rett's disorder (a genetic abnormality mostly affecting girls), and childhood disintegrative disorder (CDD), noted for its relatively late onset of symptoms (2–10 years of age). Other specific conditions have also been attributed to the ASDs, including attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD) and other learning disabilities such as dyslexia (difficulty reading and writing), dysgraphia (difficulty writing), dyscalculia (difficulty using numbers) and dyspraxia (difficulty in coordinating movement).



autism are too numerous to mention here, but ASDs are likely to be due to a combination of innate genetic and external environmental causes.

What is biomedical intervention?

The fundamental concept driving biomedical interventions for ASD is the profound interaction between the intestine and the brain (Fig 2). It has been proposed that damage to the gastrointestinal (GI) lining allows partially digested proteins to enter the bloodstream and cross the blood-brain barrier to affect the normal development and function of the brain, leading to many of the characteristic symptoms of ASD. These peptides, derived from the major wheat and milk proteins gliadin and casein, are called gliadomorphins and casomorphins, respectively, for their ability to affect the brain in a way similar to endogenous opioid peptides and the drug morphine.

A Cochrane review of combined gluten-free, casein-free diets in autistic subjects noted the significant reduction in autistic behaviours while on the diet, but other

characteristic symptoms (cognitive skills, linguistic ability and motor ability) were not significantly reduced.⁶ Left uncorrected, it is hypothesised that persistent GI damage results in reduced nutrient/mineral/vitamin absorption and dysbiosis of GI flora, which is manifested as an overgrowth of undesirable bacteria (eg *Clostridium* spp) and yeasts (eg *Candida* spp.). Biomedical intervention aims first to address the profound nutritional deficiencies that may be involved in the induction of autistic behaviours.

Probiotics and toxins

It is impossible to do justice to the detailed presentations made by the speakers during the conference; however, some highlights illustrate the range of topics covered.

Dr Jacquelyn McCandless gave several presentations over the course of the conference, focusing on the diagnosis and biomedical treatment of ASD. McCandless outlined an eight-point biomedical treatment plan for ASD (Table 1) emphasising dietary restriction (gluten-free, casein-free, soya-free) to reduce the amount of partially digested

and antigenic dietary proteins released into the bloodstream, nutrient therapy (supplementation of minerals, especially zinc and magnesium and vitamins A, C, D and E), and GI pathogen treatment (systemic antifungals and antibiotics and supplementation with probiotics such as *Lactobacillus acidophilus* and *Bifidobacterium bifidus*). Once the intestine is healed – a process that may take several months – measures can be taken to correct other components of metabolism that may be dysfunctional. These may include supplementing the metabolic methylation pathways, removing heavy metal contamination with chelating agents or enhancing the immune system.

Dr Kenneth A Bock (Rhinebeck Health Center and Center for Progressive Medicine, New York) emphasised the importance of individualising treatment when planning a biomedical intervention programme for children affected by ASD. Bock reviewed the potential damage to the neurological and immune systems from environmental toxins. A key finding was the fact that small amounts of compounds, below the concentrations considered individually toxic, may act synergistically with profound adverse effects on physiological function.⁷ Coupled with an exposure to a cocktail of environmental toxins, the body's ability to detoxify these substances is often impaired in people with ASD. This leads to an overload of toxins in the body, which may result in oxidative stress and chronic inflammatory conditions such as colitis, atopic dermatitis and asthma.

Neuroinflammation has been found in autistic patients.⁸ Reducing neuroinflammation by enhancing the body's natural detoxification pathways may improve the clinical course of ASD. To achieve this, Bock uses the 'therapeutic quintet' of methylcobalamin (the metabolically active form of vitamin B₁₂ in the central nervous system), folinic acid (a metabolically active form of folic acid), trimethylglycine and thiamine tetrahydrofurfuryl disulphide (methyl and sulphate donors, respectively, in detoxification reactions) and glutathione (an

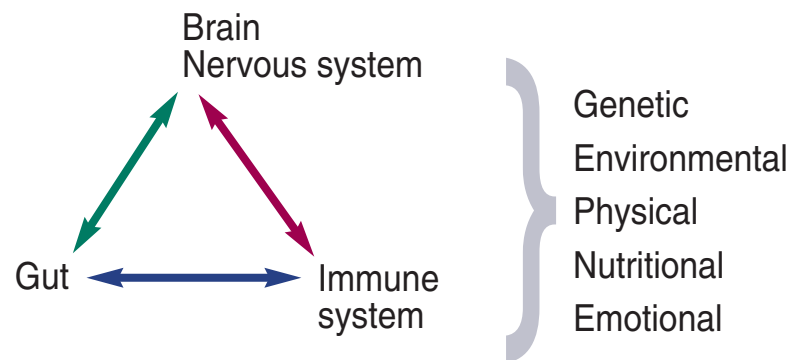


Fig 2. Interplay of factors influencing ASD. The brain/nervous system, intestine and immune system are interrelated. They may influence the onset and/or severity of ASD symptoms via a number of different factors: genetic predisposition (epigenetics, single nucleotide polymorphisms, mutations), environmental (heavy metal accumulation, thimerosal-containing vaccines, infections), physical (leaky gut, dysbiosis), nutritional (vitamin/mineral deficiencies/imbances) and emotional (hormones, stress).

antioxidant and free-radical scavenger). Bock underscored the importance of including behavioural and educational therapies as components in any recovery programme.

Dr James A Neubrander (Edison, New Jersey) reviewed the function of methylcobalamin and its derivatives in the methionine/homocysteine recycling pathway and how they affect several metabolic pathways important in maintaining intracellular function. Neubrander has advocated the use of methylcobalamin in the biomedical treatment of ASD for many years. He considers a long-term course of methylcobalamin injections (75 mg/kg/week) as the primary strategy in the treatment of ASD. Methylcobalamin is very well tolerated at high doses and improves executive function, speech and language, and socialisation and emotion in children with ASD.

Oxidative stress

Dr Jill James (Biochemical Genetics Laboratory, Arkansas Children's Hospital Research Institute) is an expert on gene-nutrient interactions that increase susceptibility to autism. She introduced the basic biochemistry and interdependence of folate/methionine/glutathione metabolism. The importance of glutathione as a key regulator of oxidative stress was developed. Interestingly, the vaccine preservative thimerosal has been shown to deplete glutathione *in vitro*, supporting the biomedical use of glutathione supplements in ASD.

In detailed studies on the metabolic profiles of children with ASD, James documented abnormal methylation and oxidative stress that correlated with the presence of specific genetic lesions and single nucleotide polymorphisms in genes related to methionine metabolism (transcobalamin II), antioxidant capacity (glutathione-S-transferase) and methylation (catechol-O-methyltransferase).⁹ However, no single polymorphism can predict increased risk for ASD. Specific combinations of these polymorphisms may interact to affect metabolic pathways that are important in the pathogenesis of ASD. James noted that the abnormal metabolic profile in children with ASD strengthens the hypothesis that an inability to control oxidative stress may be central to the development of the neurological, immunological and GI dysfunction that occurs in ASD.

Gastrointestinal issues

Dr Timothy Buie (Harvard Medical School) is a gastroenterologist renowned for his expertise in diagnosing children with GI complications of autism. Buie demonstrated the difficulties in diagnosing medical issues in autism. The presentation incorporated actual video film of three patients with what appeared to be classical symptoms of autism. These patients all had non-obvious GI conditions that when identified and treated appropriately resulted in a marked improvement in their 'autistic' behaviour.

Table 1. Biomedical treatment protocol for autism spectrum disorders.

| | |
|--|---|
| • Dietary restriction | (gluten-free, casein-free, soya-free) |
| • Nutrient therapy | (vitamin/mineral supplementation) |
| • GI pathogen treatment | (antibiotic – eg metronidazole/gentamycin/vancomycin) |
| | (antifungal – eg fluconazole/itraconazole/nystatin) |
| • Methylation strategies | (methylcobalamin) |
| • Detoxification | (heavy metal chelation – eg EDTA, DMSA, DMPS) |
| • Immune enhancement | (omega-3 fatty acids, glutathione, probiotics) |
| • Antiviral treatment | (natural antivirals – eg garlic, olive leaf extract, oregano oil) |
| | (pharmaceutical antivirals – eg valaciclovir, famciclovir, aciclovir) |
| • Hyperbaric oxygen therapy, neurofeedback | |

Gastrointestinal issues have been a marked feature of autistic symptomology since the earliest studies. Indeed, the seminal paper on autism by Leo Kanner in 1943 noted that six of the 11 subjects investigated had "feeding or dietary" issues.¹⁰ However, these were attributed to autistic behavioural issues rather than to a co-existing or potentially causative medical condition.

A recent study evaluated 50 children with ASD and two control groups matched for age, gender and ethnicity. The control groups comprised 50 children with typical development and 50 with developmental disorders other than ASD. Gastrointestinal symptoms were reported in 70% of children with ASD, 28% of children with typical development and 42% of children with other developmental disorders.¹¹

Buie also highlighted some of the pitfalls of GI/autism research, with a large number of the reported studies indicating a link between GI problems and ASD being anecdotal. There are a lack of population-based data, with some studies suffering from referral and selection bias. Many of the current claims are uncorroborated by other researchers. Another limitation is that much of the current work attempts to offer GI issues as a cause of autism. A more promising approach might be to see GI issues as a contribution to autistic behaviour. However, there is clear evidence that medical issues, including GI disorders, exacerbate ASD. Recognition and treatment

'An inability to control oxidative stress may be central to the development of the neurological, immunological and GI dysfunction that occurs in ASD'

'Autistic symptoms frequently extend beyond the brain, often involving, for example, the GI tract and immune system'

of these medical conditions will improve functional outcomes and the quality of life in people with ASD.

A brain disorder?

Dr Martha Herbert (Massachusetts General Hospital and Harvard Medical School) posed the question: "Is autism a brain disorder or a disorder that affects the brain?" She discussed the growing body of research evidence which suggests that biomedical problems like inflammation and oxidative stress indicate that the brain may not be the prime target but rather caught in the crossfire of system-wide abnormalities whose treatment can lead to improved brain function.

Herbert explained that there are several reasons why a strong genetic, brain-based modular model of behaviour (ie gene expression affects brain structure/chemistry, which in turn affects behaviour) is inadequate when attempting to understand ASD (Fig 3). First, numerous genetic studies for ASD-related genes have produced highly variable and inconsistent results. In addition, the gross brain abnormalities that have been observed in some ASD subjects are not compatible with the rather precise nature of the modular model. Co-existing autistic features such as sleep disturbance, epilepsy and sensory issues also cannot be explained by the model. Furthermore, autistic symptoms frequently extend beyond the brain, often involving, for example, the GI tract and immune system. Finally, altered gene expression alone cannot account for the dramatic increase in ASD cases seen in the autism epidemic.

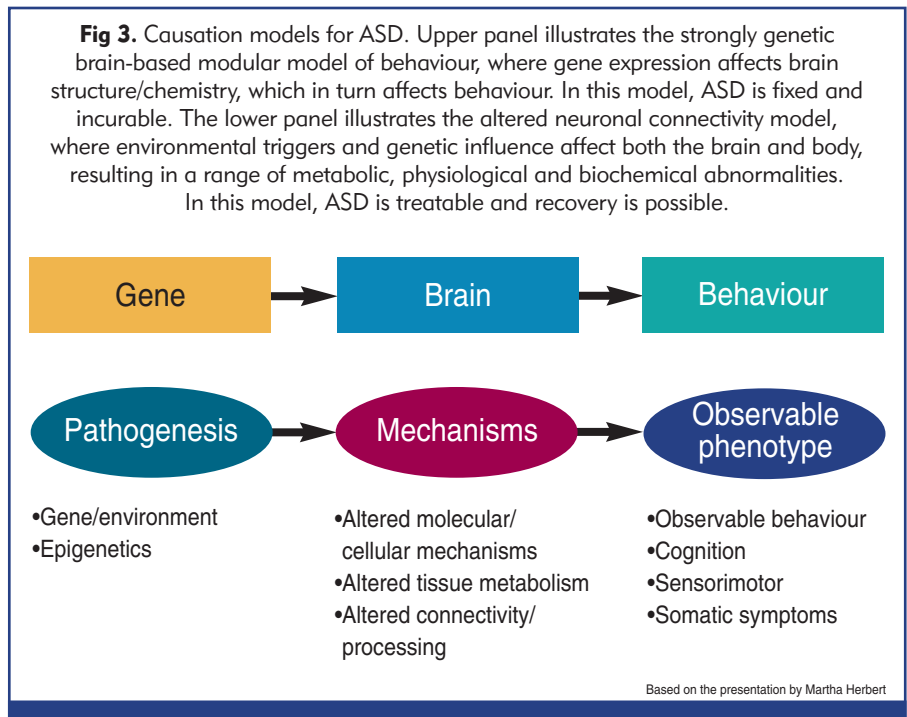
Rather than viewing ASD as a genetically predetermined and irreversible defect in the brain, it equally could be seen as a problem with neuronal network connectivity resulting from a physically sick brain. As noted earlier, neuroinflammation has been documented in ASD.⁸ Oxidative stress and inflammation can affect an array of cellular brain functions influencing energy production, the maintenance of cellular lipid membranes, neurotransmitter production and specificity and neuronal glial cell support activities, any of which ultimately may affect behaviour.

In summary, Herbert revised the model for the causation of ASD. Environmental triggers and genetic influences affect both the brain and the body, resulting in a range of metabolic, physiological and biochemical abnormalities. These abnormalities are treatable and recovery from autism has been documented. Indeed, one of the 11 cases of autism recorded in 1943 recovered following treatment for an immune disorder.

Heavy metals

Nutrition and behaviour were among the topics discussed by Dr Lillian Ko (Hong Kong Society for Child Health and Development). She presented an overview of ASD in Hong Kong and China. In 1985, a government-run child assessment centre identified 48 cases of ASD. In 2004, 388 cases were reported. Ko focused on the link between behaviour and heavy metal accumulation and toxicity. Mercury and lead are known to affect mental health and behaviour. The main source of mercury in Hong Kong is contaminated fish and seafood. Given China's rapid economic growth and concomitant environmental pollution, the problem of heavy metal toxicity in children in mainland China looks set to increase. Based on an incidence of five per 10,000, there could be 200,000 cases of ASD among China's 380 million children. Ko favours heavy metal detoxification using chelation therapy.

Heavy metal detoxification was the theme of the presentation given by Dr Anju Usman (True Health Medical Center, Illinois). She reiterated the view that many ASD subjects have environmentally-induced toxicity that is preventable, treatable and reversible. Heavy



metal toxicity, particularly from mercury and lead, is believed to be a prime candidate for triggering ASD.

Mercury is a potent neurotoxin and exposure is common, with the classical symptoms of poisoning being strikingly similar to autism.¹² Conjugation of heavy metals to glutathione is the primary mechanism of excretion and autistics have been shown to have low glutathione levels.¹³ After challenge with oral chelating agents (dimercaptosuccinic acid, DMSA) autistics excreted almost six-fold more mercury than did controls.¹⁴ Other useful chelating agents include ethylenediaminetetraacetic acid (EDTA) and dimercaptopropanesulfonic acid (DMPS).

A door to our world

Dr Tim Trodd (Hong Kong private practitioner) concluded the conference with a presentation on the practical aspects of treating ASD based on data gathered from some of the patients under his care. Among the wide range of topics covered in his talk, Trodd

described the use of DMSA as a heavy metal chelating agent in children with ASD. Eight local children with ASD were found to have high concentrations of mercury (mean 12.4 µg/mg creatinine) compared with a similar number of neurotypical children from the USA (mean 1.1 µg/mg creatinine). Trodd speculated that local children may have accumulated mercury from a variety of sources including thimerosal-containing vaccines (eg hepatitis B, diphtheria/tetanus [DT], diphtheria/tetanus/pertussis [DTP], influenza), high fish consumption, and mercury-containing dental amalgams. Interestingly, a recent study provides the first epidemiological evidence to show that the number of neurological disorders has decreased in the USA as thimerosal has been removed from childhood vaccines.¹⁵

Trodd summarised the key messages of the conference. First, the sharing of new knowledge and the development of a plan to execute that knowledge enable effective treatments to begin immediately. Second, the establishment of networks of parents and

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Fig 4. Panel of experts. From left to right: Lillian Ko, Martha Herbert, Tim Buie, Jacquelyn McCandless, Tim Trodd and Andrew Horton (APNF committee).

practitioners has the potential to spread the new knowledge to help the thousands and millions of children in south-east Asia with ASD. Last, treatment can only succeed if an holistic approach involving not only biomedical therapy but also psychological, behavioural and educational interventions is adopted.

As Trodd pointed out: "Biomedical interventions can build a door into our world – the other therapies can help pull the child through that door." ■

'Epidemiological evidence shows that neurological disorders have decreased in the USA as thimerosal has been removed from childhood vaccines'

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Dr Richard A Collins FIBMS is a research grant administrator in Hong Kong.

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