

# The Epidemic of Autism: Growing Neurobiological Links to Genetics, Environment and Behaviour

Dr. Derrick MacFabe, M.D.

## Director

**The Kilee Patchell-Evans Autism Research Group  
Departments of Psychology and Psychiatry (Division of  
Developmental Disabilities), Schulich School of  
Medicine and Dentistry, University of Western Ontario,  
London, Ontario, Canada, N6A 5C2  
dmacfabe@uwo.ca**

**Autism Spectrum Disorders-A Rapidly Increasing Problem of Western Society:** Autism comprises a spectrum of severe neurodevelopmental disorders of increasing incidence characterized by profound language impairment, impaired socialization, repetitive motor behaviour, sensory disturbances, severely restricted interests and self injury. There is also a high association with seizure disorder. Autism's prevalence, initially thought to be between 7 and 20 per 10,000, may now be greater than 1 in 150, an observation that cannot solely be accounted for by increased surveillance. Autism may co-exist with a number of neuropsychiatric conditions, including pervasive developmental delay, Asperger syndrome, fetal alcohol syndrome, thalidomide and valproate exposure, and a number of known genetic conditions. Remarkably, both classic neurological activities and gross brain function in most autistics are relatively intact, and in approximately 5 to 10% of documented cases, there is an idiosyncratic hypercompetency in some aspects of visual spatial, acoustic, computational and artistic behaviour. Autism is more common in males. Researchers such as Simon Baron-Cohen at Cambridge University have suggested that prenatal exposure to sex hormones may play a role. Cohen suggests that autism may result from a hyper masculine brain that is more suited to processing objects, as opposed to a feminized brain, superior to processing facial expression.

**Large Brains, Abnormal Cell Migration and Brain Inflammation:** Autism was originally thought to be caused by social factors such as poor parenting. However current research is now examining autism as a definable systemic disorder resulting in a number of diverse factors that may affect brain development and function both pre- or post-natally. Specifically, gross neuroanatomy of brains of patients with autistic disorder was thought to be largely unremarkable. Neuropathological work pioneered by Margaret Bauman, and recent imaging studies by Martha Herbert at Harvard, have shown subtle disorders in brain development, particularly involving areas concerned with language, movement, facial expression and social behaviour. Areas of interest include the cerebral and cerebellar cortices, the hippocampus, cingulate, amygdala and basal ganglia. Studies suggest that persons with autism

show enlarged brain size, particularly in the first few years of life, with altered migration and increased density of neurons in the above areas. Neuroimaging has found increased neocortical cortical and white matter thickness in young patients with increased cortical micro columns.

A recent neuropathological study by Carlos Pardo at Johns Hopkins University has shown evidence of inflammatory processes in the brain of young as well as adult patients. Notable findings include marked increases in reactive astrocytes, activated microglia, proinflammatory cytokines, as well as anti neuronal antibodies. Together these findings suggest that systemic immune mediated effects may be ongoing throughout the life of the individual.

**Genetic Sensitivity to Environmental Factors:** Despite the presence of multiple suspected genetic loci, a purely genetic link is elusive and appears over-simplistic. Notably, autism in identical twins is only approximately half of complete concordance and often of varying severity. Intrauterine factors occurring at critical periods in brain development probably play a role, given the similarities with neurological abnormalities from intrauterine exposure to ethanol, valproic acid, terbutaline or thalidomide, and prenatal infections. Supportive of this notion are studies that have examined the effects of early prenatal exposure to these agents in rodents. Administrations of these agents near the time of neural tube closure produce brain structural changes and altered social behaviour similar to some aspects of human autism. Geographical clustering of autism has been noted and links to broad environmental risk factors such as halogenated hydrocarbons and metals such as lead, cadmium and mercury have been proposed. Anecdotal reports note the acute presentation of symptoms in a subset of patients after apparently normal development in the first few years of life. This possible regression is associated with gastrointestinal symptoms, upper respiratory infections or following vaccination for paediatric viral diseases. Regarding the latter, the link between autism and the administration of the Thimersol-containing mumps measles rubella vaccine has received great media attention but has not been proven. This raises the possibility that other risk factors during this critical time period in paediatric brain development may be involved. The current consensus is that autism may comprise a family of disorders resulting from a genetic sensitivity to intrauterine or early post-natal exposure to a variety of environmental toxic or infective factors.

**Neurochemistry and Pharmacological Treatment:** The behavioural and biochemical aspects of autism resemble other conditions such as schizophrenia, obsessive compulsive and anxiety disorders, Tourette's syndrome and

epilepsy, and a number of rare paediatric neurological syndromes, which interestingly may involve inborn errors of metabolism. Drugs affecting dopaminergic transmission, such as haloperidol and risperidone, reduce impulsivity of movement and aggression, but do little to improve social integration. Abnormalities in serotonin physiology have been noted, including increased genetic expression of serotonin reuptake transporters, polymorphisms on 5HT2A receptor genes and increased platelet serotonin in autistic patients. Supportive of these findings, serotonin reuptake inhibitors have been found to improve symptoms in some patients. The findings are interesting given the role that serotonin plays in depression, obsessive compulsive behaviour, aggression, and anxiety, all common in autism.

As well, the role of other neurotransmitter systems, particularly glutamate, acetylcholine and GABA are currently under investigation. Recent work in rodents examining oxytocin in social behaviour and vasopressin in aggression by Susan Carter at the University of Illinois at Chicago. These compounds play major roles both in neurodevelopment and social behaviour, and may offer possible explanations of the male preponderance of the disorder.

**Autism and Seizure Disorder-Underreported?** The link between autism and seizure disorders is great and may be underreported. Indeed it may difficult to assess using conventional electroencephalographic techniques in this hard-to-examine population. Autism is a major component of tuberous sclerosis, which also shows severe cortical development problems and seizure disorder, and the Landau-Kleffner syndrome of acquired aphasia and seizure. Of particular interest are non convulsive seizures, such as those occurring in complex partial epilepsies. In this conditions, symptomology resembles many aspects of autism spectrum disorders, including inattention, aggression, and repetitive semi purposeful motor activity. Seizure disorder also involves fundamental biological processes associated with brain development, learning and memory and is an emerging area of autism research.

**Autism as an Immune or Metabolic Disorder:** Many investigators are addressing the concept of autism as a general metabolic disorder involving environmental factors, such as metals or environmental organic compounds, or more likely, a genetic sensitivity to these compounds in specific sub populations. Collectively, these result in increased oxidative stress, via cumulative production of reactive oxygen free radicals and resultant inflammation which produce widespread damage to the central nervous system both pre and post-natally. Work done by Jill James at the University of Arkansas, and Abha and Ved Chauhan at

Staten Island, have found evidence of elevated free radicals, reductions in detoxifying agents (i.e. glutathione), antioxidant metal binding proteins (i.e. transferrin and ceruloplasmin), and impairments in brain methylation pathways in autism. Interestingly, these findings were observed in a number of autistic patients from divergent genetic phenotypes involving folate or glutathione metabolism, mitochondrial function, and catecholamine synthesis. This suggests that oxidative stress may be a final common pathway from a number of seemingly divergent inheritable metabolic disorders associated with autism.

Research, led by Paul Ashwood at the M.I.N.D. Institute at University of California, Davis, has focused on systemic immunological abnormalities in autism. It is thought that these neuroimmune interactions, presumably commencing in embryogenesis and persisting throughout the life of the individual, contribute to the neuromigratory abnormalities, enhanced innate neuroinflammatory response and anti-brain antibodies previously discussed. Findings include abnormal T helper cell cytokine profiles, decreased T cell mitogen response, and imbalances in serum immunoglobulin levels. These may be linked to autoimmune disorders also common in first degree relatives of autistic patients and may be associated with genetic variances on human leukocyte antigen (HLA)- DRB1 and complement C4 alleles.

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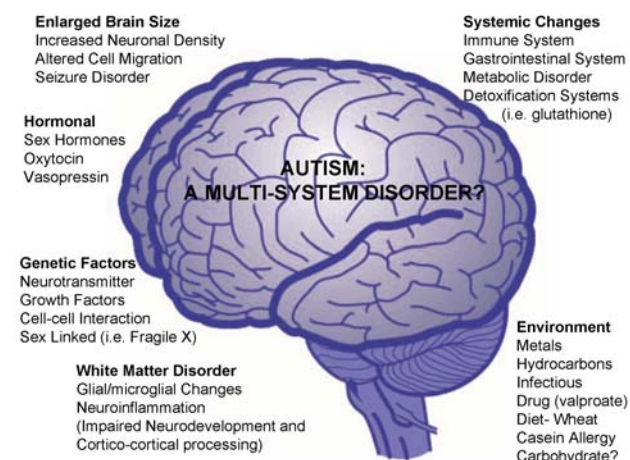
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However, it should be noted that oxidative stress and neural inflammation is common in a number of neurological disorders of very different clinical presentation and pathophysiology. It is unclear if these responses are causative to autism, or a compensatory response to some other etiological factor. Nonetheless, this finding may ultimately lead to promising future treatments utilizing currently available immunomodulatory agents in autism.

**Dietary, and Digestive Links to Autism:** An interesting, emerging field of research is focussed on the role of diet and gut function in the pathophysiology of autism. It is often forgotten that the environment of the digestive tract is probably the most "hostile" of environments to which humans are exposed. Disorders of gut physiology, including dysmotility and altered gut permeability, coupled with pathological lesions resembling, but not identical to, gluten or casein enteropathy have been noted in many patients. Many parents report abrupt worsening of their child's behavioural symptoms, with associated gut symptomatology, following ingestion of refined wheat or dairy products, and paradoxical craving of these foods. This suggests some gut-borne factor with neuroactive properties may contribute to this disorder. Furthermore, clinical reports and studies by Sydney Finegold at UCLA, note an association with pre or post natal infectious processes, antibiotic exposure and gut clostridial species in a subset of autistic patients. The latter is of particular interest in medicine, because of the increasing emergence of antibiotic resistant strains in the hospital and outpatient populations.

A unifying hypothesis incorporating a common underlying factor for the seemingly diverse genetic, environmental, neurodevelopmental, immunological, metabolic and behavioural sequelae of autism is lacking. There is clearly a need for experts from diverse scientific disciplines to interface and utilize novel research paradigms to tackle this severe disorder.



**The Kilee Patchell-Evans Autism Research Group Gut Bacterial Metabolites, A Possible Common Link in the Pathophysiology and Behaviour of Autism:** The Kilee Patchell Evans Autism Research Group is a recently formed multidisciplinary research team comprised of basic and clinical neuroscientists situated at the University of Western Ontario, in London, Ontario, Canada (<http://psychology.uwo.ca/autism.htm>). Core members include the author, Klaus-Peter Ossenkopp, Peter Cain,

Martin Kavaliers, Elizabeth Hampson, and Fred Possmayer. The mandate of the Group is to combine the efforts of researchers from the various disparate aspects of autism, specifically neurodevelopment, neurochemistry, seizure, obsessive compulsive, anxiety disorders, social behaviour, genetics, cellular metabolism, neuroimmunology and infectious disease to understand the basic biological processes of this disorder.

The obvious ethical limitations of direct studies on human subjects often incapable of informed consent is difficult, extremely costly and time consuming. In addition, the extremely limited availability of human autopsy material collectively make the development of a suitable animal model absolutely necessary. Since autism is a behavioural disorder, of particular importance is the detailed analysis of many aspects of motor output in experimental animals which lead to complimentary studies in humans. Rodents are the most extensively studied experimental mammals in brain development, physiology and behaviour. Their rapid development and large litter size make feasible developmental and interventional studies virtually impossible in humans. Current studies examining some key hypotheses in autism pathogenesis, notably fetal valproate, thalidomide, Borna disease virus exposure, coupled with genetic "knock out" studies involving oxytocin and reelin, have begun to elicit promising initial observations in brain anatomical development, neurochemistry, and behaviour.

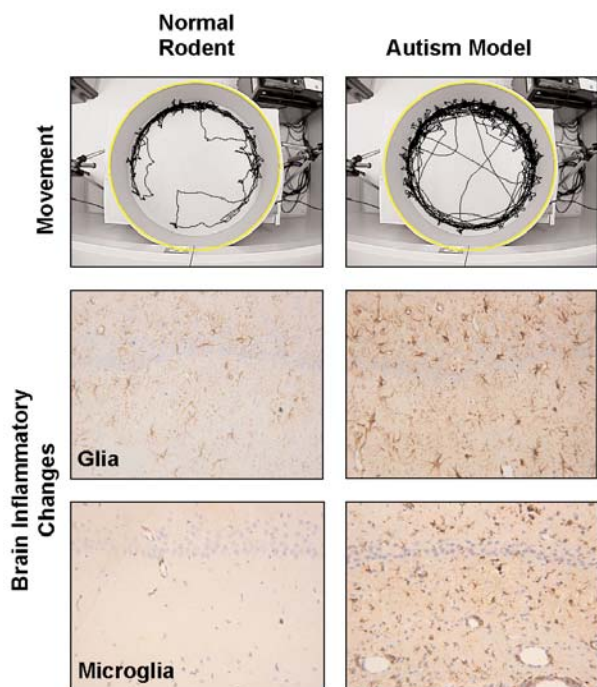
Recent work performed by our Group concerns the role of a panel of gut borne factors in the pathogenesis of autism spectrum disorders through a novel rodent model. Our studies focus on the short chain fatty acid propionic acid (PPA). Interestingly, PPA is a compound present in diet, a component of normal fatty acid metabolism and also a major by-product of gut bacteria, particularly those associated with antibiotic induced diarrhoea. It is also elevated in human propionic acidemia, one of a family of inherited paediatric disorders which produce developmental delay, seizure, movement disorder and gut dysfunction. PPA is also elevated following ethanol, valproate exposure and disorders of biotin and B12 metabolism, all of which produce developmental delay. PPA is known to readily enter the systemic circulation and is known to widespread effects on gut, immune and brain function. Regarding the latter, PPA affects general brain energy metabolism, cellular pH, calcium signalling, gene induction, neurotransmitter synthesis and release, and intercellular communication via cytokines and gap junctions. Together, these factors play a major role in neurodevelopment, seizure, learning and movement, and sensitivity to a variety of environmental stresses plausibly linked to autism. PPA produces developmental and behavioural abnormalities when administered to rodents. Thus PPA is an ideal target compound linking diet, immune and gut function to autism implicated brain physiology and behaviour.

We are currently examining the effects of PPA and related gut metabolic compounds, at the behavioural, electrical, neuropathological and biochemical levels. Research done by graduate students Jennifer Hoffman and Sandy Shultz in our laboratory have shown that PPA, when infused in small amounts into the brains of experimental rodents, immediately produces bouts of hyperactivity, repetitive behaviour and social impairment, resembling those found in autism spectrum disorders. Interestingly, animals also



display brain electrical changes resembling some types of human epilepsy, which often co-exist with autism. Repeated exposure to these compounds increases the severity and duration of these effects, suggesting that these compounds exert permanent effects on brain and behaviour.

Moreover, brain tissue from PPA treated animals, when examined neuropathologically, shows primarily an innate inflammatory process consisting of reactive astrogliosis and activated microglia resembling that found in brain tissue donated from deceased persons with autism. In addition there is an increase in the protein phosphoCREB, a factor associated with widespread gene expression implicated in learning, memory and addictive behaviour. The main brain changes appear to involve the glia, the non neural component of the brain. Glia are critical in the maintenance of a stable environment for neurons, learning and memory, as well as the rapid transmission of information throughout the brain, particularly during periods of neurodevelopment and brain repair. Furthermore, biochemical analysis of brain tissue from PPA treated rodents by post-doctoral fellow Karina Rodriguez-Capote has shown increased oxidative stress and impaired glutathione metabolism, similar to that found in human autism. Thus, abnormalities found in these experimental animals may lead to problems in information processing, movement, brain electrical, immunological and metabolic activity. Thus the PPA model may provide a link between autism and some environmental risk factors, possibly involving the diet or digestive tract.



Automated tracking of rodent model of autism shows hyperactivity and repetitive movement. Microscopic examination of brain tissue (hippocampus) from autism model shows inflammatory changes (increased staining density) in glia and microglia (connective tissue of the brain) similar to tissue obtained from brains of human autism patients (modified from MacFabe et al, 2007, Behavioural Brain Research).

We are now in the process of further characterizing the molecular mechanisms by which PPA and related compounds exert their biochemical, electrophysiological and behavioural effects at the pre and post natal levels. Of particular interest will be the assessment of the above risk factors, either from environment or genetic sensitivity, in large

populations of persons with autism and their families. With the assistance of Dr. Jeanette Holden, Queens University, Director of the Canadian American Autism Research Consortium (website: <http://www.asdcarc.com/>), a patient registry of over 8,000 participants, persons with autism with or without digestive system symptoms are encouraged to participate in these and related studies.

**Summary and Future Directions:** Clearly the complexity and enormous social burden of the autistic family of disorders will be a formidable task in Western medicine. When one considers the lifelong occurrence of a severely affected individual, and the possible link with a number of similar behavioural conditions, including aggression and mood disorders, the total social and financial effects on society are immense and may rival Alzheimer disease, long considered the major neurological problem of this era. The incidence of autism may be on the increase. There is an urgent need for early diagnosis to develop effective evidence-based treatments, with modifications in treatment ethics tailored to persons often incapable of informed consent. This can only be accomplished with rational examination of animal models which link directly to clinical observation, careful assessment of possible risk factors, and the safe administration of future treatment strategies, administered both alone and to compliment available behavioural therapies. Recent research and information exchange in the fields of genetics, neurodevelopment, immune function, energy metabolism, infectious disease and gastroenterology have resulted in a major paradigm shift, where autism will no longer be considered a static primary brain disorder, but an ongoing systemic disorder which affects many organ systems, including the brain. However, with currently available techniques, and through the multidisciplinary collaboration of the molecular, behavioural and clinical medical sciences, effective solutions to this immense problem are attainable.

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Dr. Derrick MacFabe, M.D.



Dr. Derrick MacFabe received his M.D. from McMaster University. He is assistant Professor and Director of the Kilee Patchell-Evans Autism Research Group at the Departments. of Psychology (Neuroscience) and Psychiatry (Division of Developmental Disabilities), Schulich School of

Medicine and Dentistry, at the University of Western Ontario, in London, Ontario Canada (<http://psychology.uwo.ca/autism.htm>). The formation of this multi- disciplinary group was made possible by a generous personal donation of Mr.

David Patchell-Evans, President and CEO of GoodLife Fitness Clubs, who himself is the father of Kilee, a child suffering from autism, and the Autism Canada Foundation (<http://www.autismcanada.org/home.htm>). Dr. MacFabe's research was recently awarded one of the "Top 50 Scientific Discoveries in Canada" by the Natural Sciences and Engineering Research Council of Canada.

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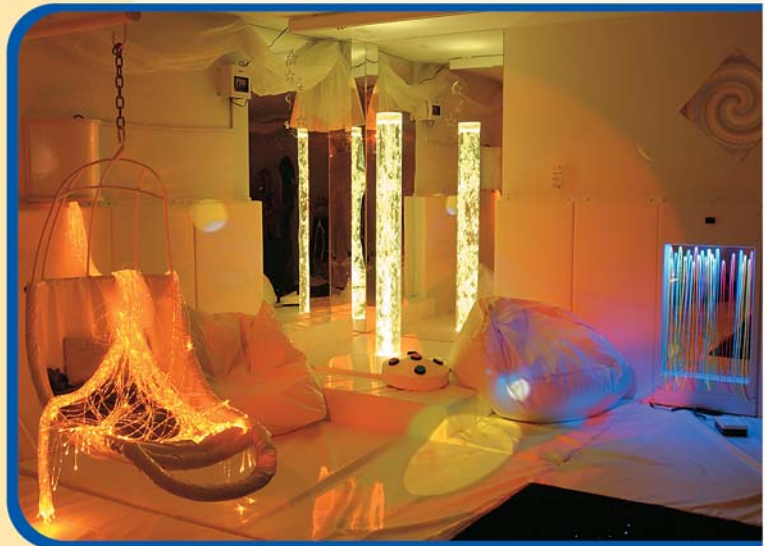
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