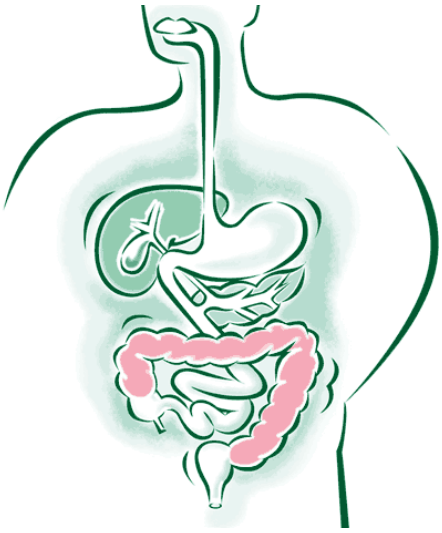
# Gastrointestinal Issues in ASD

## The Research



Many Autism Spectrum Disorder (ASD) children suffer gastro-intestinal (GI problems such as abdominal pain, chronic diar-rhoea, constipation, vomiting, gastroesophageal reflux, and intestinal infections. ASD children are more likely to require gut medications and be hospitalised for gut related distur-bances. Gastrointestinal abnormalities often seem to correlate with the severity of ASD behavioural problems. Recent re-search is investigating a gut-brain interaction where gut abnor-malities may be involved in the pathogenesis or severity of ASD.

Whether (GI) abnormalities in autistic individuals actually con-tribute to the development, persistence, or intensity of core autism symptoms is unknown. It is plausible that GI issues that result in distress or discomfort can potentiate problem behaviours, including self-injurious and stereotypic vocal or motor behaviours. For example, abdominal discomfort in an autistic indi-vidual may be related to presentations of abnormal mouthing or posturing behaviours, self-injury to the abdomen or other areas to detract from GI pain, or vocal groaning or screaming. In addi-tion, other co morbidities, including sleep disturbance and abnormal feeding behaviours such as pica, can arise as a result of GI complications, as well as acid reflux. In addition, some symptoms of autism may develop as a result of both neural and GI dysfunction, whereby the inability of an autistic individual to communicate GI discomfort or distress forms the underlying basis for abnor-mal clinical presentations.

**The intensity of particular GI abnormalities is reported to correlate with the severity of core autism behavioural symptoms suggests that GI problems can contribute to the manifestation of ASD-related behaviours.**

Autistic children with co morbid GI symptoms display more severe irritability, anxiety, and social withdrawal, among other behavioural problems, supporting a role for the gut-brain connection in ASD. In addition, many reports provide compelling evidence that modified diets or antibiotic treatment can effectively ameliorate autism-related behavioural problems.

### Gastrointestinal disorders and issues in ASD include:

- Unique pathology and microscopic changes in the gastrointestinal tract
- Unique ASD gut variant confirmed by gene studies
- Abnormal gut microflora (microbiota)
- Gut immune abnormalities
- Carbohydrate malabsorption
- Increased intestinal permeability
- Neurological connection (gut-brain axis)

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Changing the way we think about treating autism.

## Gastrointestinal Symptoms in ASD

Several studies have indicated a higher prevalence of GI problems such as abdominal pain, constipation, chronic diarrhoea, vomiting, and gastroesophageal reflux disease in ASD children and adults.

**Table 1.** Frequency of gastrointestinal symptoms in 143 children undergoing ileocolonoscopy.

| Gastrointestinal symptom | n | % |
|---|---|---|
| Diarrhea (alone) | 83 | 58% |
| Constipation (alone) | 22 | 15.4% |
| Diarrhea (alone, or in combination with constipation) | 112 | 78.3% |
| Constipation (alone, or in combination with diarrhea) | 51 | 35.7% |
| Both diarrhea and constipation | 29 | 20.3% |
| Abdominal pain | 85 | 59.4% |
| Abdominal distension | 30 | 21.0% |
| Mucoid stool | 27 | 18.9% |
| Hematochezia | 11 | 7.7% |

Source: Arthur Krigsman et al.

Many children adopt a characteristic posture designed to put pressure on the lower abdomen, which is an adaptive behaviour designed to reduce pain. Clinically, it is valuable to consider intestinal inflammation in the differential diagnosis of children with autism who present with diarrhoea, constipation, alternating diarrhoea and constipation, sleep disturbances, behavioural outbursts, or unusual posturing (Table 1). Unfortunately, most medical professionals dismiss the significance of these symptoms and children continue to suffer. Parents need to push harder to have their children properly assessed and treated.

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Gastrointestinal issues in autism spectrum disorder. Hsiao EY. Harv Rev Psychiatry. 2014 Mar-Apr;22(2):104-11.

Clinical Presentation and Histologic Findings at Ileocolonoscopy in Children with Autistic Spectrum Disorder and Chronic Gastrointestinal Symptoms. Arthur Krigsman, Marvin Boris, Alan Goldblatt and Carol Stott. Autism Insights 2010:2 1–11.

## Gastrointestinal Pathology in ASD

A 2002 UK study using data from the UK General Practice Research Database, concluded that "Children with autism are no more likely than children without autism to have had gastrointestinal disorders at any time before the diagnosis of autism." and "Less than 10% of children diagnosed with autism have a history of gastrointestinal disorders, and for most the symptoms are mild." **These conclusions from the retrospective data of UK general practitioners is at odds with research studies that clearly show that ASD children do have a very high incidence of abnormal gastrointestinal pathology.** A 2003 study reported significant GI symptoms in 70% of ASD subjects compared with 28% of children with typical development. A study in 2006 documented GI symptoms in 80% of their ASD population. Similar percentages have been reported in other studies.

In a study by Horvath and co-workers, the upper gastrointestinal tract of 36 children diagnosed with autism and experiencing **abdominal pain, chronic diarrhoea, bloating, night-time awakening, or unexplained irritability** was examined by endoscopy with biopsy. Abnormal findings reported included **reflux esophagitis** in 25 of the children, **chronic gastritis** in 15, and **chronic duodenitis** in 24. Low activity of **intestinal carbohydrate digestive enzymes** was observed in 21 children.

In a more recent 2010 study, Dr Arthur Krigsman and his colleagues reported on 143 patients with ASD/developmental disorder, undergoing ileocolonoscopy and biopsy as part of routine investigations of persistent GI symptoms. The GI symptoms included: diarrhoea, constipation and abdominal pain. **In non-verbal patients abdominal pain was indicated by frequent, unexplained excessive irritability, awakening from sleep in a state of unusual irritability or agitation, uncharacteristic aggression and "pain posturing", in which the child assumes a leaning position, providing direct pressure to the lower abdomen.** The age range in the patient group was between 12 months and 18 years.

In most cases, biopsies were obtained in at least 6-8 colonic locations and 2-3 terminal ileal locations targeting areas of subtle mucosal irregularity and areas of healthy appearing mucosa. The results in Table 2 shows the high percentage of children found with varying GI inflammatory issues.

**Table 2.** Anatomical regions of the colon: Inflammation and LNH. Difference between denominators reflects the number of adequate biopsies taken from each site.

| Region of bowel | No. of biopsies | Inflammation | | | | | | LNH | |
|---|---|---|---|---|---|---|---|---|---|
| | | Acute | | Chronic | | Both | | | |
| | | n | % | n | % | n | % | n | % |
| Terminal Ileum | 127 | 26 | 20.5 | 31 | 24.4 | 13 | 10.2 | 85 | 66.9 |
| Cecum | 135 | 28 | 20.7 | 29 | 21.5 | 12 | 8.9 | 17 | 12.6 |
| Right colon | 131 | 30 | 22.9 | 35 | 26.7 | 13 | 9.9 | 16 | 12.2 |
| Hepatic | 126 | 22 | 17.5 | 31 | 24.6 | 10 | 7.9 | 17 | 13.5 |
| Transverse | 139 | 28 | 20.1 | 39 | 28.1 | 12 | 8.6 | 21 | 15.1 |
| Splenic | 118 | 26 | 22.0 | 25 | 21.2 | 9 | 7.6 | 12 | 10.2 |
| Left colon | 126 | 33 | 26.2 | 27 | 21.4 | 11 | 8.7 | 14 | 11.1 |
| Sigmoid | 132 | 37 | 28.0 | 27 | 20.5 | 10 | 7.6 | 17 | 12.9 |
| Rectum | 138 | 28 | 20.3 | 27 | 19.6 | 8 | 5.8 | 14 | 10.1 |

Lymphoid Nodular Hyperplasia (LNH)

The study also looked for an association of microscopic histology findings with incidence of constipation or diarrhoea. Of the 83 patients presenting with **diarrhea without constipation**, of these, 59 (79.7%) **had inflammation in either the ileum, the colon or both locations**. **Constipation without associated diarrhea**, of these, 12 (63.2%) **had ileal or colonic inflammation**. Of the 74 patients presenting with diarrhea alone and for whom ileal investigation was successful, 56 (75.7%) had positive identification of histological **lymphoid nodular hyperplasia (LNH)**. For the 19 patients presenting with constipation only, 14 (73.7%) of these had LNH. While LNH has long been thought of as a 'normal' paediatric variant commonly encountered in developmentally normal children undergoing ileocolonoscopy, it is also a prominent component of the inflammatory response in gastrointestinal infectious processes such as *H. Pylori,* gastritis, *Shigellosis, C. difficile* colitis, and *yersiniosis*, among others. The study also found increased bowel pathology in regressive autism than in early onset developmental delay.

ASD children frequently have accompanying GI symptoms which may be intense, and directly impact quality of life. In Australia, I have found that medical professionals are very reluctant to do a comprehensive gastrointestinal investigation of an ASD child, unless there is severe evidence of an inflammatory bowel issue.

**If there is suspicion of underlying gastrointestinal issues in your child, a Comprehensive Digestive Stool Analysis (CDSA) is an easy option to consider. A CDSA will detect whether gastrointestinal inflammation, dysbiosis or pathogens are impacting their behaviour and quality of life.**

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## Gastrointestinal Gene Studies

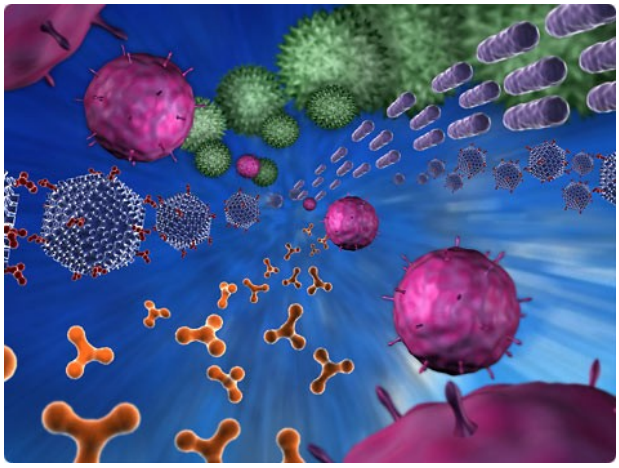
Following on from the previous section on gastrointestinal pathology in ASD children, a gene profiling study adds further evidence of a unique variant, distinctive from other inflammatory bowel conditions.

Recent gene profiling of gastrointestinal mucosal biopsy tissue from ASD children and three non-ASD control groups (Crohn's disease, ulcerative colitis, and a histologically normal group) has shown a gene profile unique to ASD children. Gene expression profiles in intestinal biopsy tissue from patients with Crohn's disease, ulcerative colitis, and ASD, while having significant overlap with each other, also show distinctive features for each group. Results demonstrate that ASD children have a gastrointestinal mucosal molecular profile that overlaps significantly with known inflammatory bowel disease (IBD), yet has distinctive features that **further supports the presence of an ASD-associated IBD variant, or, alternatively, a prodromal phase of typical inflammatory bowel disease**.

**Reference**

Identification of Unique Gene Expression Profile in Children with Regressive Autism Spectrum Disorder (ASD) and Ileocolitis. Stephen J. Walker, John Fortunato, Lenny G. Gonzalez, Arthur Krigsman. 2013. PLoS ONE 8(3): e58058. doi:10.1371/journal.pone.0058058.

## The Gastrointestinal and Immune Connection in ASD



The gastrointestinal tract has a direct connection with the immune system and an imbalanced immune response has been well established in ASD children. The GI tract works very closely with the immune system to maintain balance and protects our body against microorganisms and foreign antigens. Intestinal mucosa is continuously challenged by a huge amount of foreign antigens and microorganisms from the environment. The organised regulation of the intestinal barrier maintains mucosal immune function and prevents inflammation.

Different elements of our intestinal barrier include epithelial cell integrity, mucus production, epithelial paracellular (between cell) permeability, and innate (first line of defence) immune response. Abnormal changes in any of these components may lead to inflammatory diseases of the intestine. Gastrointestinal effects on the immune system can also influence brain and behaviour. Functional GI disorders are strongly linked to GI inflammation, intestinal permeability, and altered composition of the gut microbiota. **Various immunological abnormalities have been observed in the GI tracts of autistic individuals, including leukocyte infiltration, complement activation, lymphoid hyperplasia, and pro-inflammatory cytokine responses.**

Other studies indicate that the immune response to factors produced by bacteria in the gut leads to increased systemic levels of inflammatory chemicals, such as IL-1β, which significantly alter the permeability of the gut epithelial layer and the blood-brain barrier.

**References**

Gastrointestinal Issues in Autism Spectrum Disorder. Elaine Y. Hsiao, PhD. 2014. Harvard Review of Psychiatry. 22; 2; 104-111.

Model-based hypothesis of gut microbe populations and gut/brain barrier permeabilities in the development of regressive autism. Downs R, et al. 2014 Sept 18. Med Hypotheses. pii: S0306-9877(14)00330-2.

## Gastrointestinal Microbiota in ASD

Several studies have reported significantly higher oral antibiotic use in children with autism. Oral antibiotics were primarily used for treating otitis media (ear infections), which may suggest an impaired immune system. Commonly used oral antibiotics affect the normal gut microbiota, which play an important role in the breakdown of plant polysaccharides, promoting gastrointestinal motility, maintaining water balance, producing some vitamins, and competing against pathogenic bacteria. Loss of normal gut flora can result in the overgrowth of pathogenic flora, which can in turn cause constipation, loose stools and other intestinal problems.

**An increasing number of studies are confirming that ASD individuals have an altered gut microbiota (or dysbiosis).** Studies of faecal cultures and DNA extracts have found certain bacterial clusters over represented in ASD children with gastrointestinal complaints compared with children with similar GI complaints but typical neurobehavioral development. There is also evidence that altered microbiota may have a role in regressive-autism. **The evidence indicates that changes in the composition of the commensal microbiome can alter behaviour, including anxiety-like behaviour, emotional or depressive behaviour, locomotor activity, and other symptoms.** Changes in the gut microbiome may help explain anecdotal reports of improvement in behavioural functioning in response to dietary changes, if such changes serve a probiotic function and improve bowel symptoms (eg, bloating, abdominal pain, flatulence) among certain children with ASD.

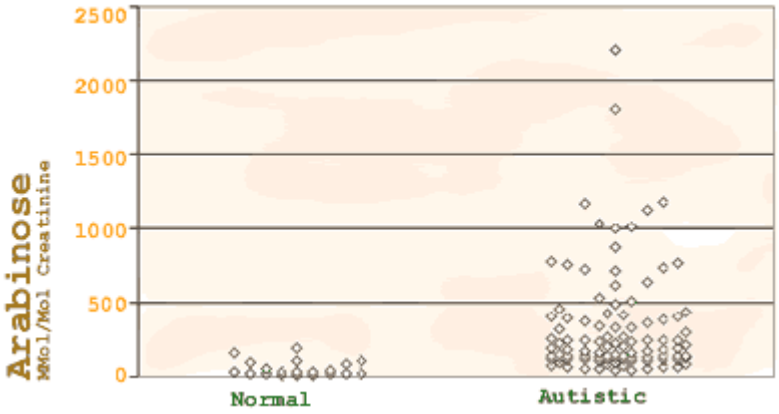
Studies have found higher levels of *Bacteroidetes* in severely autistic individuals, and higher levels of *Firmicutes* in controls. Additionally, *Desulfovibrio* species were present in higher numbers. *Sutterella* species have recently been found in the ileum of ASD patients with GI abnormalities, while no control patients with GI disturbances had the bacteria. *Clostridium bolteae*, is often found in the intestine of ASD children and has been proposed to possibly aggravate the GI symptoms in ASD individuals.

There is evidence supporting a role for the GI microbiota and their fermentation products in the etiology and/or symptoms of ASD, and their potential use as biomarkers. Enteric short-chain fatty acids, particularly propionic acid, produced from GI bacteria, may play a role in the aetiology of some forms of ASD. **Propionic acid is a neurotoxin which has been known to cause symptoms characteristic of autism when injected into the brain of rats.** It also has effects on (1) neurotransmitter systems, (2) intracellular acidification and calcium release, (3) fatty acid metabolism, (4) gap junction signalling, (5) immune function, and (6) alteration of gene expression. More recent data indicates that ***Desulfovibrio* bacteria may play an important role in regressive autism**.

Clostridia species comprise part of the gut microbiota and produce both an enterotoxin (a toxin that targets the intestines) and a neutotoxin. The number of Clostridia species found in the stool of ASD children is higher than healthy children. **Specifically higher levels of *Clostridiun bolteae* and *Clostridum* clusters I and XI have been reported.** Significantly increased levels of the Clostridium derived neurotoxic metabolite **para-cresol**, along with various other bacterially modulated metabolites, is detected in the urine of autistic children, suggesting a possible interaction between gut dysbiosis, intestinal permeability, and metabolic dysfunction in autism. Antibiotics targeting Clostridia like vancomycin, have been shown to be effective in reducing autistic symptoms in some children. There have been other anecdotal reports of children that improve while taking antibiotics. This demonstrates the importance of the gut microbiome and its relationship with ASD.

A childhood neurodevelopmental condition, **PANDAS (pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection)**, is caused by a group A β-haemolytic Streptococcus (GABHS: Streptococcus pyrogenes). The body can produce antibodies to this bacteria which can cross-react with neural tissues, thereby causing the neurobehavioural symptoms associated with the condition. These symptoms are often shared with autism and include cognitive inflexibility, obsessive and compulsive behaviours and vocal or postural tics. Anti-GABHS antibodies have been detected in sub-sets of ASD individuals. One study has shown a 40% elevation of antibodies to Streptococcal protein, compared to 9% in control subjects.

Yeast/fungi are widely known to accompany the use of broad spectrum antibiotics. Yeasts, like Candida, can affect the central nervous system and the immune system. ***Candida albicans*** produces **arabinose**, which can be detected in urine. In some children with autism, arabinose concentrations may exceed 50 times the upper limit of normal. A scattergram of urine arabinose values comparing normal and autistic children in the same age range is given below.




Arabinose, reacts with the amino group of lysine in a wide variety of proteins and may then form cross-links with arginine residues in an adjoining protein, thereby cross-linking the proteins and altering both biological structures and functions of a wide variety of proteins. The blockage of these active lysine sites may cause functional vitamin deficiencies even when nutritional intake is adequate. There are many other yeast metabolites that can be detected in urine, including tartaric acid. **Tartaric acid** is a toxic compound known to damage the muscles and the kidney. Tataric acid inhibits portions of the Krebs cycle to produce energy for the body. One of the reasons for the hypoglycemia we see in ASD may be due to the inhibition of the Krebs cycle by tartaric acid. The Krebs cycle is the main provider of raw materials such as malic acid that can be converted to blood sugar when the body uses up its glucose supply. If sufficient malic acid cannot be produced, the body cannot produce the sugar glucose, which is the main fuel for the brain. Therefore the presence of yeast metabolites may have profound effects on ASD individuals.

**Improvements commonly cited by parents of autistic children treated with antifungal therapy include: decreased hyperactivity, more eye contact, increased vocalization (more words and more usage), better sleep patterns, better concentration, increased imaginative play, reduced stereotypical behaviours (such as spinning objects), and better academic performance.**

**Every ASD child should have an Organic Acid Test (OAT) which includes a yeast metabolite profile as well as dysbiosis markers for Clostridia.**

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http://www.greatplainslaboratory.com/yeast.html

## Deficient Carbohydrate Digestion and ASD

The intestinal layer comprising of mucus and epithelial cells, must maximize nutritional uptake of dietary components while maintaining a barrier to toxins and infectious agents. Although some aspects of these functions are dependent on the individuals ability as determined by their genetic profile, others are acquired through a symbiotic relationship with microbial flora. Dietary carbohydrates enter the intestine as monosaccharides (glucose, fructose, and galactose), disaccharides (lactose, sucrose, and maltose), or complex polysaccharides. Carbohydrates are digested by disaccharidases (enzymes) expressed by specialised cells in the brush border of the small intestine and transported as monosaccharides across the intestinal epithelium (see **Figure A** below).

Although humans lack the enzymes that breakdown the plant cell wall polysaccharides, oligosaccharides, storage polysaccharides, and resistant starches, intestinal bacteria containing these enzymes and expand our capacity to breakdown dietary polysaccharides. As an end product of polysaccharide fermentation, bacteria produce short-chain fatty acids (butyrate, acetate, and propionate) that serve as energy substrates for colonic cells, modulate colonic pH, regulate colonic cell proliferation and differentiation, and contribute to hepatic glucose utilisation and cholesterol synthesis (See **Figure B** below).

Study findings in ASD children with gastrointestinal issues have found that :

1. levels of disaccharidases and hexose transporters are reduced
2. significant microbial dysbiosis in the small and large intestines
3. the dysbiosis is associated with deficiencies in host disacharidase and hexose transporter ability

A model has been proposed where deficiencies in disaccharidases and hexose transporters alters the mix of carbohydrates in the distal small intestine (ileum) and proximal large intestine (cecum), resulting in the supply of additional nutrients for bacteria. These changes manifest in significant and specific changes in composition of the microbiota of ASD children with GI symptoms. It has been reported that up to 93% of ASD children with GI symptoms had decreased expression of at least one of three disaccharide enzymes. Also decreased levels of two important hexose transporters, SGLT1 and GLUT2 were found. The reduced capacity for digestion and transport of carbohydrates can have profound effects on the microbiota in the gut.

Within the intestine, unabsorbed carbohydrates can lead to osmotic diarrhoea, non-absorbed sugars may also serve as substrates for intestinal microflora that produce fatty acids and gases (methane, hydrogen, and carbon dioxide), promoting additional GI symptoms such as bloating and flatulence (see **Figure C** below). Since ASD children often have a high preference for carbohydrate foods, deficient digestion and absorption of these carbohydrates in turn may alter the balance of bacteria, in the gut and contribute significantly to the GI symptoms seen in ASD children.

Metabolic interactions between intestinal microflora and their hosts are only beginning to be understood. Nonetheless, there is already abundant evidence that microflora can have system-wide effects and influence immune responses, brain development and behaviour.

**If your child has gastrointestinal issues, consider some testing to see if there are issues with abnormal gut flora or inflammation with a Comprehensive Digestive Stool Analysis (CDSA). Also consider a Single Carbohydrate Diet (SCD) or a Gut and Psychology Syndrome diet (GAPS), as many parents have and helped to heal their children's abdominal issues and their discomfort.**

**References**

Impaired Carbohydrate Digestion and Transport and Mucosal Dysbiosis in the Intestines of Children with Autism and Gastrointestinal Disturbances. Williams BL, Hornig M, Buie T, Bauman ML, Cho Paik M, et al. 2011, PLoS ONE 6(9): e24585. doi:10.1371/journal.pone.0024585

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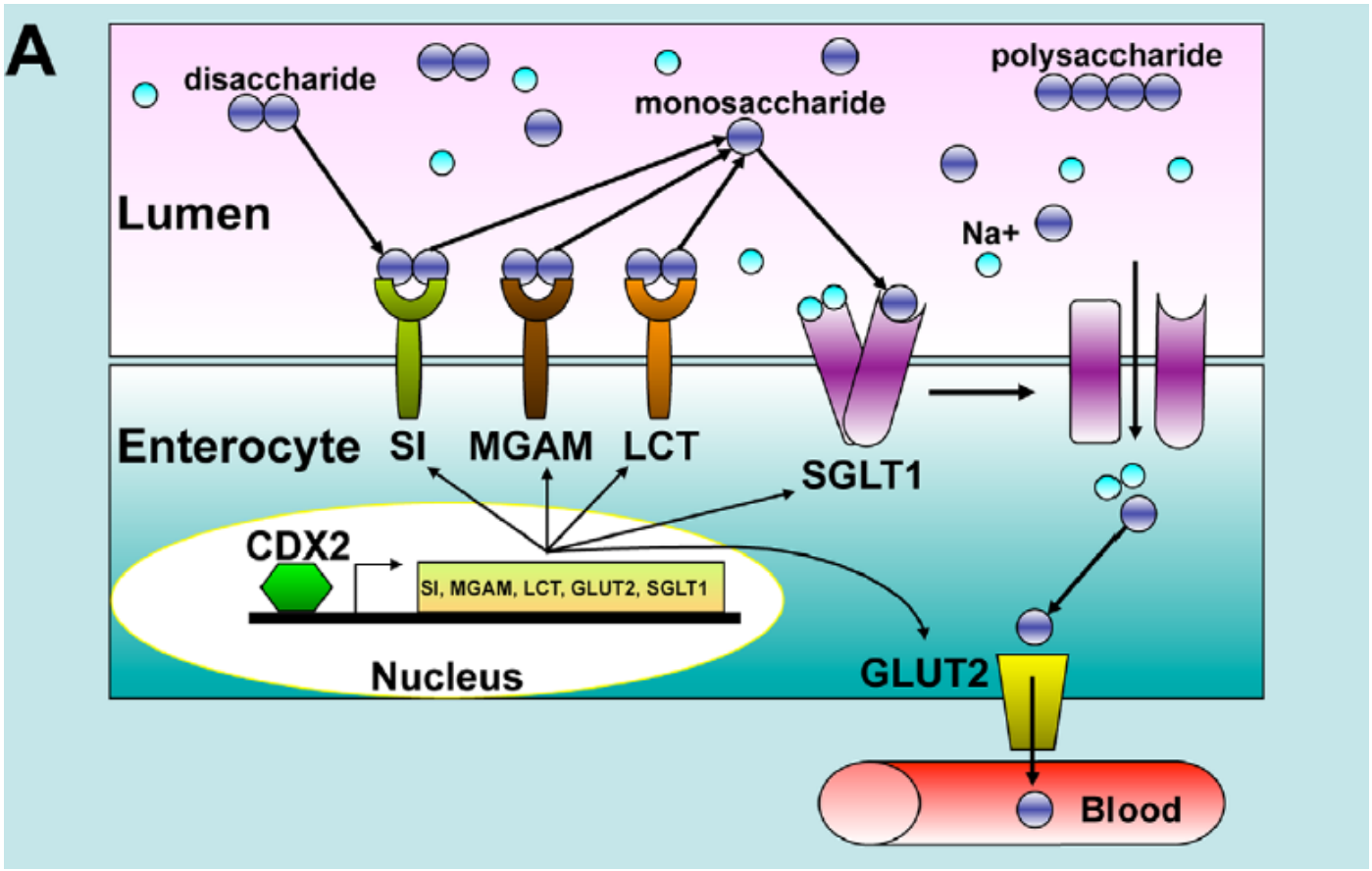
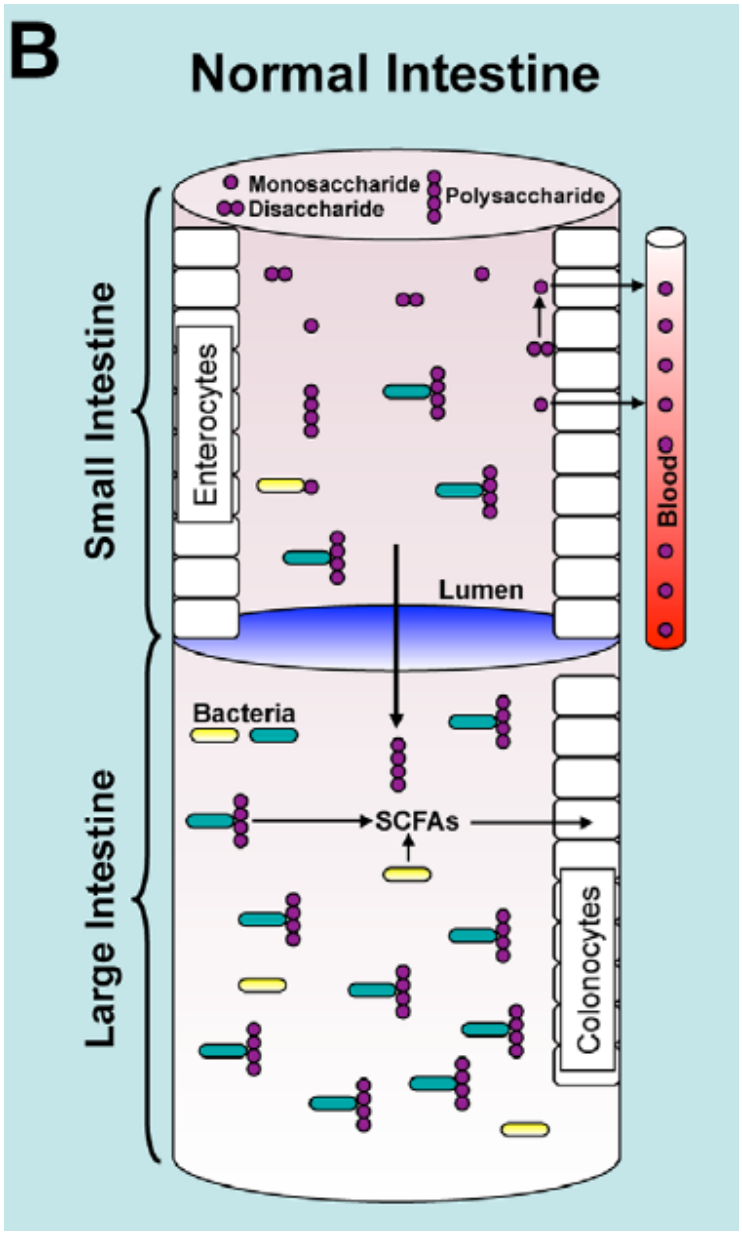
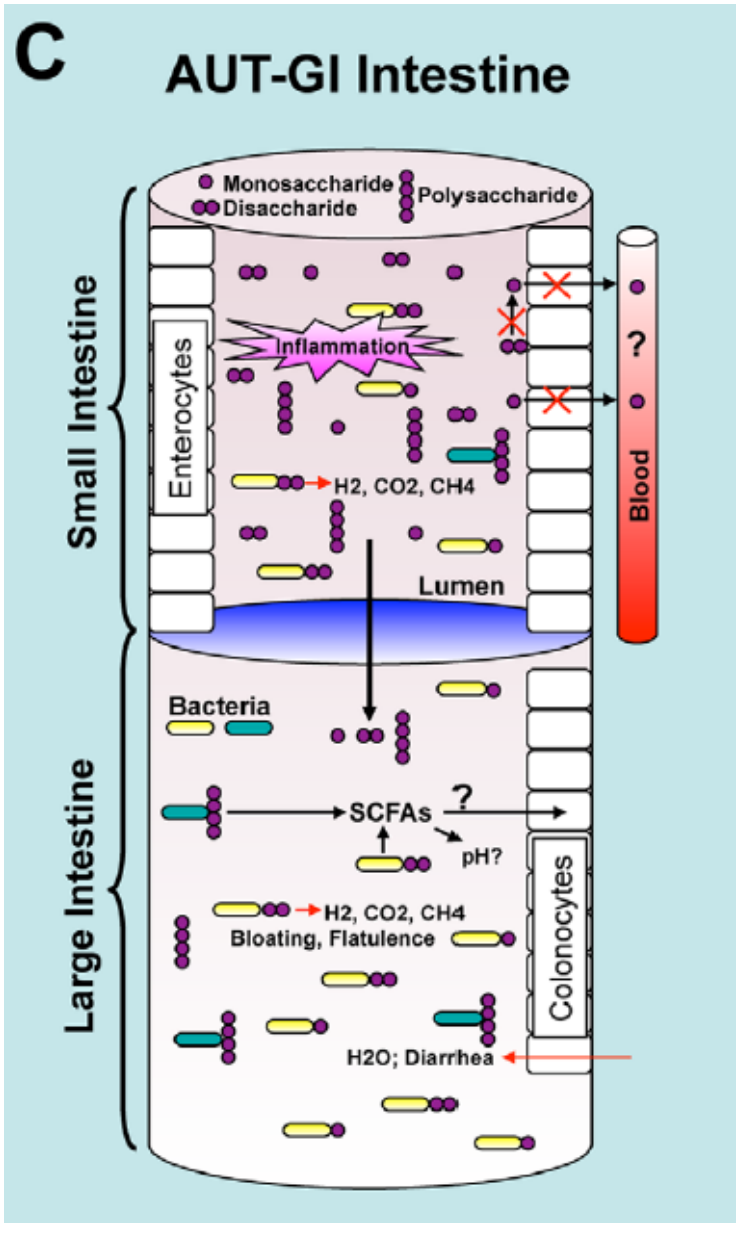


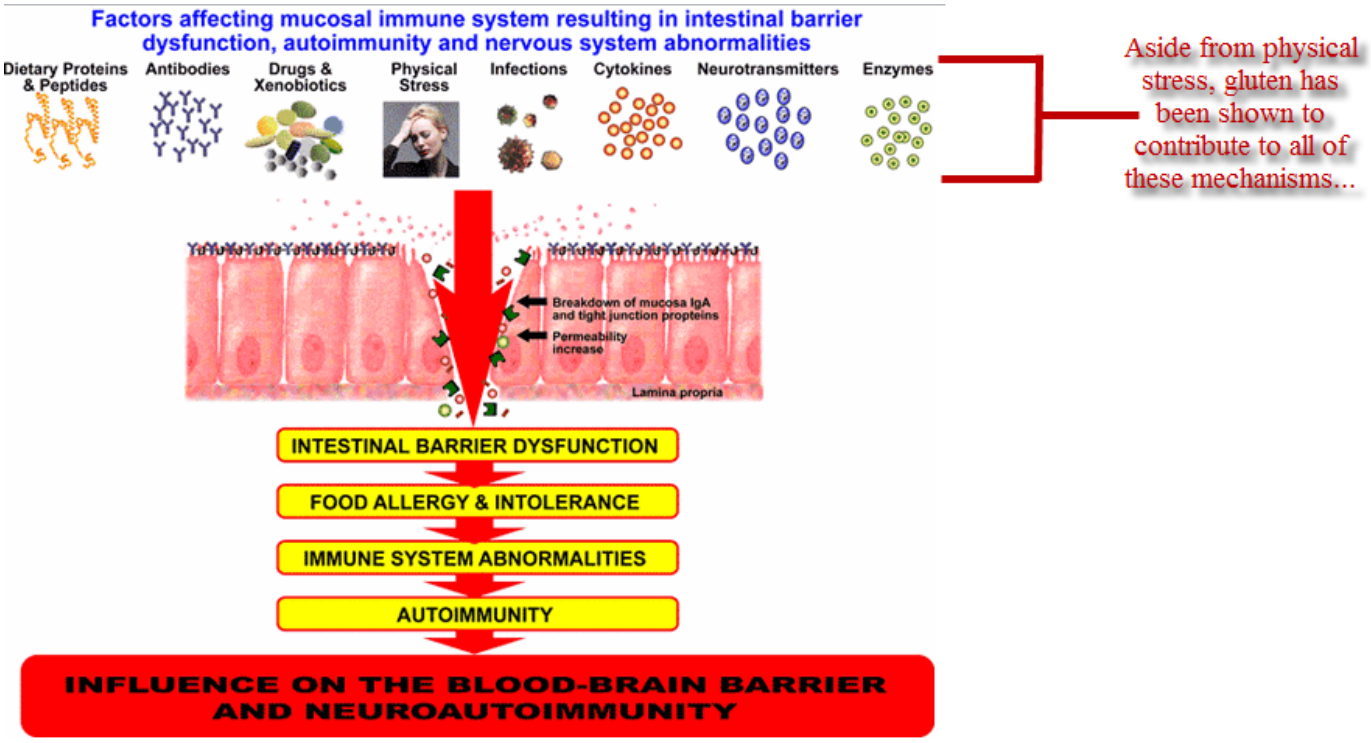




**Source:** Williams BL, Hornig M, et al.

## Intestinal Permeability

A major feature of the gastrointestinal tract is its ability to regulate the trafficking of macromolecules between the environment and the host through the gut barrier with its intercellular tight junctions. The protein **zonulin** is a component of intercellular tight junctions that is involved in regulating gut permeability. Small-intestinal exposure to bacteria and gluten are two of the more powerful triggers for zonulin induced weakening of tight junctions. Gut infections have been implicated in the pathogenesis of several pathologic conditions, including allergic, autoimmune, and inflammatory diseases, by causing impairment of the intestinal barrier (intestinal permeability). In addition to bacterial exposure, **gliadin** (a protein class found in wheat) which is the environmental trigger of celiac disease, has been shown to alter the intestinal permeability by the release of zonulin.




**In one study a high incidence of intestinal permeability was found among patients with autism (36.7%) and their relatives (21.2%) compared with normal subjects (4.8%). Patients with autism on a gluten-casein-free diet had significantly lower intestinal permeability scores, compared with those who were on an unrestricted diet and controls.** The results obtained support the leaky gut hypothesis and indicate that measuring intestinal permeability could help to identify a subgroup of patients with autism who could benefit from a gluten-free diet. The intestinal permeability alterations found in first-degree relatives suggest the presence of an intestinal (tight-junction linked) hereditary factor in the families of patients with autism.

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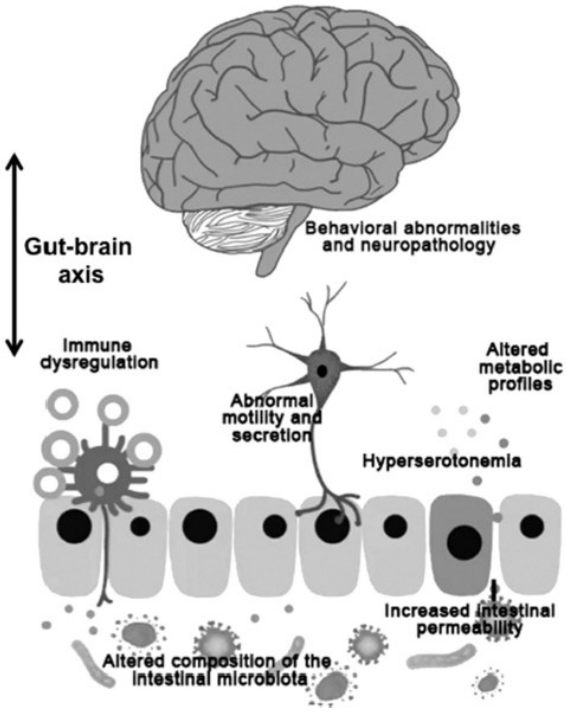
## The Gut Brain Connection




Gastrointestinal abnormalities, such as increased intestinal permeability, altered composition of the intestinal microbiota, and dysregulated gastrointestinal motility and secretion, are described in subsets of individuals with ASD. Such changes can affect the development of other autism-associated subsets. For example, gastrointestinal disruptions can influence the production or metabolism of serotonin from the gut. Also, increased intestinal permeability can lead to the leakage of bacterially derived or bacterially modulated metabolites across the intestinal epithelial and into the bloodstream, which may underlie the elevated levels of bacterial metabolites and alterations in the urinary and serum metabolites seen in autistic individuals. Gastrointestinal issues can lead to widespread immune dysregulation, as is observed in autism, which can lead to neurological issues. Overall, changes in the gastrointestinal tract can influence behaviour and brain function via the gut-brain axis, driven by direct connections of the intestinal epithelium to the brain. **This mechanism governs the communication of information from the epithelial tissues in the gut to the brain, regulating such gut processes as motility, secretion, satiety and a number of complex behaviours, including emotional and cognitive behaviour, and anxiety or stress.**

**Reference**
Gastrointestinal Issues in Autism Spectrum Disorder. Elaine Y. Hsiao, PhD. 2014. Harvard Review of Psychiatry. 22; 2; 104-111.