Lecture Overview

- What is autism – DSM IV criteria
- Current autism statistics
- What is autism – Really?
- What are some causes and risk factors for autism?
- Co-morbid conditions
Inflammatory bowel disorders in autism
Common avoidance because of the diagnosis.
Bernard Rimland, Ph. D, and the roots of biomedical intervention for autism.
GI Pathogens – *Organic Acids Test*
Candida overgrowth and autism
Clostridia bacteria and autism
Lecture Overview (continued)

- Dopamine toxicity effects
- Gut microbiome and the brain
- The Vagus Nerve – the neuroanatomical/neurophysiological role between the gut and brain
- What about Osteopathy?

**Action Steps:**

- What you can do as an Osteopathic Physician to help this desperate community of people.
6 or more identifiers from 3 major categories:

- **Social interaction impairments**
  - Failure to use eye contact, body posture, facial expression
  - Failure to develop peer relationships
  - Lack of social interaction, sharing, or enjoyment with others
  - Lack of social or emotional reciprocity

- **Communication impairments**
  - Delay or total lack in speech development
  - Inability to initiate or maintain conversational speech
  - Stereotyped or repetitive use of language

- **Repetitive and stereotyped behaviors, interests, and activities**
  - Abnormal intensity or focus on stereotyped or restricted patterns of interest
  - Inflexible adherence to rituals and routines
  - Repetitive movements (hand-flapping, finger flicking or twisting, or complex body movements)
  - Preoccupation with parts of objects

[www.cdc.gov/ncbddd/autism](http://www.cdc.gov/ncbddd/autism)
For many years autism was rare - occurring in just five children out of 10,000.

Early 1990s - rate of autism diagnosis increased significantly world wide with figures as high as 60 per 10,000 children.

In March 2012, the Centers for Disease Control (CDC) stated that 1 in 88 children in the U.S. is diagnosed with an Autism-Spectrum Disorder.

2006-2008: 1 in 6 children in U.S. had developmental disability (autism, speech and language impairments, cerebral palsy, etc.).

http://www.cdc.gov/ncbddd/autism/data.html
As of March, 27th 2014

1 in 68

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention
What Are Some Causes and Risk Factors?


“We do not know all of the causes of ASD. However, we have learned that there are likely many causes for multiple types of ASD. There may be many different factors that make a child more likely to have an ASD, including environmental, biologic and genetic factors.”

Most scientists agree that genes are one of the risk factors that can make a person more likely to develop ASD.

Children who have a sibling with ASD are at a higher risk of also having ASD.
What Are Some Causes and Risk Factors?

- ASD tends to occur more often in people who have certain genetic or chromosomal conditions, such as fragile X syndrome or tuberous sclerosis.
- When taken during pregnancy, the prescription drugs valproic acid and thalidomide have been linked with a higher risk of ASD.
- There is some evidence that the critical period for developing ASD occurs before, during, and immediately after birth.
- Children born to older parents are at greater risk for having ASD.
What is Autism – Really?
Andrew – *before and after Autism diagnosis*

Andrew Kohatsu  
“Andy”  
8-4-2005  
“Real Smiles  
Clear eyes  
Happy eyes”

100%  
“With us” and aware now

The pictures were taken by me, Andy’s sister Janelle.  
He’s always ignored me, now he wants my attention all the time.  
He tries to tickle my feet and he thinks its sooo funny! He’s teasing me!  
>=( ^_^)
The Faces of Autism

This is Cody. He loves to give hugs & his excitement over the little things is contagious.

He likes roller coasters & watching videos on YouTube. His favorite television show is The Price is Right & he would live at Walt Disney World if it was possible.

This is autism.
The Scary Reality of Autism For Many Families
Meet Noah
Severe Self-Injurious Behavior
Padded Room
Exhausted From Self-Abusive Behavior
Family Trapped and On The Edge Emotionally
Self-injurious behavior associated with alterations in the somatosensory system in children with autism spectrum disorder

Emma G. Durens - Dallas Card - S. Wendy Roberts - Kathleen M. Mak-Fan - M. Mullar Chakravarty - Jason P. Lorch - Margot J. Taylor

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Abstract: Children with autism spectrum disorder (ASD) frequently engage in self-injurious behaviors, often in the absence of reporting pain. Previous research suggests that altered pain sensitivity and repeated exposure to aversive stimuli are associated with morphological changes in somatosensory and limbic cortices. Further evidence from post-mortem studies with self-injurious adults indicates altered connections in the structure and organization of the temporal lobes; however, the effect of self-injurious behavior on cortical development in children with ASD has not yet been determined. Thirty children and adolescents (mean age = 10.6 ± 2.5 years; range 7–15 years; 20 males) with a clinical diagnosis of ASD and 30 typically developing children (4F/36, mean age = 10.7 ± 2.5 years; range 7–15 years; 20 males) underwent T1-weighted magnetic resonance and diffusion tensor imaging. No between-group differences were seen in cerebral volume, surface area or cortical thickness. Within the ASD group, self-injury scores negatively correlated with thickness in the right superior parietal lobule (r = 0.35, p = 0.001), bilateral primary somatosensory cortices (SI: right r = 0.44, p = 0.004) and the volume of the left ventro-posterior (VP) nucleus of the thalamus (r = 0.52, p = 0.003). Based on these findings, we performed an atlas-based region-of-interest diffusion tensor imaging analysis between SI and the VP nucleus and found that children who engaged in self-injury had significantly lower fractional anisotropy (r = 0.4, p = 0.04) and higher mean diffusivity (r = 0.5, p = 0.02) values in the territory of the left posterior limb of the internal capsule. Additionally, greater incidence of self-injury was associated with increased radial diffusivity values in bilateral posterior limbs of the internal capsule (left: r = 0.5, p = 0.002; right: r = 0.5, p = 0.009) and corona radiata (left: r = 0.6, p = 0.005; right: r = 0.5, p = 0.009). Results indicate that self-injury is related to alterations in somatosensory cortical and subcortical regions and their supporting white matter pathways. Findings could reflect use-dependent plasticity in the somatosensory system or disrupted brain development that could serve as a risk marker for self-injury.

Keywords: Autism spectrum disorder - Injury - Grey matter - White matter - Pain

Somatosensory System Imbalance

Brain volume problems
Abstract
The authors examined 183 children with autistic symptoms and found that the age-specific incidence rates of seizures in this sample were between 3 and 28 times the rates for children in the general population. The subjects classified as totally autistic were at high risk of developing seizure from early childhood well into adolescence, but especially so at puberty. The partially autistic children had an increased risk of seizures only up to age 10. The authors suggest that the high incidence of seizures at puberty observed in this study may be specific to children with total autistic symptomatology and may represent a distinct pathological process associated with autism.
Centers for Disease Control: “several medical conditions are significantly over-represented in people with ASD compared to the general population and other developmental conditions.” Individuals with ASD have much higher than expected rates of various medical conditions studied, including:

- Ear and respiratory infections
- Asthma, allergic rhinitis and atopic dermatitis
- Sleep disorders
- Headaches, migraines
- Seizures
- Gastrointestinal disorders
- Early mortality – death rates ranging from 3 to 10 times higher than general population

Common GI Problems In Autism
Like Everyone Else

Just like everyone else, people with autism may suffer from:

- Gastritis
- GERD
- Colitis
- Irritable Bowel Syndrome
- Constipation
- Motility-based disorders
- Food allergy and sensitivity
- Overgrowth syndromes
How Prevalent Are GI Issues in Autism

*J Dev Behav Pediatr.* 2006 Apr;27 (Valicenti-McDermott M. et. al.) - evaluated children with ASD and two control groups matched for age, sex and ethnicity (one with non-autism-related developmental disorders, and the other developmentally normal). There were 50 children in each group – findings concluded:

- 70% of the children with ASD had GI Issues compared to 42% of the children with developmental disorder other than ASD.
- 28% of children with typical development.

Chaidez V, Hansen RL, Hertz-Picciotto I. Department of Public Health Sciences, University of California, Davis, 1616 DaVinci Ct, Davis, CA, 95618, USA, vachaidez@ucdavis.edu.

Abstract:
To compare gastrointestinal (GI) problems among children with: (1) autism spectrum disorder (ASD), (2) developmental delay (DD) and (3) typical development (TD), GI symptom frequencies were obtained for 960 children from the Childhood Autism Risks from Genetics and Environment (CHARGE) study. We also examined scores on five Aberrant Behavior Checklist (ABC) subscales comparing ASD children with high versus low frequency GI symptoms. Compared to TD children, those with ASD [aOR 7.92 (4.89-12.85)] and DD [aOR 4.55 (2.51-8.24)] were more likely to have at least one frequent GI symptom. Restricting to ASD children, those with frequent abdominal pain, gaseousness, diarrhea, constipation or pain on stooling scored worse on irritability, social withdrawal, stereotypy, and hyperactivity compared with children having no frequent GI symptoms.

Summary: Frequent GI problems affect young children with ASD and DD more commonly than those with TD. Maladaptive behaviors correlate with GI problems, suggesting these comorbidities require attention.
Food allergy in this population is common - food allergy can affect any site in the GI tract. Research in the past points to the following food allergy prevalence rates in autistic children:

- 5-8% of neurotypical children without autism (Sampson, 1999) suffer food allergies.
- 36% of autistic children (Lucarelli, 1995) suffer food allergies.
Higher Plasma Concentration of Food-Specific Antibodies in Persons With Autistic Disorder in Comparison to Their Siblings

Vladimir Trajkovski
Aleksandar Petlichkovski
Olivija Efinska-Mladenovska
Dejan Trajkov
Todor Arsov
Ana Strezova
Ljubomir Ajdinski
Mirko Spiroski

Institute of Immunobiology and Human Genetics, Faculty of Medicine, University Ss. Kiril and Metodij, Skopje, Republic of Macedonia
Neurologic and Psychiatric Manifestations of Celiac Disease and Gluten Sensitivity

Jessica R. Jackson,
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William W. Eaton,
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Neurologic and Psychiatric Manifestations of Celiac Disease and Gluten Sensitivity

Jessica R. Jackson, Maryland Psychiatric Research Center, University of Maryland School of Medicine, Box 21247, Baltimore, MD 21228, USA

Abstract

Celiac Disease (CD) is an immune-mediated disease dependent on gluten (a protein present in wheat, rye or barley) that occurs in about 1% of the population and is generally characterized by gastrointestinal complaints. More recently the understanding and knowledge of gluten sensitivity (GS), has emerged as an illness distinct from celiac disease with an estimated prevalence 6 times that of CD. Gluten sensitive people do not have villous atrophy or antibodies that are present in celiac disease, but rather they can test positive for antibodies to gliadin. Both CD and GS may present with a variety of neurologic and psychiatric co-morbidities, however, extraintestinal symptoms may be the prime presentation in those with GS. However, gluten sensitivity remains undertreated and underrecognized as a contributing factor to psychiatric and neurologic manifestations. This review focuses on neurologic and psychiatric manifestations implicated with gluten sensitivity, reviews the emergence of gluten sensitivity distinct from celiac disease, and summarizes the potential mechanisms related to this immune reaction.
Gluten sensitivity

Gluten sensitivity as a neurological illness

M Hadjivassiliou, R A Grünwald, G A B Davies-Jones

From gut to brain

It has taken nearly 2000 years to appreciate that a common dietary protein introduced to the human diet relatively late in evolutionary terms (some 10 000 years ago), can produce human disease not only of the gut but also the this disease was the gut. The first report of neurological manifestations associated with CD was by Carnegie Brown in 1908. In his book entitled Sprue and its treatment he mentioned two of his patients who developed “peripheral neuri-
**Table 1** Neurology of coeliac disease (based on a review of 35 papers of single or multiple case reports from 1964 to 2000)

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
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<tbody>
<tr>
<td>Total number of patients</td>
<td>83</td>
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<tr>
<td>Male to female ratio</td>
<td>44:39</td>
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<tr>
<td>Mean age</td>
<td>48</td>
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<td>Neurological diagnosis</td>
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<td>Ataxia</td>
<td>29</td>
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<tr>
<td>Peripheral neuropathy</td>
<td>29</td>
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<tr>
<td>Myopathy</td>
<td>13</td>
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<tr>
<td>Ataxia with myoclonus</td>
<td>9</td>
</tr>
<tr>
<td>Myelopathy</td>
<td>4</td>
</tr>
<tr>
<td>Dementia (usually with additional features)</td>
<td>6</td>
</tr>
</tbody>
</table>
Figure 1. Brain of a patient with gluten ataxia showing onset of cerebellar atrophy over a period of 15 months before diagnosis of gluten ataxia.
Abnormal peptides in both patients with autism and schizophrenia.

High titers of IgG antibodies to gliadin (wheat) found in 87% of patients with autism and 86% of patients with schizophrenia.

High titers of IgG antibodies to bovine casein found in 90% of patients with autism and 93% of patients with schizophrenia.

A gluten and casein free diet caused significant improvement in 81% of patients with autism within 3 months.
Main Point: A1 (beta-casein), A2 (beta-casein), B casein

- A few thousand years ago European dairy cows carrying the A2 beta-casein mutated to A1.
- This change in gene coding switched proline (pro) in A2 to histidine (his) in A1 (B-casein found in Jersey Cows, and is a subtype of A1) :
When peptide is acted upon by digestive enzymes there is a release of a morphine-like chemical (aka. casomorphin) that can have opiate activity as well as interfere with serotonin metabolism.
Childhood Autism Rating Scale (CARS)

Measuring the amount of casomorphin in urine and severity of autism
Gliadorphin:

\[ \text{tyr-pro-gln-pro-gln-pro-phe} \]

\[ \text{tyr-pro} \]

\[ \text{gln-pro-gln-pro-phe} \]

DPP IV

\[ \text{DPP IV} \]

Inhibits

\[ \text{gln-pro-phe} \]
Clinical Improvements Observed:
- Better bowel function, i.e. less constipation and/or diarrhea
- Improved skin tone, reduced rashes, i.e. eczema
- Improved sleep, mood, and emotional volatility
- Improved pain tolerance, decreased self-injurious behavior.
- Improved language, eye contact, focusing/attention
- Increased appetite for other foods

Trial Diet: 100% - no infractions (if at all possible for at least 3 months – ideally 6+ months). Start with casein 1st for 3 weeks, then start to eliminate gluten.
A1 and B-casein replaced with pea protein. Has similar protein composition to whole milk.

http://nbnus.net/b-unique%20article.pdf
“If the gastrointestinal disorder is recognized and medical treatment is effective, the problem behaviors may diminish. When abdominal pain or discomfort is a setting event, psychotropic medications are likely to be ineffective and may even aggravate the problem if they have adverse gastrointestinal effects.”

3 Common Scenarios Surrounding Constipation Issues in Autism

1. Child has urgency to have bowel movement, but difficulty evacuating it.
   ◦ OTC laxatives, magnesium citrate, fiber, miralax

2. Child has urgency to have bowel movement, but refuses to let it out, i.e. anxiety, fear, sensory issue.
   ◦ OTC laxatives, magnesium citrate, fiber, miralax
   ◦ Behavioral therapy intervention

3. Child lacks the sensory input from digestive system and/or poor peristaltic activity.
   ◦ OTC laxatives, magnesium citrate, fiber, miralax
   ◦ Looks for complicating factors, i.e. digestive pathogens, food sensitivities.
   ◦ GI Referral
Posturing across the edge of a table, the arm of a chair or couch, or pressing abdomen into the floor is not normal. It may be a sign of intestinal pain.
Many of Noah’s behavioral issues associated with bowel discomfort

- Many times preceding Noah’s behavioral issues, i.e. aggression, self-injury he would posture over furniture.
- This would coincide with worsening stool pattern – constipation to loose stools.
- In fact, all along mother reports that digestion “never appeared normal.”
Is self-injurious behavior a normal part of autism? In many children it is triggered because of pain. This behavior warrants investigation and any sign of intestinal issues need to be assessed for underlying pathology.
Occasional loose stools are normal part of our existence. However, as Dr. Krigsman explains in his article, “if most or all of the stools are unformed – it is pathologic.”
“Gastrointestinal Pathology in Autism: Description and Treatment”
by Arthur Krigsman, M.D.

Normal Tissue

Eosinophil infiltration of esophagus – can be triggered by reflux disease which is common in ASD.
Dr. Krigsman describes finding bile refluxing into the esophagus.

Breath smelled like feces.

Caused by slow intestinal motility.

H. pylori and even Candida infections are found.

Food avoidance, pounding on chest, holding stomach in association with tantrums, aggression, etc. Could it be caused by pain?
Poor intestinal motility can lead to severe reflux.

Some ASD kids have motility problems leading to distended abdomens.

**Distention Types Seen in ASD:**

- **Lower (pregnant)** – intestines and colon are full of gas and stool
- **Upper (just below rib cage)** – food is stuck in stomach
Inflammation of the Ileum

- The Ileum is the last part of the small intestine.
- High immunologically reactive area – large amount of lymphoid tissue.
- An area that is commonly affected in ASD.

Signs and Symptoms:
- Diarrhea or constipation
- Self-injurious behavior (SIB)
- Food avoidance
- Poor sleep
- Poor absorption and growth

Severe inflammation of the Ileum
Large Bowel Inflammation

Inflammatory Polyp

Ulcerations in Large Bowel
Noah & Inflammatory Bowel Disease

- Noah referred to Dr. Arthur Krigsman for evaluation.
- Scope examination reveals abundant inflammatory lesions throughout bowel.
- Treatment approach similar to Chron’s disease, i.e. Entecort, Pentasa.
Noah Today

- Violent outbursts almost non-existent.
- Still with anxiety, but manageable
- Digestion – having formed stools for first time in years.
- Still needs behavioral intervention, but severity of prior behavioral problems significantly reduced.
- Family still struggling with insurance company, financial challenges, etc. in fight with insurance company for ongoing medical treatment.
- Medical situation appears stable

IBD Stable

Noah Calmer and Less Volatile Emotionally
How Did I Get Involved With This Community Of Patients?
Autism Research Institute

Autism is Treatable
Bernard Rimland, Ph.D.

1928 - 2006
Dedicated to Exploring the Various Medical Complexities Seen With Autism

Defeat Autism Now!
What is Biomedical Intervention for Autism?

The attempt to improve the autistic condition by identifying the co-morbid conditions - structural, biochemical, organ specific - and treating these medically (when appropriate). Biomedical intervention incorporates all aspects of health treatment:

- **Dietary modification**
- **Medications**
- **Nutritional supplements**
- **Commonly used in conjunction with speech, occupational, behavior, and physical therapy.**

Multi-system disorder that affects the brain versus just being a brain disorder
Medical Comorbidities in Autism Spectrum Disorders
A Primer for Health Care Professionals and Policy Makers
Second Edition: July 2014

I also realized that the desperation amongst many parents was they were being given the ‘cold shoulder’ by some in the medical profession. Their kids being essentially cast aside because of their autism diagnosis.

“Perpetuating the myth of autism as a primarily genetic disorder is a disservice to those who might benefit from treatment and diverts attention from non-genetic causes.”

Prof. Richard Deth, Northeastern University, Boston
Failure to Evaluate & Treat By Some In The Medical Community – Prejudiced by the Diagnosis?

Child w/o Autism (example)
- Physical milestones delayed
- Chronic diarrhea – 5+ BM’s per day
- Recurrent sinus, ear & upper respiratory infections
- Eczema
- Bloating, gas and distended abdomen
- Anxiety, attention issues
- Irritable, poor sleep

Child with Autism (example)
- Physical milestones delayed
- Chronic diarrhea – 5+ BM’s per day
- Recurrent sinus, ear & upper respiratory infections
- Eczema
- Bloating, gas and distended abdomen
- Anxiety, attention issues
- Irritable, poor sleep
Treating the Medical Issues of Children with ASD

“I work with kids who have multiple medical problems including nutritional imbalances, digestive and detoxification problems, food sensitivity issues, etc.”

The common denominator is all of these kids happen to have a diagnosis of autism.
What Are The Medical Complexities Of Spectrum Disorders

} Genetics
  ◦ PON1, Methylation (MTHFR), etc.

} Nutritional Imbalances
  ◦ Zinc and mineral deficiencies, copper excess, cholesterol deficiency and more

} Food Sensitivities
  ◦ Gluten and casein peptides, multiple food allergies, phenol sensitivity, etc.

} Biochemical Imbalances – too many to list

} Digestive Problems
  ◦ Constipation, diarrhea, Inflammatory Bowel Disease

Referenes: www.autism.com
What Are the Medical Complexities of Spectrum Disorders

} Chronic Infections
  ◦ Bacteria, i.e. clostridia, yeast, Lyme, chronic virus infections

} Heavy Metal Toxicity
  ◦ Mercury, lead, arsenic – combination of toxic stress

} Neuroinflammation & Neurotoxicity
  ◦ Microglia activation
  ◦ Glutamate sensitivity

} Neurochemistry Problems
  ◦ Serotonin, dopamine, oxytocin, MAO-A, acetylcholine imbalances, Cerebral Folate Deficiency

References: www.autism.com
There is no one drug, supplement or “magic bullet” therapy for autism.
GI Pathogens

How They Can Negatively Influence Brain Function and Behavior?
Organic Acids Testing (urine)
## Organic Acid Profile

### Yeast/Fungal

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### Bacterial

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### Oxalate-related

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### Glycolysis

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### Krebs Cycle

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<td>2-Methylsuccinic</td>
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### Neurotransmitters

<table>
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<tr>
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<th>Low</th>
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<tbody>
<tr>
<td>HVA</td>
<td>0.0 ± 7.5</td>
<td>8.40</td>
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<td>VMA</td>
<td>1.0 ± 4.7</td>
<td>13.66</td>
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<tr>
<td>5-Hydroxindolacetic</td>
<td>0.0 ± 20.0</td>
<td>4.90</td>
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### Pyrimidines

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<tbody>
<tr>
<td>Uracil</td>
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<td>8.72</td>
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<tr>
<td>Thymine</td>
<td>0.0 ± 2.0</td>
<td>0.51</td>
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### Fatty acid metabolism

<table>
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<td>1.87</td>
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<td>succinate</td>
<td>0.0 - 10.0</td>
<td>3.28</td>
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<tr>
<td>ethylmalonic</td>
<td>0.0 - 10.0</td>
<td>7.00</td>
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<td>adipic</td>
<td>0.0 - 12.0</td>
<td>13.79</td>
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<tr>
<td>suberic</td>
<td>0.0 - 2.0</td>
<td>10.84</td>
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<td>suberic</td>
<td>0.0 - 2.0</td>
<td>0.72</td>
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### Toxic indicators

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### Vitamin indicators

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### Amino acid metabolism

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### Miscellaneous

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<td>indole-like compound</td>
<td>0.0 - 60.0</td>
<td>22.98</td>
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</table>
William Shaw, Ph.D., is board certified in the fields of clinical chemistry and toxicology by the American Board of Clinical Chemistry. Before he founded The Great Plains Laboratory, Inc., Dr. Shaw worked for the Centers for Disease Control and Prevention (CDC), Children's Mercy Hospital, University of Missouri at Kansas City School of Medicine, and Smith Kline Laboratories. He is the author of Biological Treatments for Autism and PDD, originally published in 1998 and Autism: Beyond the Basics, published in 2009. He is also a frequent speaker at conferences worldwide.

Dr. Shaw is the stepfather of a child with autism and has helped thousands of patients and medical practitioners to successfully improve the lives of people with autism, AD(H)D, Alzheimer's disease, arthritis, bipolar disorder, chronic fatigue, depression, fibromyalgia, immune deficiencies, multiple sclerosis, OCD, Parkinson's disease, seizure disorders, tic disorders, Tourette syndrome, and other serious conditions.
CLIA Compliance

The Great Plains Laboratory is fully certified under the federally mandated Clinical Laboratory Improvement Amendments (CLIA). All referral laboratories used by The Great Plains Laboratory are also CLIA certified. The CLIA license means the laboratory has met a number of federal standards for operating a laboratory.

Proficiency Testing

The Great Plains Laboratory voluntarily participates in all proficiency programs offered by the College of American Pathologists (CAP).
Insurance accepted:

- Blue Cross/Blue Shield
- Medicare, Medicaid, Tricare

Discount on cash payments

Physician pricing options
Chronic Candidiasis – a potential instigator of health issues
EFFECT OF 10 DAYS OF NYSTATIN

N = 22  PRE

p = 0.034

ARABINOSE

Courtesy - William Shaw, Ph.D
Handwriting improvement after antifungal therapy - Discover magazine

Before Antifungal

After Antifungal 1 month later
Effectiveness of nystatin in polysymptomatic patients. A randomized, double-blind trial with nystatin versus placebo in general practice

Heiko Santelmann, Even Laerum, Joergen Roennevig\textsuperscript{a} and Hans E Fagertun\textsuperscript{b}

In the 116 patients selected by the FRDQ-7 questionnaire, nystatin therapy reduced overall symptoms significantly as compared with placebo, even after correction for sugar- and yeast-free diet. When assessing individual improvement only, six of the Nystatin showed the most striking effect for mental, abdominal and urogenital complaints. Since we did not perform microbiological studies in the patients and the positive effect of nystatin may be due to its effect on other fungi, a connection between \textit{C. albicans} and FRD remains unproved.

Nystatin is well known for its antifungal effect on \textit{C. albicans} which is found in all segments of the gastrointestinal tract in 10–80\% of humans,\textsuperscript{14,15,19} as well as on other yeasts and moulds.
Patients with chronic candidiasis have many of the same symptoms as those with the chronic fatigue syndrome, except for the recurrent flu-like symptoms of the latter disorder.

The positive response of a large number of patients with the chronic fatigue syndrome (CFS) to an oral antifungal agent and a diet for intestinal candidiasis has been described.
84% of 1100 patients with CFS had clearing of symptoms after the antifungal ketoconazole.

Only 12 of 685 on disability stayed on disability.
Common Symptoms

Chronic Fatigue: 100%
Cold Extremities: 100%
Impaired Memory: 100%
Frequent Urination: 95%
Depression: 94%*
Sleep Disorder: 94%
Balance Problems: 89%
Muscle Twitching: 80%
Dry Mouth: 68%
Muscle Aches: 68%
Headache: 68%
Sore Throat: 20%
### Yeast/Fungal section of Organic Acids Test from Great Plains Laboratory – [www.greatplainslaboratory.com](http://www.greatplainslaboratory.com)

<table>
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<td>tartaric</td>
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<tr>
<td>carboxycitr</td>
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<td>4.32</td>
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</table>
Silly/goofy/giddy, inappropriate laughter - acts drunk.

Sugar and carbohydrate cravings intensified.

Heightened sensory seeking behavior, anxiety, and emotional instability.

Strange behavior such as seeking pressure, hanging upside down, heightened seeking of masturbation.
Symptoms Improved by Antifungals

Increased focus and concentration
Improved receptive and expressive language
Reduced bowel symptoms
Increased eye contact and socialization
Reduced self-stimulatory behavior
Reduced aggressive and self-abusive behaviors
Reduced candida symptoms such as thrush
Reduced skin rashes
Nystatin Prescription:
- **Tablet** = 500,000 units – 1 to 2 TID to QID
- **Oral Suspension** (100,000 units/ml) – $\frac{1}{4}$ to 1 teaspoon 3-4x/day.

NOTE: will normally use for 30 to 60+ days in many cases. Longer use for chronic situations.
Yeast Treatments – Medications

Diflucan (Fluconazole):

- **Tablet** = 100mg, 150mg, 200mg – typical use is once daily.
- **Oral Suspension** – 10mg/ml or 40mg/ml – take once daily.
- Average dosing = 5mg/kg/day
- Length (variable) – 15 to 30 days+
- Can rotate with other antifungals, i.e. Nystatin.
- MUST monitor liver function every to 6 to 8 weeks.

Other medications such as Sporanox and Lamisil can be used similarly (note: Nizoral – no longer use)
Autism and Gastrointestinal Bacterial Imbalances

What Does The Research Say?
Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour

John F. Cryan\textsuperscript{1,2} and Timothy G. Dinan\textsuperscript{1,3}

Abstract | Recent years have witnessed the rise of the gut microbiota as a major topic of research interest in biology. Studies are revealing how variations and changes in the composition of the gut microbiota influence normal physiology and contribute to diseases ranging from inflammation to obesity. Accumulating data now indicate that the gut microbiota also communicates with the CNS — possibly through neural, endocrine and immune pathways — and thereby influences brain function and behaviour. Studies in germ-free animals and in animals exposed to pathogenic bacterial infections, probiotic bacteria or antibiotic drugs suggest a role for the gut microbiota in the regulation of anxiety, mood, cognition and pain. Thus, the emerging concept of a microbiota–gut–brain axis suggests that modulation of the gut microbiota may be a tractable strategy for developing novel therapeutics for complex CNS disorders.
The effects of Clostridia bacteria metabolism on gastrointestinal function and mental health and neurotransmitter balance

William Shaw Ph.D.
The Great Plains Laboratory
www/GPL4U.com
11 children with regressive-onset autism were recruited for an intervention trial using a minimally absorbed oral antibiotic. Entry criteria included antecedent broad-spectrum antimicrobial exposure followed by chronic persistent diarrhea, deterioration of previously acquired skills, and then autistic features. Short-term improvement was noted using multiple pre- and post-therapy evaluations. These included coded, paired videotapes scored by a clinical psychologist blinded to treatment status; these noted improvement in 8 of 10 children studied. Unfortunately, these gains had largely waned at follow-up.

“Although the protocol used is not suggested as useful therapy, these results indicate that a possible gut flora-brain connection warrants further investigation, as it might lead to greater pathophysiologic insight and meaningful prevention or treatment in a subset of children with autism.”
Demonstrate GI barrier defects and microbiota alterations in the maternal immune activation (MIA) mouse model that is known to display features of ASD.

Oral treatment of MIA offspring with the human commensal \textit{Bacteroides fragilis} corrects gut permeability, alters microbial composition, and ameliorates defects in communicative, stereotypic, anxiety-like and sensorimotor behaviors. MIA offspring display an altered serum metabolomic profile (4-ethylphenylsulphate), and \textit{B. fragilis} modulates levels of several metabolites.

Treating naive mice with a metabolite that is increased by MIA and restored by \textit{B. fragilis} causes certain behavioral abnormalities, suggesting that gut bacterial effects on the host metabolome impact behavior.

"Taken together, these findings support a gut-microbiome-brain connection in a mouse model of ASD and identify a potential probiotic therapy for GI and particular behavioral symptoms in human neurodevelopmental disorders."
“It was observed that mentally ill patients, in general, seem to excrete much larger amounts of HPHPA than do most normal people.”

“Most patients with mental retardation excrete very low amounts of HPHPA.”
Increased urinary excretion of a 3-(3-hydroxyphenyl)-3-hydroxypropionic acid (HPHPA), an abnormal phenylalanine metabolite of Clostridia spp. in the gastrointestinal tract, in urine samples from patients with autism and schizophrenia

William Shaw

The Great Plains Laboratory, Inc., Lenexa, Kansas, USA

A compound identified as 3-(3-hydroxyphenyl)-3-hydroxypropionic acid (HPHPA) was found in higher concentrations in urine samples of children with autism compared to age and sex appropriate controls and in an adult with recurrent diarrhea due to Clostridium difficile infections. The highest value measured in urine samples was 7500 mmol/mol creatinine, a value 300 times the median normal adult value, in a patient with acute schizophrenia during an acute psychotic episode. The psychosis remitted after treatment with oral vancomycin with a concomitant marked decrease in HPHPA. The source of this compound appears to be multiple species of anaerobic bacteria of the Clostridium genus. The significance of this compound is that it is a probable metabolite of m-tyrosine (3-hydroxyphenylalanine), a tyrosine analog which depletes brain catecholamines and causes symptoms of autism (stereotypical behavior, hyperactivity, and hyper-reactivity) in experimental animals.
Structure of 3- (3- hydroxyphenyl)-3- hydroxypropionic acid

Hydroxyl group

HO

Phenyl group

Propionic acid

\[
\text{CHOHCH}_2\text{COOH}
\]
Clostridia by electron microscopy
Clostridia species that produce HPHPA precursors
Shaw, Nutritional Neuroscience 2010 Vol 13 No 3: 1–10

- C. difficile-pseudomenbranous colitis
- C. sporogenes
- C. botulinum-food poisoning
- C. mangenotii
- C. ghoni
- C. bifermentans
- C. caloritolerans
<table>
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<td>C. sporospheroides</td>
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<td>C. putifaciens</td>
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<td>C. propionicum</td>
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<tr>
<td>C. malenomenatum</td>
<td>C. tetanomorphum</td>
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Status of approximately 80 other species of Clostridia in GI tract unknown.
### Organic acid test–urine

#### Bacterial

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<th>Upper Limit</th>
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<td>4-hydroxyphenylacetic</td>
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<tr>
<td>HPHPA</td>
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#### Neurotransmitters

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<tr>
<td>VMA</td>
<td>1.0</td>
<td>4.7</td>
<td>7.17</td>
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H indicates normal levels.
Critical effect of intestinal bacteria on brain neurotransmitters

Organic acid test

Organic acid test

Organic acid test
Critical effect of intestinal bacteria on brain neurotransmitters

Organic acid test

Organic acid test

Dopamine Beta Hydroxylase

Homovanillic Acid (HVA)

Vanillylmandelic Acid (VMA)

Epinephrine

Norepinephrine
Effect of HPHPA on neurotransmitters-severe autism (case 1)

HPHPA mmol/mol creatinine

HVA, VMA mmol/mol creatinine

Time (calendar date)

HPHPA

HVA (dopamine)

VMA (norepinephrine)

Clostridia

Effect of HPHPA on neurotransmitters-severe autism (case 2)

![Graph showing the effect of HPHPA on neurotransmitters.]
Distribution of values for HPHPA Clostridia metabolite in urine samples of male infants, control boys, and boys with autism.

3-(3-hydroxyphenyl)-3-hydroxypropionic acid HPHPA - mmol/mol creatinine

- Control infants (N = 14)
- Control boys 2-13 years (N = 30)
- Autistic Boys 2-13 years (N = 211)
Clostridium difficile is an important nosocomial pathogen, resulting in antibiotic-associated disease ranging from mild diarrhoea to the life-threatening pseudomembranous colitis. Upon antibiotic exposure, it is believed that the normal bowel microflora of patients is disrupted, allowing C. difficile to proliferate.

C. difficile is among only a few bacteria able to ferment tyrosine to p-cresol, a phenolic compound that is toxic to other microbes via its ability to interfere with metabolism.

Therefore, the ability of different C. difficile strains to produce and tolerate p-cresol may play an important role in the development and severity of C. difficile-associated disease. In this study, it was demonstrated that two C. difficile hypervirulent 027 strains (Stoke Mandeville and BI-16) are more tolerant to p-cresol than other C. difficile strains including 630, CF4 and CD196. Surprisingly, it was shown that Clostridium sordellii also has a high tolerance to p-cresol, suggesting an overlap in the tolerance pathways in these clostridial species.
Formation of p-cresol from tyrosine by Clostridia difficile bacteria

[Chemical structures]

- Tyrosine
- 4-hydroxy-phenylpyruvic
- 4-hydroxy-phenylacetic
- p-cresol
- p-cresol sulfate

14728–14733 PNAS August 25, 2009 vol. 106 no. 34
Demonstrate GI barrier defects and microbiota alterations in the maternal immune activation (MIA) mouse model that is known to display features of ASD.

Oral treatment of MIA offspring with the human commensal *Bacteroides fragilis* corrects gut permeability, alters microbial composition, and ameliorates defects in communicative, stereotypic, anxiety-like and sensorimotor behaviors.

MIA offspring display an altered serum metabolomic profile: 4-ethylphenylsulphate 

Treating naive mice with a metabolite that is increased by MIA and restored by *B. fragilis* causes certain behavioral abnormalities, suggesting that gut bacterial effects on the host metabolome impact behavior.

“Taken together, these findings support a gut-microbiome-brain connection in a mouse model of ASD and identify a potential probiotic therapy for GI and particular behavioral symptoms in human neurodevelopmental disorders.”
The researchers further dissected what was going on by screening for chemicals in the blood that differed between autistic and wild-type mice. One compound, 4-ethylphenylsulphate (4EPS), stood out:

1. It was found at levels 46 times higher in autistic mice.
2. Injecting 4EPS into wild-type mice resulted in autism-like behaviors. It’s still unclear if *B. fragilis* is producing 4EPS, however.

4EPS – Is similar in chemical structure to 4-Cresol which is known to inhibit Dopamine Beta-Hydroxylase.
Toxicity of excess dopamine

Homovanillic acid (HVA)
Dihydroxyphenylacetic (DOPAC)

Cycled thousands of times

Neurodegeneration

Apoptosis of brain cells in presence of excess dopamine
Dopamine is a very reactive molecule compared with other neurotransmitters, and dopamine degradation naturally produces oxidative species.

More than 90% of dopamine in dopamine neurons is stored in abundant terminal vesicles and is protected from degradation.

However, a small fraction of dopamine is cytosolic, and it is the major source of dopamine metabolism and presumed toxicity.
Cytosolic dopamine undergoes degradation to HVA, as well as extremely toxic dopamine metabolites and oxidative species which deplete brain glutathione.

These toxic metabolites caused by excess dopamine may cause severe neurodegeneration of neural pathways that utilize dopamine as a neurotransmitter.
Overstimulation of dopamine tracts

Substitution of dopamine into norepinephrine tracts and sympathetic nervous system.

Damage to neurons producing excess dopamine due to oxidative damage of abnormal dopamine metabolites.

Depletion of glutathione in brain making it susceptible to other toxic chemicals.
Properties of Clostridia bacteria

} Strict anaerobe - *dies when exposed to oxygen*
} Causes tetanus, diarrhea, and botulism (food poisoning).
} Forms spores that are highly resistant to heat and antibiotics.
} About 100 species of Clostridia in GI tract
} Controlled by vancomycin, metronidazole, and Lactobacillus acidophilus GG.
Spore formation—most difficult challenge to prevent recurrence

- Recurrences occur after use of metronidazole and/or vancomycin.
- Spores not killed by common disinfectants like alcohol hand wipes - *may actually help spores spread*.
- Only bleach kills spores.
- Carriers without symptoms may spread spores.
Effect of metronidazole on urine HPHPA levels in autism
William Shaw Nutritional Neuroscience 2010 Vol 13 No 3: 1–10

Urine HPHPA mmol/mol creatinine

Days after start of treatment

Start metronidazole

Stop metronidazole
**Treatment Considerations**

**Clostridia Behavior Examples:**
- Irritable
- *Agitated*
- *Aggressive*
- *Biting, kicking, screaming*
- “Head-banging”
- Decreased eye contact
- Not engaged
- Stools more loose

**Yeast Behavior Examples:**
- Stimming
- Toe-walking
- Decreased eye contact
- *Silly/goofy/giddy, inappropriate laughter*
- Not engaged
- Echolalia
- Sugar and carbohydrate cravings intensified
- Stools loose or constipated
- Irritable
Flagyl, aka. metronidazole (pill or suspension) – 250mg to 500mg 3x/day for 10 to 14 days. Cyclical dosing is appropriate.

Vancomycin, aka. vancocin (pill or suspension) – 125mg to 500mg 3x/day for 10 to 14 days. Cyclical dosing is appropriate.

NOTE: Approximate dosing range is 30mg to 40mg/kg split dosed three times daily.

Cyclical Dosing Option:
- One dose TID for 10 days, then
- Every 3rd day – one treatment day (one dose TID) for 3 weeks.
Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve

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Edited by Todd R. Klaenhammer, North Carolina State University, Raleigh, NC, and approved July 27, 2011 (received for review February 27, 2011)

There is increasing, but largely indirect, evidence pointing to an effect of commensal gut microbiota on the central nervous system (CNS). However, it is unknown whether lactic acid bacteria such as *Lactobacillus rhamnosus* could have a direct effect on neurotransmitter receptors in the CNS in normal, healthy animals. GABA is the main CNS inhibitory neurotransmitter and is significantly involved in regulating many physiological and psychological processes. Alterations in the brain GABAergic system have been observed in various psychiatric disorders, and GABAergic medications are effective therapy. Thus, GABAergic systems are important pharmacological targets for clinically relevant antianxiety agents (e.g., benzodiazepines acting on GABA\(_A\) receptors), and alterations in the GABAergic system have important roles in the development of stress-related psychiatric conditions.

Probiotic bacteria are living organisms that can inhabit the gut and contribute to the health of the host (14). Accumulating clinical evidence suggests that probiotics can modulate the stress response and inflammation in the gut and brain. Furthermore,
The Bidirectional Gut-Brain Axis

The ability of the brain to influence the intestinal microbiota

Perturbation of your normal habitat via stress-induced changes in gastrointestinal:
- Physiology
- Epithelial function
- Mucin production
- EE cell function
- Motility
- Release of Neurotransmitters

GBA

Microbiota-gut interplay

The ability of the microbiota to influence brain, behavior, and mood

Activation of neural pathways to the brain

Activation of musosal immune responses

Production of metabolites that directly affect the CNS

“Animal studies have also shown that stress can change the composition of the microbiome, where the changes are associated with increased vulnerability to inflammatory stimuli in the gut.”

“Stress is known to inhibit gut contraction, one of the crucial defense strategies against bacterial colonization of gut mucosa.

Early psychological trauma of maternal separation resulted in persistent mucosal barrier dysfunction in neonatal rats, including host defense to luminal bacteria, by mechanisms involving peripheral CRH receptors.”
Chronic Stress Response

Potential Sources of Stress

- Anger - Fear
- Worry/Anxiety
- Depression
- Guilt
- Overwork
- Physical and Mental strain
- Excessive exercise
- Sleep deprivation
- Light-cycle disruption
- Late hours
- Surgery
- Trauma/Injury
- Whiplash – Head injury
- Inflammation
- Pain
- Temperature extremes
- Toxic exposure
- Infections
- Chemicals - Heavy metals
- Electromagnetic fields
- Radiation
- Geophysical
- Malabsorption
- Maldigestion
- Illness
- Low blood sugar - Poor diet
- Nutritional deficiencies
- Allergies
- Foods
- Mold – Pollens

Sympathetic System

Stressor

Epinephrine

HP

Reduced HP Sensitivity to Negative Feedback

NFL

ACTH ↑↑↑

Adrenal Cortex

Total Cortisol

Free Cortisol

Elevated Cortisol to DHEA Ratio*

Energy Production
- Insulin sensitivity ↓
- Glucose utilization ↓
- Blood sugar ↑
- Gluconeogenesis ↑

Other Influences
- Osteoporosis (bone loss) ↑
- Fat accumulation (waist) ↑
- Protein breakdown ↑
- Salt & water retention ↑

Other Influences
- Pregnenolone Steal (Cortisol Escape)

Energy Production

Immune Activity
- Secretory IgA ↓
- Antigen penetration ↑
- Circulating IgG ↑
- NK cell activity ↓
- Interleukin 2 ↓
- T-Lymphocytes ↓

* Abnormal Ratio of Cortisol to DHEA indicates Pregnenolone Steal (Cortisol Escape)

Clinical Conditions
- Chronic viral infections (EBV, CMV, Herpes I-II, etc.)
- Insomnia
- Yeast overgrowth
- Hypoglycemia
- Allergies
- Hunger
- Fatigue
- PMS
- Headaches
- Depression
- Autoimmune disease
- Irritable bowel
- Cancer
- Digestive problems
- Cardiovascular disease
- ADD/ADHD

KEY

Association
Stimulus
Outcome
Inhibition

HP = Hypothalamus - Pituitary
NFL = Negative Feedback Loop
NE = Norepinephrine
“Evidence indicates that the **vagus nerve** is involved in immunomodulation - attenuates the production of pro-inflammatory cytokines in experimental models of inflammation.”

“The microbiome also plays an important role in anxiety-like and depressive behaviors - effects are diminished in vagatomized animals.”

“Suggest either the direct communication between the bacteria and the brain or through the brain-gut axis.”
Vagal Transport of Neurotoxins

“Oral antibiotics disrupt the microbiome and favor environment for opportunistic bacteria. *Clostridium tetani*, an anaerobic bacillus produces a potent neurotoxin, tetanus neurotoxin (TeNT) that is transported by the vagus nerve from the GI to the CNS.”

Inhibitory neurons that release the neurotransmitter GABA are a preferred target for tetanus neurotoxins – and the Purkinje cells of the cerebellum, which often appear highly abnormal in autistic individuals, are inhibitory neurons that release GABA.
**HEALTH**
- Normal range of social and feeding behaviors
- Functional social- and food-reward center(s)
- Normal gastrointestinal functions
- Normal gut permeability and gut motility
- Normal level of cytokines
- Age-appropriate level of brain neurotrophins
- Balanced gut microbiome

**AUTISM**
- Altered social and feeding behaviors
- Altered function(s) of social and food-reward center(s)??
- Gastrointestinal problems
- Increased gut permeability "leaky-gut”; altered gut motility
- Increased levels of cytokines
- Altered levels of brain neurotrophins
- Increased biodiversity of gut microbiome; dysbiosis
Let’s Bring It Back to Osteopathy
Children with Chiari frequently have tendency to headaches, neck pain, speech and swallowing difficulties, sensori-motor disorders, gastro-esophageal reflux, disordered respiration and sleep apnea - the same findings that characterize ASD (Rimland, B. Autism Research Review International, 2005). Other shared deficits include loss of smooth ocular pursuit, dysarthria, abnormal motor initiation, disordered neuro-endocrine modulation within the reticular activating system and possibly cerebellar mediated alterations of cerebral activity (Courchesne, E. Neuroanatomic Imaging. Suppl 781-790, 2001). This overlap of characteristics suggests that these disorders may be co-morbid conditions. Furthermore, in the course of routine surgical correction of Chiari disorders, members of CSF have measured substantial improvement in pain, function, and quality of life in ASD patients (Bolognese, Kula 2010; Henderson, 2008, 2010).
Action Steps

Things You Can Do Right Away To Help Families Struggling Autism
What You Can Do To Help More Individuals With Autism

- Don’t be fooled by the autism label
- Be open to evaluating them medically
- Be willing to work with parents – many times all that a parent wants is a doctor who will try their best to help them.
- Ask parents for their help in research - articles, videos, other parents experience regarding their child’s symptoms.
Begin ordering Organic Acids Test – first test I always do:

- Consider trial of Nystatin for 4 to 8 weeks if high yeast markers are present.
- Consider antibiotic therapy if clostridia markers are present.

Comprehensive blood testing to look for nutritional deficiencies, thyroid imbalances, and lipid profiles (often times have low total cholesterol).
What You Can Do To Help More Individuals With Autism

} Recommend Gluten and Casein-Free Diet (GFCF) – consider trial for 3 months.


} Place kids on general supplements (see New Beginnings Start Package)
New Beginnings Nutritionals – www.nbnus.com

Contact:
Lori Knowles

What You Can Do To Help More Individuals With Autism

- Treat individuals with osteopathic manipulative medicine – not always easy, but definitely beneficial.
- Provide parents with educational material.
Support Networks

} TACA – www.tacanow.org
} Generation Rescue –
www.generationrescue.com
} National Autism Association –
www.nationalautismassociation.com
} Autism Research Institute – www.autism.com
Monthly Webinars

www.greatplainslaboratory.com/home/eng/recorded_webinars.asp
Autism Action Plan.com
Patient (and physician) subscription website with daily access to Dr. Woeller for questions and answers, as well as videos, articles, protocols and more.
September 19-21, 2014 – San Antonio, TX.

October 4, 2014 – Seattle, WA

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