The Biosciences Behind Autism: Explaining the Scientific Basis for Biomedical Interventions used for the Treatment of Autistic Spectrum Disorders

Autism One/Generation Rescue
2011 Conference Chicago
The Westin Hotel
Lombard, IL
May 25-29, 2011

Lauren W. Underwood, PhD

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The information provided today is for educational purposes only, and *should not* be used in place of profession medical and/or nutritional supervision. If medical advice is needed, this service should be given by a licensed medical provider.

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Today's Presentation

Will present discuss the scientific basis of available medical treatment options for autism, and review some of the medical approaches for implementing them.

Outline

- The science of the body
- Dietary changes/modifications
- Metabolic imbalance and the basis of biochemical treatment
- Nutritional supplements

Autism *Spectrum* Disorders

ADHD | Asperger Syndrome | PDD-NOS | Autism

Psychologically defined

Communication | Stereotypical behaviors | Social interaction

Understanding the underlying pathophysiologies that result in the biomedical conditions associated with autism

Neurotypical | Autism

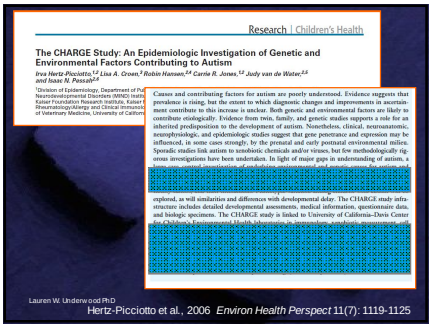
Autisms *Spectrum* of Symptoms

Metals
Pesticides
Toxin build up

Inflammation
allergy

Oxidative Stress
Detoxification issues

Low Glutathione
Detoxification issues



Research | Children's Health

The CHARGE Study: An Epidemiologic Investigation of Genetic and Environmental Factors Contributing to Autism

Irva Hertz-Picciotto,[1,2] Lisa A. Croen,[3] Robin Hansen,[2,4] Carrie R. Jones,[1,2] Judy van de Water,[2,5] and Isaac N. Pessah[2,5]

[1]Division of Epidemiology, Department of Public Health Sciences, [2]Medical Investigation of Neurodevelopmental Disorders (MIND) Institute, [3]Division of Research, Kaiser Permanente Northern California, Kaiser Foundation Research Institute, Kaiser Permanente, [4]Department of Pediatrics, and [5]Department of Molecular Biosciences, School of Veterinary Medicine, University of California, Davis, California, USA

Causes and contributing factors for autism are poorly understood. Evidence suggests that prevalence is rising, but the extent to which diagnostic changes and improvements in ascertainment contribute to this increase is unclear. Both genetic and environmental factors are likely to contribute etiologically. Evidence from twin, family, and genetic studies supports a role for an inherited predisposition to the development of autism. Nonetheless, clinical, neuroanatomic, neurophysiologic, and epidemiologic studies suggest that gene penetrance and expression may be influenced, in some cases strongly, by the prenatal and early postnatal environmental milieu. Sporadic studies link autism to xenobiotic chemicals and/or viruses, but few methodologically rigorous investigations have been undertaken. In light of major gaps in understanding of autism, a [illegible] exploited, as will similarities and differences with developmental delay. The CHARGE study infrastructure includes detailed developmental assessments, medical information, questionnaire data, and biologic specimens. The CHARGE study is linked to University of California–Davis Center for Children's Environmental Health. Phenotypic, symptom, exposure, and

Hertz-Picciotto et al., 2006 *Environ Health Perspect* 11(7): 1119-1125

Autism is treatable

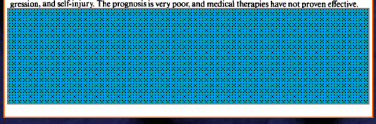
- Recent research shows that autism is treatable
- Early interventions lead to the best outcomes
- Be aware of symptoms, and begin addressing them as soon as possible
- Complementary approaches often provide optimal results

There is still not a cure, but there are many treatments to consider

Behavioral Treatment and Normal Educational and Intellectual Functioning in Young Autistic Children

O. Ivar Lovaas
University of California, Los Angeles

Autism is a serious psychological disorder with onset in early childhood. Autistic children show minimal emotional attachment, absent or abnormal speech, retarded IQ, ritualistic behaviors, aggression, and self-injury. The prognosis is very poor, and medical therapies have not proven effective.



Lovaas, O.I., 1987 *J Consult Clinic Psych* 55(1): 3-9

Biomedical treatment options

- Step 1: STABILIZE **gastrointestinal tract**
  - Improve diet
  - Improve nutrition by using supplements, including
    - antioxidants,
    - essential vitamins
  - Consider GFCF diet
  - Resolve intestinal issues, i.e.
    - dysbiosis
    - increased intestinal permeability
- Step 2: DETOXIFY & REGULATE **immune system**
  - Complementary/alternative treatments
    - supplement with Methylation/sulfation co-factors
    - HBOT
    - IVIG
    - methyl B12

American Academy of Pediatrics

CLINICAL REPORT

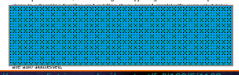
Management of Children With Autism Spectrum Disorders

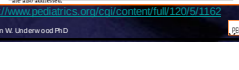
Guidance for the Clinician in Rendering Pediatric Care

Scott M. Myers, MD, Chris Plauche Johnson, MD, MEd, the Council on Children With Disabilities

ABSTRACT

Pediatricians have an important role not only in early recognition and evaluation of autism spectrum disorders but also in chronic management of these disorders. The primary goals of treatment are to maximize the child's ultimate functional independence and quality of life by minimizing the core autism spectrum disorder features, facilitating development and learning, promoting socialization, reducing maladaptive behaviors, and educating and supporting families. To assist pediatri-





http://www.pediatrics.org/cgi/content/full/120/5/1162

How do you begin to treat autism biomedically?

- Look for a physician or other healthcare practitioner who considers an integrative approach to treatment
  - combining mainstream medical therapies and CAM (Complementary and Alternative Medicine) therapies
- No single treatment works for every child
- What works for one child may not work for another, and a successful course of treatment often includes a combination of approaches

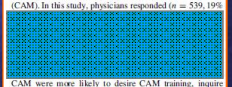
J Autism Dev Disord (2009) 39:996–1005
DOI 10.1007/s10803-009-0714-7

ORIGINAL PAPER

Complementary Alternative Medicine for Children with Autism: A Physician Survey

Allison E. Golnik · Marjorie Ireland

Abstract Previous studies suggest over half of children with autism are using complementary alternative medicine (CAM). In this study, physicians responded ($n = 539$, 19%



CAM were more likely to desire CAM training, inquire about CAM use, be female, be younger, and report greater autism visits, autism education and CAM knowledge. Physicians were more likely to desire CAM training, inquire about CAM and view CAM as a challenge for children with autism compared to children with other neurodevelopmental and chronic/complex conditions.

Golnick and Ireland, 2009 *J Autism Deve Disord* 39: 996-1005

Expected key benefits of biomedical treatment for autism

- Improvements in *immune function*, resulting in healthier children who seem to be very resistant to coughs, colds, runny noses, ear infections and who seem to get over viral infections quicker than the rest of the family.
- Improvements in *digestive function*, resulting in more normal stool frequency and consistency; reduction or elimination of lower abdominal pain or discomfort; reduction or elimination of loose stools or diarrhea.

Children seem to thrive

Expected outcomes associated with biomedical treatment for autism

- Improved appetite and a wider variety of foods tried and consumed, increased nutrition

THEN . . .

- Better socialization and initiation of communication with family and peers;
- Increase in more *normal* social interactions and social play
- Improved vocabulary and sentence structure;
- Improved cognitive function
- Improved higher order functions

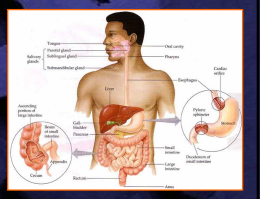
The science of the body and what can go wrong

The science of the body

- The body is made up of specific systems, including skeletal, circulatory, digestive, immune, cardiovascular, and nervous
- Digestive system
  - Anatomy and function
  - Food allergies/food intolerances
  - Leaky gut/intestinal dysbiosis
  - Basic biochemistry
- Immune system function

Digestive system

- Mouth
  - Tongue and glands
- Esophagus
- Stomach
- Small intestine
  - Duodenum
  - Jejunum
  - Ileum
- Large intestine/Colon
- Rectum
- Anus
- Liver
- Pancreas



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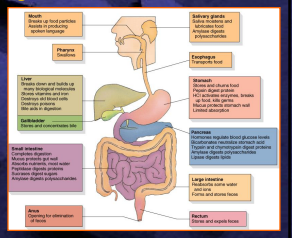
Digestion-digestive tract function

- The digestive system is a series of hollow organs joined in a long tube from the mouth to the anus.
- The main function of the digestive system is to break down the food we eat into smaller parts so the body can use them for energy and cell nourishment
  - Digests
  - Absorbs nutrients
  - Carries vitamins and nutrients into bloodstream
  - Chemical detoxification
  - Excretion



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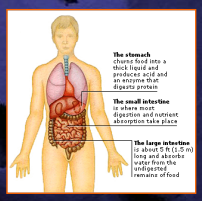
How do you get nutrients from foods?

- The process of breaking down food into molecules the body can absorb is called digestion.
- The digestive system begins with the mouth and involves many organs in the abdomen.
- The digestive organs produce enzymes which break down food chemically.



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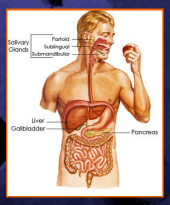
Which organs make digestive enzymes?

- The **salivary glands**, **stomach**, **pancreas**, and **small intestine** all produce digestive enzymes.
- These enzymes break down proteins, carbohydrates, and fats into the units they are made up of—amino acids, sugars, and fatty acids.
- These tiny units are so small they can pass into the **villi** lining the intestine.



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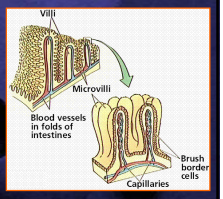
How are nutrients from foods absorbed?

- The lining of the small intestine is covered with microscopic projections called villi which dramatically increase its surface area.
- Molecules of nutrients dissolve in fluids in the intestine and pass into the villi.
- From there, nutrients pass through the thin walls of the blood vessels in the villi, and into the body.



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What can go wrong with the digestive system?

1. Maldigestion/Malabsorption
2. Increased intestinal permeability
3. Intestinal dysbiosis
   i. Constipation
   ii. Diarrhea
   iii. Enterocolitis
4. Allergy

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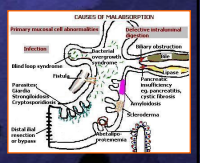
1. Maldigestion/Malabsoprtion

- Maldigestion is a gastrointestinal issues characterized by malfunctions with the digestive system which cause it to work improperly i.e. poor motility, insufficient enzyme function
- Chronic poor digestion can lead to malabsorption, which results in an inability of the nutrients required from diet to fuel the cells and tissues of the body, and consequently health problems result



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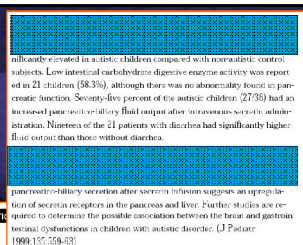

ORIGINAL ARTI

Gastrointestinal abnormalities in children with autistic disorder

Kandy Horvath, MD, PhD, John C. Papadimitriou, MD, PhD, Anna Rabsztyn, Cynthia Drachenberg, MD and J. Tyler Tildon, PhD

nificantly elevated in autistic children compared with nonautistic control subjects. Low intestinal carbohydrate digestive enzyme activity was reported in 21 children (58.3%), although there was no abnormality found in pancreatic function. Seventy-five percent of the autistic children (27/36) had an increased pancreatic/biliary fluid output after intravenous secretin administration. Nineteen of the 21 patients with diarrhea had significantly higher fluid output than those without diarrhea.

pancreatic/biliary secretion after secretin infusion suggests an upregulation of secretin receptors in the pancreas and liver. Further studies are required to determine the possible association between the brain and gastrointestinal dysfunctions in children with autistic disorder. (J Pediatr 1999;135:559-63)

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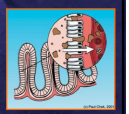
Horvath et al., 1999 *J Pediatr* 135(5):559-63

2. What is increased intestinal permeability?

***Definition*: an abnormal or unfavorable increase in intestinal permeability**

- Epithelia are either 'tight' or 'leaky' depending on the ability of the tight junctions to prevent water and solute movement
- The intestinal lining is supposed to be the protective barrier between the gut and the bloodstream
- If the intestinal lining becomes damaged-it is possible for incompletely digested proteins and/or other by-products to "leak" through the intestinal lining
- They can be recognized as foreign by the immune system, and/or "leak" into bloodstream



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3. Intestinal dysbiosis

- Intestinal flora (yeast and bacteria) are a normal part of digestive track
- Intestinal dysbiosis occurs when there is an *overgrowth/imbalance of intestinal flora(s)*
- Dysbiosis results from
  - Increased use of antibiotics, steroids, etc.
  - Poor diet
  - Diets high in sugar
  - Stress
  - Immune system dysregulation

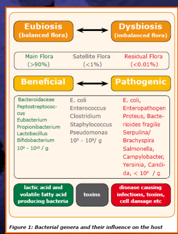

Figure 1: Bacterial genera and their influence on the host

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Gastrointestinal flora and gastrointestinal status in children with autism -- comparisons to neurotypical children and correlation with autism severity

BMC Gastroenterology 2011, **11**:22 doi:10.1186/1471-230X-11-22

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Conclusions

[redacted]
partly associated with increased probiotic use, and probably partly due to either lower production (less sacchrolytic fermentation by beneficial bacteria and/or lower intake of soluble fiber) and/or greater absorption into the body (due to longer transit time and/or increased gut permeability).

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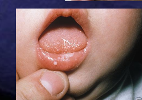
Adams et al., 2010 *BMC Gastroenterology* 11:22

Potential intestinal dysbiosis or "yeast" symptoms

- Diarrhea
- Bloating and gas
- Abdominal pain and cramping
- Fatigue
- Insomnia
- Lethargy
- Sensory disturbances
- Chemical sensitivities



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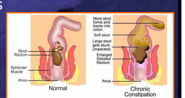
i. Constipation/ ii. Diarrhea

- Constipation-having a bowel movement fewer than three times per week
  - Stools are usually hard, dry, small in size, and difficult to eliminate.
  - Can be painful to have a bowel movement and
  - often experience straining, bloating, and the sensation of a full bowel



- Diarrhea-frequent loose or liquid bowel movements (often associated with infection, allergy and food intolerances)

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PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Constipation With Acquired Megarectum in Children With Autism

Nadeem Afzal, Simon Murch, Kumaran Thirrupathy, Leslie Berger, Andrew Fagbemi and Robert Heuschkel

Pediatrics 2003;112;939-942
DOI: 10.1542/peds.112.4.939

[redacted]
healthy children, its clinical diagnosis is often difficult in
[redacted]

Methods. We studied abdominal radiographs of 103 autistic children (87 boys) who were referred for gastroenterological assessment, in comparison with 29 control radiographs from children who were referred to the emergency department, most with abdominal pain. Radiographs were scored independently, in blinded manner, by 4 pediatric gastroenterologists and a radiologist. The severity of constipation was determined using a validated index. Details of stool habit, abdominal pain, dietary history, and laxative use were obtained from case notes.

Results. The incidence of constipation in the control subjects with abdominal pain was higher than reported for normal children. Despite this, moderate or severe constipation was more frequent in the autistic group than in the control subjects (36% vs 10%). Analysis of rectosigmoid loading showed more striking differences (54.4% of autistic children had moderate/severe loading or acquired megarectum compared with 24.1% of control subjects). Multivariate regression analysis showed consumption of milk to be the strongest predictor of constipation in the autistic group, whereas stool frequency, gluten consumption, soiling, and abdominal pain were not predictive of constipation.

[redacted]
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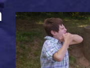
ability, constipation, child, abdominal radiographs.

Afzal et al., 2003 *Pediatrics* 112(4):939-42

If a child suffers from GI distress, like constipation, diarrhea

– Cramping, bloating causes distraction
– Posturing to relieve pain
– Pain may cause distress
– Pain may lead to self-injurious behavior



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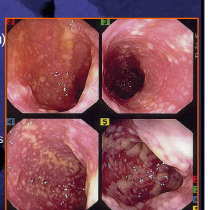
iii. Enterocolitis

- *Enterocolitis*-inflammation [*itis*](due to infection or irritation) that affects part or all of the intestines (the small [*entero*]and/or large [*col*] intestines)
  - *Hyperplasia*-general term for an increase in the number of the cells of an organ or tissue causing it to increase in size
  - *Endoscopy-looking inside*, the human body for medical reasons, by inserting a small scope in the body



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Autistic disorder and gastrointestinal disease

Karoly Horvath, MD, PhD,* and Jay A. Perman, MD†

Table 1. Comparison of the prevalence (%) of gastrointestinal symptoms in 112 children with AD and their siblings

	[redacted]	Age-matched siblings (N = 44) 6.1 ± 3.1 years
Diarrhea		0
Constipation		13.6
Gaseousness		20.5
Bloating		6.8
Abdominal pain		15.9
Reflux		4.5
Stool impaction		0
Belching		6.8
Number of gastrointestinal symptoms per child		
No symptom		70.5
One symptom		18.2
Two symptoms		4.5
Three symptoms		4.5
Four or more symptoms		2.3

Autistic disorder is a pervasive developmental disorder manifested in the first 3 years of life by dysfunction in social interaction and communication. Many efforts have been made to explore the biologic basis of this disorder, but the etiology remains unknown. Recent publications describing upper gastrointestinal abnormalities and ileocolitis have focused attention on gastrointestinal function and morphology in these children. High prevalence of histologic abnormalities in the esophagus, stomach, small intestine and colon, and dysfunction of liver conjugation capacity and intestinal
[redacted]

Curr Opin Pediatr 2002, 14:583–587 © 2002 Lippincott Williams & Wilkins, Inc.

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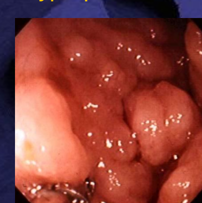
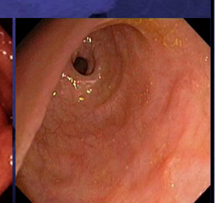
Horvath et al., 2002 *Curr Opin Pediatr* 14(5):583-7

Ileonodular Hyperplasia | **Normal Terminal Ileum**





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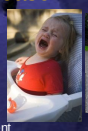
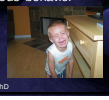
Behaviors that can be associated with gastrointestinal disease…

- Crying
- Unexplained tantrums
- Night time wakening
- General irritability
- Vocalizing complaints
- Posturing
- Irritability just prior to bowel movement
- Hyperactivity and distractibility
- Self injurious behavior



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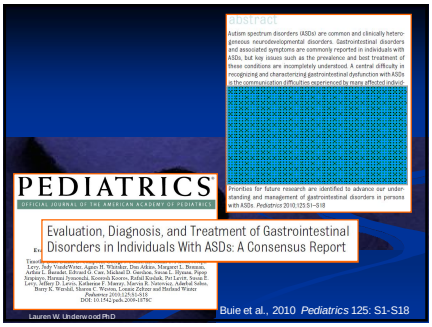

Buie et al., 2010 *Pediatrics* 125: S1-S18

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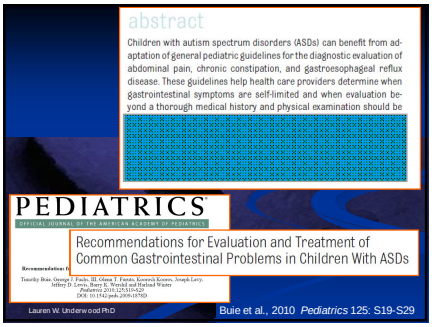

Buie et al., 2010 *Pediatrics* 125: S19-S29

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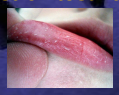
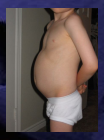
Physical visual cues for signs of potential gastrointestinal distress

- posturing
- bloated belly
- toileting issues
- dry cracked lips

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Consequences of increased intestinal permeability or intestinal dysbiosis-if left untreated . . .

- Nutrients and vitamins aren't absorbed properly---vitamin deficiencies
- Intestinal distress
- Food allergies are created
- Detoxification is compromised
- Bacteria and yeast can be mobilized
- Formation of antibodies you might not want---because of immune dysregulation

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3. Allergy: Immune system function

- Normal immune system function, depends upon ***proper*** immune system responses
- The immune response is how your body recognizes and defends itself against bacteria, viruses, and substances that appear foreign and harmful to the body
  - Protects and defends against foreign cells
  - Memory-gets smarter
  - Responds appropriately
  - Do no harm

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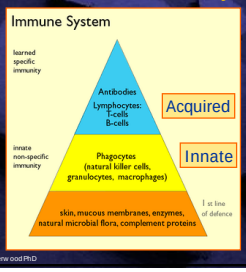
Overview of the immune system



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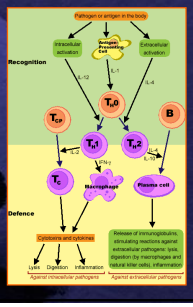
Acquired Immunity

White blood cells associated with **acquired immune system** are called **lymphocytes**
- T Cells
- B Cells



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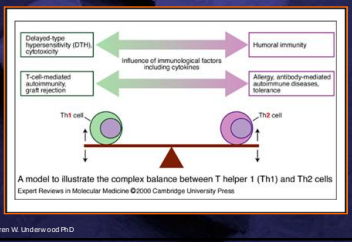
Normally, there is a balance between infection and immunity



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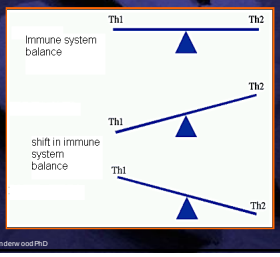
However the balance can be altered . . . .



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Journal of Neuroinflammation BioMed Central

Research Open Access

Impact of innate immunity in a subset of children with autism spectrum disorders: a case control study

Harumi Jyonouchi*[1], Lee Geng[1], Agnes Cushing-Ruby[1] and Huma Quraishi[2]

Methods: This study included the ASD children described above (ASD test; N = 26) and the following controls: ASD controls (N = 107), non-ASD controls with FA (N = 24), non-ASD controls with chronic rhinosinusitis/recurrent otitis media (CRS/ROM; N = 38), and normal controls (N = 43). We assessed

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Jyonouchi et al., 2005 *J Neuroinflammation* 5:52

What can go wrong with the immune system?

1. Hypersensitivity
2. Autoimmunity
3. Inflammation
4. Allergy
5. Immune system dysregulation

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Hypersensitivity, Autoimmunity & Inflammation

1. Hypersensitivity-an immune response that damages the body's own tissues
   1. undesirable (damaging, discomfort-producing and) reactions produced by the normal immune system
2. Autoimmunity-overactive immune responses
   1. immune system fails to properly distinguish between self and non-self, and attacks part of the body
3. Inflammation-one of the first responses of the immune system to infection
   – symptoms of inflammation are redness and swelling, which are caused by increased blood flow into a tissue

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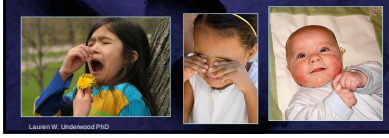
4. Allergy

- Allergy-is a disorder of the immune system that is often referred to as *hypersensitivity* affecting parts of the body not in direct contact with the allergen
  – It may involve eczema (atopic dermatitis), allergic conjunctivitis, allergic rhinitis and asthma
  – There appears to be a strong heredity component



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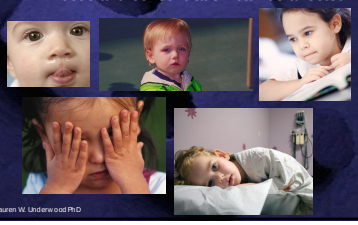
If a child suffers from allergies

– Focus and concentration can be affected



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5. Immune system dysregulation

- Immune system dysregulation causes an abnormal immune response
- there is a " shift or skewing" – lack of balance
- The immune system looses the ability to respond appropriately. . . and when this happens, it is possible that the body develops abnormal responses to things it might not normally react to . . .

like foods

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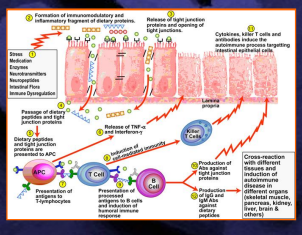
Immune system response in the digestive tract



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EVALUATION OF AN ASSOCIATION BETWEEN GASTROINTESTINAL SYMPTOMS AND CYTOKINE PRODUCTION AGAINST COMMON DIETARY PROTEINS IN CHILDREN WITH AUTISM SPECTRUM DISORDERS

Harumi Jyonouchi, MD, Lee Geng, PhD, Agnes Ruby, BS, Carma Reddy, MD, and Barry Zimmerman-Bier, MD

Study design Peripheral blood mononuclear cells (PBMCs) were obtained from 109 ASD children with or without GI symptoms (GI [+] ASD, N = 75 and GI (−) ASD, N = 34), from children with NDH (N = 15), and control subjects (N = 19). Diarrhea and constipation were the major GI symptoms. We measured production of type 1 T-helper cells (Th1), type 2 T-helper cells (Th2), and regulatory cytokines by PBMCs stimulated with whole cow's milk protein (CMP), its major components (casein, β-lactoglobulin, and α-lactoalbumin), gliadin, and soy.

Results PBMCs obtained from GI (+) ASD children produced more tumor necrosis factor-α (TNF-α)/interleukin-12 (IL-12) than those obtained from control subjects with CMP, β-lactoglobulin, and α-lactoalbumin, irrespective of objective GI symptoms. They also produced more TNF-α with gliadin, which was more frequently observed in the group with loose stools. PBMCs obtained from GI (−) ASD children produced more TNF-α/IL-12 with CMP than those from control subjects, but not with β-lactoglobulin, α-lactoalbumin, or gliadin. Cytokine production with casein and soy were unremarkable.

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Jyonouchi et al., 2005 *J Pediatrics* 146(5): 605-610

What happens if the immune system is compromised

- Immune dysregulation
  - Abnormal balance and communication between immune cells
- Chronic Inflammation
  - An abnormal, persistent activation of immune cells in the tissues
- Autoimmune reactions
  - Antibodies targeting and causing injury to normal body tissues

The immune system is closely connected to virtually every other system of the body
Disorders in the immune system can cause disease

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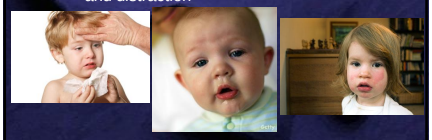
If there are immune system issues

- Increased infections, inflammation can affect attention and concentration
- Allergic reactions can cause pain, irritation and distraction



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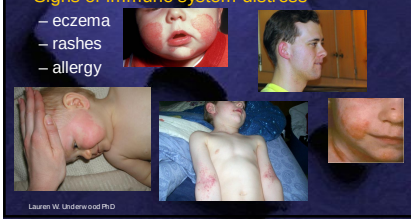
Physical signs reflecting issues associated with the immune system

- Signs of immune system distress
  - eczema
  - rashes
  - allergy



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Dietary changes/modifications and treatments in autism

Lauren W. Underwood PhD

Although clinicians typically assume that feeding problems co-exist with a diagnosis of autism, no previous research has compared the eating behavior of children with autism to typ-

the number of foods eaten within each food group for both the child and the family.

KEY WORDS: Autism; food refusal; food selectivity; pediatric feeding.

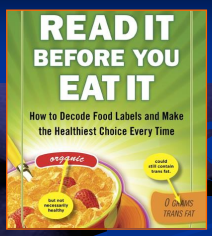
A Comparison of Eating Behaviors between Children with and without Autism

Kimberly A. Schreck,[1,4] Keith Williams,[2] and Angela F. Smith[3]

Schreck et al., 2004 *J Autism Dev Disord* 34(4):433-8

Lauren W. Underwood PhD

Healthier Diet



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Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised,

Summary

Background We undertook a randomised, double-blinded, placebo-controlled, crossover trial to test whether intake of artificial food colour and additives (AFCA) affected childhood behaviour.

Methods 153 3-year-old and 144 8/9-year-old children were included in the study. The challenge drink contained sodium benzoate and one of two AFCA mixes (A or B) or a placebo mix. The main outcome measure was a global hyperactivity aggregate (GHA), based on aggregated z-scores of observed behaviours and ratings by teachers and parents, plus, for 8/9-year-old children, a computerised test of attention. This clinical trial is registered with Current Controlled Trials (registration number ISRCTN74481308). Analysis was per protocol.

Findings 16 3-year-old children and 14 8/9-year-old children did not complete the study, for reasons unrelated to childhood behaviour. Mix A had a significantly adverse effect compared with placebo in GHA for all 3-year-old children (effect size 0·26 [95% CI 0·01–0·35], p=0·044) but not mix B versus placebo. This result persisted when analysis was restricted to 3-year-old children who consumed more than 85% of juice and had no missing data (0·32 [0·05–0·60], p=0·02). 8/9-year-old children showed a significantly adverse effect when given mix A (0·12 [0·02–0·23], p=0·023) or mix B (0·17 [0·03–0·28], p=0·008) when analysis was restricted to those children consuming at least 85% of drinks with no missing data.

McCann et al., 2007 *Lancet* 370(9598):1560-1567

Lauren W. Underwood PhD

Are special diets important and which one do I choose?

- Many autistic children suffer from inflammatory response/immune system dysregulation
- Many autistic children don't/can't digest their foods efficiently
- diet options: GF/CF, SCD, BED, LOD,
  - Pick one that works best for you and your family
- regardless of diet choice, it is important to ensure proper nutrition

Lauren W. Underwood PhD

GF/CF Diet

Lauren W. Underwood PhD

A gluten-free diet as an intervention for autism and associated spectrum disorders: preliminary findings

PAUL WHITELEY Autism Research Unit, Univ
JACQUI RODGERS University of Sunderland,
DAWN SAVERY Autism Research Unit, Univer
PAUL SHATTOCK Autism Research Unit, Univ

abstract The opioid-excess hypothesis of autism suggests that autism is the consequence of the incomplete breakdown and excessive absorption of peptides with opioid activity (derived from foods which contain gluten and casein), causing disruption to biochemical and neuroregulatory processes. Biochemical evidence has indicated the presence of increased levels of peptides in the urine of people with autism, and previous behavioural studies have demonstrated a connection between the long term exclusion of gluten and casein from the diet and improvements in the behaviour of some children with autism. The introduction of a gluten-free diet to children with autism and associated spectrum disorders (n = 22) was monitored over a 5 month period using a battery of parental and teacher interview/questionnaire sessions, observation reports, psychometric tests and urinary profiling. [redacted] was no significant decrease in specific urinary compounds excreted when compared with controls and a gluten challenge group.

Lauren W. Underwood PhD

Whiteley at al., 1999 *Autism* 3(1):45-65

Special Article

Celiac Disease Presenting as Autism

Stephen J. Genuis, MD, FRCSC, DABOG, DABEM, FAAEM, and Thomas P. Bouchard, BSc

Gluten-restricted diets have become increasingly popular among parents seeking treatment for children diagnosed with autism. Some of the reported response to celiac diets in children with autism may be related to amelioration of nutritional deficiency resulting from undiagnosed gluten sensitivity and consequent malabsorption. A case is presented of a 5-year-old boy diagnosed with severe autism at a specialty clinic for [redacted]

Keywords: autism; autistic spectrum disorder; gluten sensitivity; celiac disease; nutrition; malabsorption

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Genuis and Bouchard 2010 *J Child Neurol* 25(1): 114-119

Casein/casomorphin and gluten/gliadorphin

- Casein is a protein found in milk and products containing milk
- Casomorphin (or caseomorhin) is a peptide derived from the milk protein casein
- Gluten and gluten-like proteins are found in wheat and other grains
- Gliadorphin (or gluteomorphin) is a peptide derived from the wheat protein gluten

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Diet: Gluten-free Casein-free Diet

- A restrictive diet that removes all food items that contain both
  gluten and casein
- The are two main theories currently present in scientific literature that explain why some people with autism and PDD respond positively to a GFCF diet
  1. *improperly broken down dietary peptides*
  2. *immune system dysregulation*

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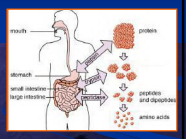
1. Improperly broken down dietary peptides

- Some people with ASD cannot properly digest gluten and casein, which break down into substances that act like opiates in their bodies
- Improperly broken-down foods can have an affect upon behavior
- According to this theory, these "drug-like" substance alters the person's behavior, perceptions, and responses to his environment



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Immune Response to Dietary Proteins, Gliadin and Cerebellar Peptides in Children with Autism

A. VOJDANI[a,b,c], T. O'BRYAN[a], J.A. GREEN[a], J. MCCANDLESS[a], K.N. WOELLER[a], E. VOJDANI[a], A.A. NOURIAN[a] and E.L. COOPER[a]

[a]Section of Neuroimmunology, Immunosciences Lab., Inc., 8693 Wilshire Blvd., Ste. 200, Beverly Hills, California 90211, USA; [b]Laboratory of Comparative Neuroimmunology, Department of Neurobiology, David Geffen School of Medicine at UCLA, University of California, Los Angeles, Los Angeles, California 90095, USA; [c]Omni-Care-ups, Glenview, Illinois 60025, USA; [d]The Ecosystem Center, Oregon City, Oregon 97045, USA; [e]Private Practice, Woodland Hills, California 91367, USA; [f]Stonehill Centers, San Diego, California 92121, USA; [g]Neuroscience Undergraduate, UC Berkley, Berkley, California 94709, USA

Received 3 May 2004; Revised 12 July 2004; In final form 27 July 2004

The mechanisms behind autoimmune reaction to nervous system antigens in autism are not understood. [redacted] tage of autism patients showed elevations in antibodies against gliadin and cerebellar peptides simultaneously. For examining cross-reaction between dietary proteins and cerebellar antigens, antibodies were prepared in rabbits, and binding of rabbit anti-gliadin, anti-cerebellar peptides, anti-MBP, anti-milk, anti-egg, anti-soy and anti-corn to either gliadin- or cerebellar-antigen-coated wells was measured. In comparison to [redacted]

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Vojdani et al., 2004 *Nutr Neurosci* 7(3):151-61

Treat with digestive enzymes

- Enzyme activity:
  - is dependent upon specific cofactors and coenzymes (vitamins and minerals
  - can be inhibited by toxins, fungi, oxidative stress and malnutrition
  - can be optimized with proper nutrition and elimination of toxins
- Enzyme function:
  - Saccharidase breaks down sugars
  - Lipase breaks down fats
  - Protease breaks down proteins

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Beneficial Effects of Enzyme-based Therapy for Autism Spectrum Disorders

by Mark A. Brudnak PhD, ND,* Bernard Rimland PhD,† Roy E. Kerry MD‡,§, Margaret Dailey CRNP,‖ Robert Taylor MD, Bruce Stayton MD ¶, Frank Waickman MD,# Michael Waickman MD,# Jon Pangborn, PhD and Ilene Buchholz RN‖,**

† Autism Research Institute, San Diego, California; ‡‡ 57 0th Avenue Greenville, Pennsylvania 16125; , Durham, North Carolina 27704 ¶ Independence, Missouri 64052; ‡ Akron, Ohio 44320; ‖, Ste 100, San Diego, California 92130

table for further analysis. **Results:** The novel enzyme formula, ENZYM-ED, beneficially and safely affected all 13 of the parameters measured. Improvements were noted up to 90%, depending on the parameter measured, of the respondents who completed the entire course of therapy. Statistical analysis revealed that even assuming an extremely high baseline, twelve of the thirteen parameters were significant improve- [redacted]

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Brudnack et al., , 2003 *Townsend Letters for Doctors and Patients 104-107*

2. Immune system dysregulation

- Immune system loses its ability to respond properly
- Body develops abnormal responses to things it might not normally react to
- An abnormal immune response can result in
  - Allergy
  - Inflammation
  - Hypersensitivity
  - Autoimmunity

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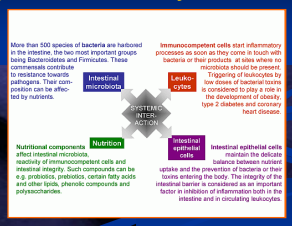
Immunological response to dysregulated immune system



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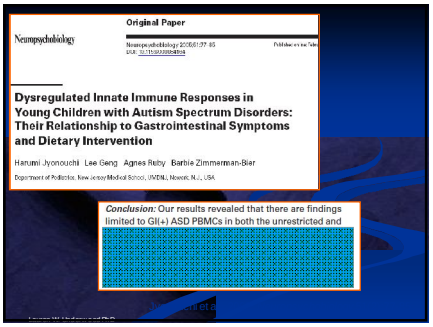

Food allergy vs. Food intolerance

- Food allergies
  - An immune system response . . . *to foods*
  - Body mistakes a protein in food as harmful, and creates a defense against it (antibody)
- Food intolerances
  - Digestive system response to foods
  - *Not* an immune system response
  - Something in food irritates digestive system or person is unable to breakdown/digest food

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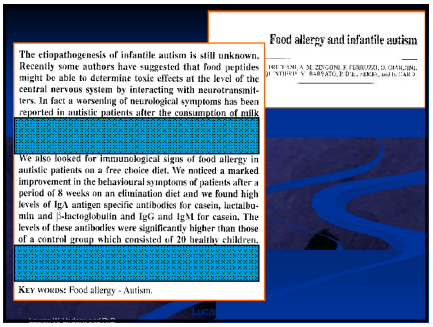
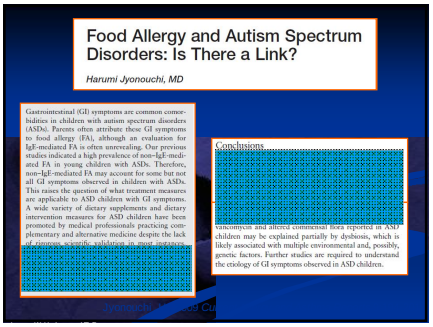
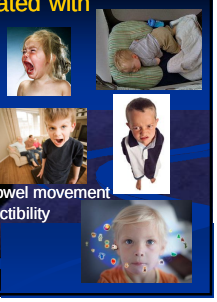




Symptoms associated with abdominal pain…

- Crying
- Unexplained tantrums
- Night time wakening
- General irritability
- Vocalizing complaints
- Posturing
- Irritability just prior to bowel movement
- Hyperactivity and distractibility
- Self injurious behavior



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Nutritional Supplementation

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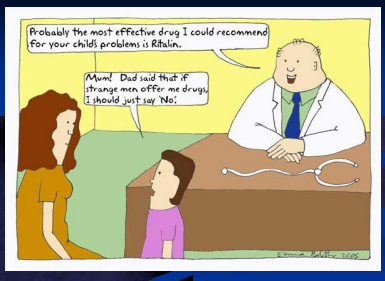

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Why nutritional supplementation?

- Nutritional deficiency
  - involves a lack of one or more nutrients obtained from food essential for normal cell and body function
  - occur due to
    - Mal-absorption/poor absorption in the small intestine
    - Unhealthy eating, or
    - Self-imposed/imposed dietary restrictions
    - Poor utilization of nutrients because of genetic or environmental factors
- Oxidative Stress
  - imbalance between the production and manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage.

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There are nutritional deficiencies associated with disease

- Rickets-**vitamin D deficiency**
- Scurvy-**vitamin C deficiency**
- Beriberi-**thiamine deficiency**
- Pellagra-**niacin deficiency**
- Goiter-**iodine deficiency**

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Signs and symptoms associated with nutritional deficiency

- Neurological symptoms
- Memory loss
- Psychosis
- Bruising
- Confusion
- Impaired learning
- Growth retardation
- Loss of appetite
- Poor immune function

How can a child attend, focus, and learn?

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Commonly deficient nutrients

- Vitamin B12
- Vitamin B6
- Folate or folic acid
- Vitamin A
- Vitamin C
- Vitamin D
- Zinc
- Magnesium
- Omega 3 fatty acids

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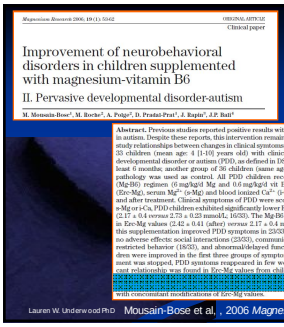


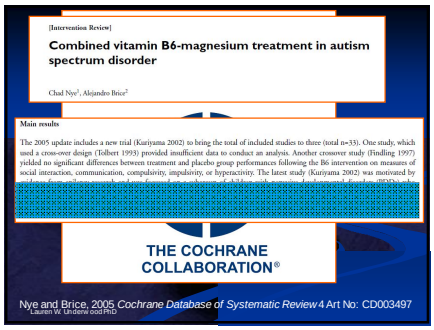
Improvement of neurobehavioral disorders in children supplemented with magnesium-vitamin B6

II. Pervasive developmental disorder-autism

M. Mousain-Bose[2], M. Roche[2], A. Polge[2], D. Pradal-Prat[2], J. Rapin[2], J.P. Bali[2]

Abstract. Previous studies reported positive results with the use of Mg-vitamin B6 in autism. Despite these reports, this intervention remains controversial. In order to study relationships between changes in clinical symptoms and biological parameters, 33 children (mean age: 4 [1-10] years old) with clinical symptoms of pervasive developmental disorder or autism (PDD, as defined in DSM-IV) were followed for at least 6 months; another group of 36 children (same age) devoided of any known pathology was used as control. All PDD children received a magnesium-vit B6 (Mg-B6) regimen (6 mg/kg/d Mg and 0.6 mg/kg/d vit B6). Intraerythrocyte Mg^{2+} (Ery-Mg), serum Mg^{2+} (s-Mg) and blood ionized Ca^{2+} (i-Ca) were measured before and after treatment. Clinical symptoms of PDD were scored (0 to 4). In contrast to s-Mg or i-Ca, PDD children exhibited significantly lower Ery-Mg values than controls (2.17 ± 0.4 *versus* 2.73 ± 0.23 mmol/L; 1653). The Mg-B6 regimen led to an increase in Ery-Mg values (2.42 ± 0.41 (after) *versus* 2.17 ± 0.4 mmol/l (before), 1/47) and this supplementation improved PDD symptoms in 25/33 children ($p < 0.0001$) with no adverse effects: social interactions (23/33), communication (24/33), stereotyped restricted behavior (18/33), and abnormal/delayed functioning (17/33); 15/33 children were improved in the first three groups of symptoms. When the Mg-B6 treatment was stopped, PDD symtoms reappeared in few weeks. A statistically significant relationship was found in Ery-Mg values from children before treatment and with concomitant modifications of Ery-Mg values.

Lauren W. Underwood PhD Mousain-Bose et al., 2006 *Magnesium Research* 19(1): 53-62



[Intervention Review]

Combined vitamin B6-magnesium treatment in autism spectrum disorder

Chad Nye[1], Alejandro Brice[2]

Main results

The 2005 update includes a new trial (Kuriyama 2002) to bring the total of included studies to three (total n=33). One study, which used a cross-over design (Tolbert 1993) provided insufficient data to conduct an analysis. Another crossover study (Findling 1997) yielded no significant differences between treatment and placebo group performances following the B6 intervention on measures of social interaction, communication, compulsivity, impulsivity, or hyperactivity. The latest study (Kuriyama 2002) was motivated by

THE COCHRANE COLLABORATION®

Lauren W. Underwood PhD Nye and Brice, 2005 *Cochrane Database of Systematic Review* 4 Art No: CD003497

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Oxidative Stress

- Caused by an imbalance between the production of reactive oxygen species (ROS), like free radicals, and a biological system's ability to readily *detoxify* the reactive intermediates or easily repair the resulting damage
- Damaging byproducts can impose stress upon the cells, and affect normal cell function, causing oxidative stress
- Oxidative stress is involved in many diseases
- *Can give antioxidants to counter-act effects of oxidative stress upon the cell*

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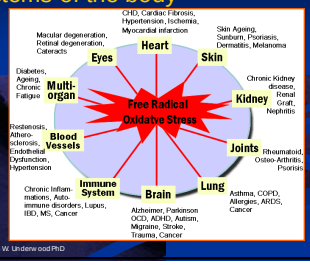
Oxidative stress can affect all systems of the body



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OXIDATIVE STRESS IN AUTISM

Woody B. McGinnis, MD

STATEMENT OF PURPOSE

Indirect markers are consistent with greater oxidative stress in autism. They include greater free-radical production, impaired energetics and cholinergics, and higher excitotoxic markers. Brain and gut, both abnormal in autism, are particularly sensitive to oxidative injury.

Higher red-cell lipid peroxides and urinary isoprostanes in autism signify greater oxidative damage to biomolecules. A preliminary study found accelerated lipofuscin deposition—consistent with oxidative injury to autistic brain in cortical areas [illegible]

the role of oxidative stress may help illuminate the pathophysiology of autism, its environmental and genetic influences, new treatments, and prevention.

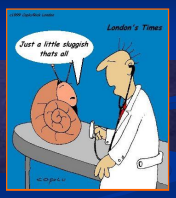
OVERVIEW

Lauren W. Underwood PhD

McGinnis, W. 2004 *Altern Therap* 10(6): 22-36

Nutritional supplementation to combat oxidative stress

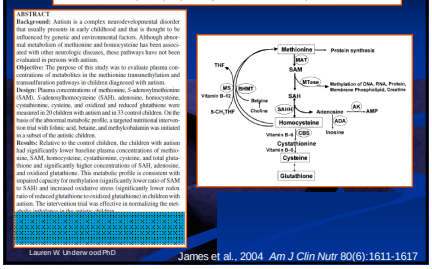
- Vitamin E
- Vitamin C
- Zinc
- Calcium
- Selenium
- Vitamin **B6** or its activated form, pyridoxal-5-phosphate (**P5P**) with Magnesium



Lauren W. Underwood PhD

Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism[1,2]

S Jill James, Paul Cutler, Stepan Melnyk, Stefanie Jernigan, Laurette Janak, David W Gaylor, and James A Neubrander



ABSTRACT

Background: Autism is a complex neurodevelopmental disorder that usually presents in early childhood and that is thought to be influenced by genetic and environmental factors. Although abnormal metabolism of methionine and homocysteine has been associated with other neurologic diseases, these pathways have not been evaluated in persons with autism.

Objective: The purpose of this study was to evaluate plasma concentrations of metabolites in the methionine transmethylation and transsulfuration pathways in children diagnosed with autism.

Design: Plasma concentrations of methionine, *S*-adenosylmethionine (SAM), *S*-adenosylhomocysteine (SAH), adenosine, homocysteine, cystathionine, cysteine, and oxidized and reduced glutathione were measured in 20 children with autism and in 33 control children. On the basis of the abnormal metabolic profile, a targeted nutritional intervention trial with folinic acid, betaine, and methylcobalamin was initiated in a subset of the autistic children.

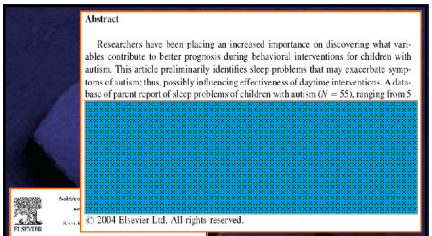
Results: Relative to the control children, the children with autism had significantly lower baseline plasma concentrations of methionine, SAM, homocysteine, cystathionine, cysteine, and total glutathione and significantly higher concentrations of SAH, adenosine, and oxidized glutathione. This metabolic profile is consistent with impaired capacity for methylation (significantly lower ratio of SAM to SAH) and increased oxidative stress (significantly lower redox ratio of reduced glutathione to oxidized glutathione) in children with autism. The intervention trial was effective in normalizing the metabolic imbalances in autistic children.

Lauren W. Underwood PhD

James et al., 2004 *Am J Clin Nutr* 80(6):1611-1617

Sleep

Lauren W. Underwood PhD



Abstract

Researchers have been placing an increased importance on discovering what variables contribute to better prognosis during behavioral interventions for children with autism. This article preliminarily identifies sleep problems that may exacerbate symptoms of autism; thus, possibly influencing effectiveness of daytime interventions. A database of parent report of sleep problems of children with autism ($N = 55$), ranging from 5

Sleep problems as possible predictors of intensified symptoms of autism[☆]

Kimberly A. Schreck[a,*], James A. Mulick[b], Angela F. Smith[a]

Lauren W. Underwood PhD

Schreck et al., 2004 *Res Dev Disabil* 25(1):57-66

Original Article

Melatonin for Insomnia in Children With Autism Spectrum Disorders

Journal of Child Neurology
Volume XX Number X
Month XXX xxxx
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We describe our experience in using melatonin to treat insomnia, a common sleep concern in children with autism spectrum disorder [illegible] with a confirmed diagnosis of autism spectrum disorders who received melatonin were identified by reviewing the electronic medical records of a single pediatrician. All parents were consulted on sleep hygiene techniques. Clinical response to melatonin, based on parental report, was categorized as (1) sleep no longer a concern, (2) improved sleep but continued parental concerns, (3) sleep continues to be a major concern, and (4) worsened sleep. The melatonin dose varied from 0.75 to 6 mg. After initiation of melatonin, parents of 27 children (25%) no longer remained sleep concerns at follow-up visits. Parents of 64 children (60%) reported improved sleep, although continued to have concerns regarding sleep. Parents of 14 children (13%) continued to report sleep problems as a major concern, with only 1 child having worse sleep after starting melatonin (1%), and 1 child having undetermined response (1%). Only 8 children had mild side-effects after starting melatonin, which included morning sleepiness and increased enuresis. There was no reported increase in seizures after starting melatonin in children with pre-existing epilepsy and no new-onset seizures. The majority of children were taking psychotropic medications.

Keywords: sleep, pervasive developmental disorder–not otherwise specified; Asperger syndrome; melatonin

Lauren W. Underwood PhD

Anderson et al., 2008 *J Child Neurol* 23: 482-485

A happier, healthier child is going to be more responsive to behavioral, social and sensory interventions

Lauren W. Underwood PhD

Detoxification

Lauren W. Underwood PhD

What we do know now

- In 2001, the Institute of Medicine (IOM) determined that such a relationship (between thimerosal and neurodevelopmental disorders) is biologically plausible, but that not enough evidence exists to support or reject this hypothesis
- Thimerosal neurotoxicity is associated with glutathione depletion –*James et al, 2005*
- Recent work by Dr. Mark Geier and David Geier have shown strong epidemiological evidence for a causal relationship between thimerosal and neurodevelopmental disorders in children-*Geier and Geier, 2007*

We live in a toxic world

According to the Environmental Defense Council, more than 4 billion pounds of toxic chemicals are released into the environment each year, of which 72 million pounds are known carcinogens.

Autism Spectrum Disorders in Relation to Distribution of Hazardous Air Pollutants in the San Francisco Bay Area

Gayle C. Windham,[1] Lixia Zhang,[2] Robert Gunier,[1] Lisa A. Croen,[3] and Judith K. Grether[1]

[1]Division of Environmental and Occupational Disease Control, California Department of Health Services, Richmond, California, USA; [2]Impact Assessment, Inc., La Jolla, California, USA; [3]Kaiser Permanente Medical Care Program Division of Research, Oakland, California, USA

OBJECTIVE: To explore possible associations between autism spectrum disorders (ASD) and environmental exposures, we linked the California autism surveillance system to estimated hazardous air pollutant (HAP) concentrations compiled by the U.S. Environmental Protection Agency.

METHODS: Subjects included 284 children with ASD and 657 controls, born in 1994 in the San Francisco Bay area. We assigned exposure level by census tract of birth residence for 19 chemicals we identified as potential neurotoxicants, developmental toxicants, and/or endocrine disruptors from the 1996 HAPs database. Because concentrations of many of these were highly correlated, we combined the chemicals into mechanistic and structural groups, calculating summary index scores. We calculated ASD risk in the upper quartiles of these group scores or individual chemical concentrations compared with below the median, adjusting for demographic factors.

RESULTS: The adjusted odds ratios (AORs) were elevated by 50% in the top quartile of chlorinated solvents and heavy metals [95% confidence intervals (CIs), 1.1–2.1], but not for aromatic solvents. Adjusting for these three groups simultaneously led to decreased risks for the solvents and increased risk for metals (AORs for metals: fourth quartile = 1.7; 95% CI, 1.0–3.0; third quartile = 1.95; 95% CI, 1.2–3.1). The individual compounds that contributed most to these associations included [redacted], cadmium, nickel, trichloroethylene, and vinyl chloride.

KEY WORDS: air toxics, autism, autism spectrum disorders, diesel, mercury, metals, neurodevelopment, neurotoxicants, solvents, vinyl chloride. *Environ Health Perspect* 114:1438–1444 (2006). doi:10.1289/ehp.9120 available via *http://dx.doi.org/* [Online 21 June 2006]

Windham et al., 2006 *EHP* 114(9): 1138-1144

ELSEVIER

Health Place. 2006 Jun;12(2):203-9.

HEALTH & PLACE

www.elsevier.com/locate/healthplace

Environmental mercury release, special education rates, and autism disorder: an ecological study of Texas

Raymond F. Palmer[a,*], Steven Blanchard[b], Zachary Stein[a], David Mandell[c], Claudia Miller[a]

[a]*University of Texas Health Science Center, San Antonio Department of Family and Community Medicine, 7703 Floyd Curl Drive, San Antonio, Texas 78229-3900, USA*
[b]*Department of Sociology, Our Lady of the Lake University, San Antonio, Texas, USA*
[c]*University of Pennsylvania Center for Mental Health Policy and Services Research, USA*

Accepted 1 November 2004

"Findings: For every 1000 pounds of mercury that is emitted from Texas smokestacks there is a 61% increase in Autism rates in that state."

Palmer et al., 2006 *Health Place* 12(2): 203-209

Why detoxification?

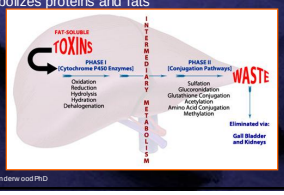
- To prevent injury to the cells and ultimately cell death
- Cell injury and cell death is bad
- In autism, toxins may be a cause of the neurological and immune dysfunction
- Detoxification may help the cells to recover which will enable for healing
- If toxins accumulate too rapidly, *without being safely eliminated*, they can cause damaging effects upon cells and tissues of the body

How does your body detoxify?

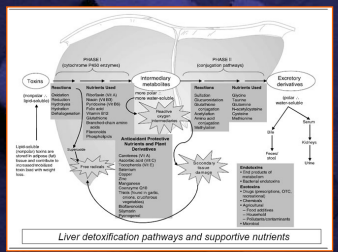
- Designed to remove/eliminate toxic substances from the body
- Primary function of liver and kidney
- Glutathione
- Once toxins are bound they are eliminated via bile and urine
- Can also be achieved via artificial (chelation) or supplementary (sauna) means . . .

The liver & detoxification

- Designed to remove toxic matter from the bloodstream
- Produces bile
- Metabolizes proteins and fats



Nutrients that support detoxification



Liver detoxification pathways and supportive nutrients

What happens if liver function is compromised?

- If detoxification systems are overloaded, destruction of nutrients necessary for proper detoxification occurs
- If detoxification pathways are overloaded, build up of toxins can occur
- If transsulfuration is disrupted, there is less antioxidant production, and oxidative stress can occur

If you don't detoxify, a vicious cycle of toxic overload perpetuates

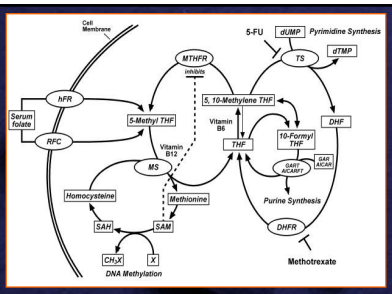
- Heavy metal exposure, environmental toxins, foreign proteins
- Detoxification problems
  - GI distress
  - Allergy
  - Immune problems
  - Infections
- Treat with
  - Antibiotics, steroids, antifungals

Lauren W. Underwood PhD

Detoxification biochemistry

- Methylation and sulfation
  - A healthy body's way to rid itself of toxic substances
  - Methylation-transferring a methyl group
  - Transsulfation-responsible for production of glutathione-the body's number one antioxidant
- Children with autistic spectrum disorders often need supplements to provide them with the raw materials their bodies need to efficiently carry out methylation and sulfation

Lauren W. Underwood PhD



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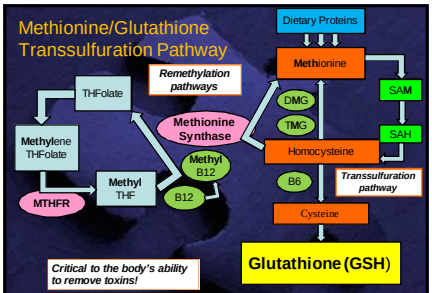
Methionine/Glutathione Transsulfuration Pathway



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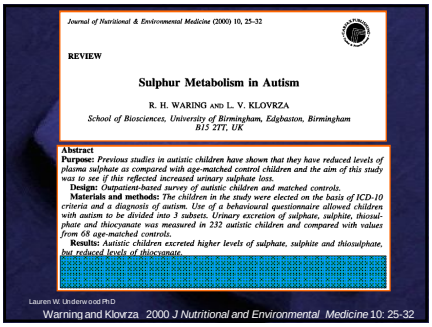


Journal of Nutritional & Environmental Medicine (2000) 10, 25–32

REVIEW

Sulphur Metabolism in Autism

R. H. WARING AND L. V. KLOVRZA

School of Biosciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

Abstract

Purpose: *Previous studies in autistic children have shown that they have reduced levels of plasma sulphate as compared with age-matched control children and the aim of this study was to see if this reflected increased urinary sulphate loss.*

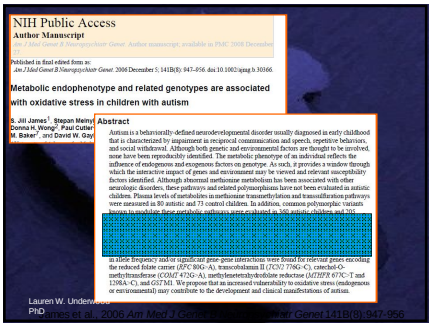
Design: *Outpatient-based survey of autistic children and matched controls.*

Materials and methods: *The children in the study were elected on the basis of ICD-10 criteria and a diagnosis of autism. Use of a behavioural questionnaire allowed children with autism to be divided into 3 subsets. Urinary excretion of sulphate, sulphite, thiosulphate and thiocyanate was measured in 232 autistic children and compared with values from 68 age-matched controls.*

Results: *Autistic children excreted higher levels of sulphate, sulphite and thiosulphate, but reduced levels of thiocyanate.*

Lauren W. Underwood PhD

Warning and Klovrza 2000 *J Nutritional and Environmental Medicine* 10: 25-32



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Author Manuscript

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Metabolic endophenotype and related genotypes are associated with oxidative stress in children with autism

S. Jill James[1], Stepan Melnyk[1], Donna H. Wong[2], Paul Cutler[1], M. Baker[2], and David W. Gay[2]

Abstract

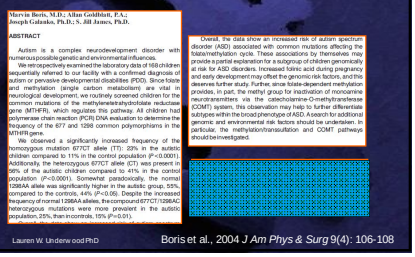
Autism is a behaviorally-defined neurodevelopmental disorder usually diagnosed in early childhood that is characterized by impairment in reciprocal communication and speech, repetitive behaviors, and social withdrawal. Although both genetic and environmental factors are thought to be involved, none have been reproducibly identified. The metabolic phenotype of an individual reflects the influence of endogenous and exogenous factors on genotype. As such, it provides a window through which the interactive impact of genes and environment may be viewed and relevant susceptibility factors identified. Although abnormal methionine metabolism has been associated with other neurologic disorders, these pathways and related polymorphisms have not been evaluated in autistic children. Plasma levels of metabolites in methionine transmethylation and transsulfuration pathways were measured in 80 autistic and 73 control children. In addition, common polymorphic variants known to modulate these metabolic pathways were evaluated in 380 autistic children and 204

in allele frequency and/or significant gene-gene interactions were found for relevant genes encoding the reduced folate carrier (*RFC* 80G>A), transcobalamin II (*TCN2* 776G>C), catechol-O-methyltransferase (*COMT* 472G>A), methylenetetrahydrofolate reductase (*MTHFR* 677C>T and 1298A>C), and *GSTM1*. We propose that an increased vulnerability to oxidative stress (endogenous or environmental) may contribute to the development and clinical manifestations of autism.

Lauren W. Underwood PhD

Am J Med Genet B Neuropsychiatr Genet. Author manuscript; available in PMC 2008 December 5.

Association of MTHFR Gene Variants with Autism



Marvin Boris, M.D.; Allan Goldblatt, P.A.; Joseph Galanko, Ph.D.; S. Jill James, Ph.D.

ABSTRACT

Autism is a complex neurodevelopment disorder with numerous possible genetic and environmental influences.

We retrospectively examined the laboratory data of 168 children sequentially referred to our facility with a confirmed diagnosis of autism or pervasive developmental disabilities (PDD). Since folate and methylation (single carbon metabolism) are vital in neurological development, we routinely screened children for the common mutations of the methylenetetrahydrofolate reductase gene (MTHFR), which regulates this pathway. All children had polymerase chain reaction (PCR) DNA evaluation to determine the frequency of the 677 and 1298 common polymorphisms in the MTHFR gene.

We observed a significantly increased frequency of the homozygous mutation 677CT allele (TT): 23% in the autistic children compared to 11% in the control population ($P<0.0001$). Additionally, the heterozygous 677CT allele (CT) was present in 58% of the autistic children compared to 41% in the control population ($P<0.0001$). Somewhat paradoxically, the normal 1298AA allele was significantly higher in the autistic group, 55%, compared to the controls, 44% ($P<0.05$). Despite the increased frequency of normal 1298AA alleles, the compound 677CT/1298AC heterozygous mutations were more prevalent in the autistic population, 25%, than in controls, 15% ($P<0.01$).

Overall, the data show an increased risk of autism spectrum disorder (ASD) associated with common mutations affecting the folate/methylation cycle. These associations by themselves may provide a partial explanation for a subgroup of children genomically at risk for ASD disorders. Increased folinic acid during pregnancy and early development may offset the genomic risk factors, and this deserves further study. Further, since folate-dependent methylation provides, in part, the methyl group for inactivation of monoamine neurotransmitters via the catecholamine-O-methyltransferase (COMT) system, this observation may help to further differentiate subtypes within the broad phenotype of ASD. A search for additional genomic and environmental risk factors should be undertaken. In particular, the methylation/transsulfation and COMT pathways should be investigated.

Lauren W. Underwood PhD

Boris et al., 2004 *J Am Phys & Surg* 9(4): 106-108

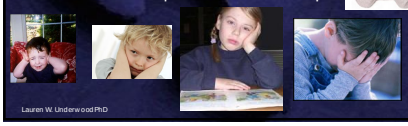
If essential nutrients for biochemical pathways and maximum metabolism are not available for proper cell function-can affect all systems of the body

Reduced GSH production

Lauren W. Underwood PhD

If detoxification problems compile . . .

- Build-up of toxins can build up in the body, which leads to increased oxidative stress,
- Oxidative stress affects systems of the body-symptoms develop—affect attention
- Additional health problems can develop



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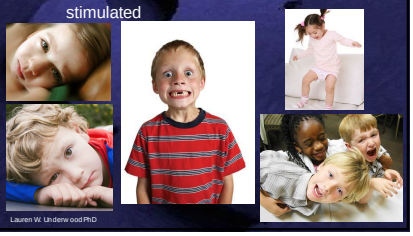
If biochemical pathways compromised

- Neurotransmission can be under or over stimulated



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Physical signs associated with detoxification issues

- Signs of detoxification issues
  - sleep issues
  - hyperactivity
  - Lethargy
  - aggression

Lauren W. Underwood PhD

How do you implement a detoxification program?

- Should be done under the direction of an experience physician or other practitioner
- Support the body's own detoxification system—nutrients,
  - Methyl B12
  - Glutathione
  - DMG/TMG
  - Folic acid
- Remove accessible toxins—detoxification via chelation
- Monitor closely

Maximize metabolism; normalize biochemical pathways

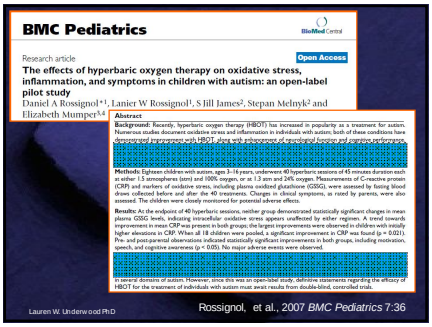
Lauren W. Underwood PhD

HBOT-Hyperbaric Oxygen Therapy

Effective way to get more oxygen into the body at the cellular level by using pressurized air chambers

- healing the gut and brain inflammation (two that may be separate issues or experienced simultaneously)
- blood flow to key areas of the brain
- dealing with gut parasites, yeast or bacteria
- or if it helps all four areas

Lauren W. Underwood PhD



BMC Pediatrics

BioMed Central

Research article

Open Access

The effects of hyperbaric oxygen therapy on oxidative stress, inflammation, and symptoms in children with autism: an open-label pilot study

Daniel A Rossignol*[1], Lanier W Rossignol[1], S Jill James[2], Stepan Melnyk[2] and Elizabeth Mumper[3,4]

Abstract

Background: Recently, hyperbaric oxygen therapy (HBOT) has increased in popularity as a treatment for autism. Numerous studies document oxidative stress and inflammation in individuals with autism; both of these conditions have demonstrated improvement with HBOT, along with enhancement of neurological function and cognitive performance.

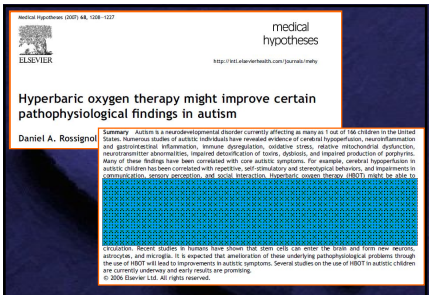
Methods: Eighteen children with autism, ages 3–16 years, underwent 40 hyperbaric sessions of 45 minutes duration each at either 1.3 atmospheres (atm) and 100% oxygen, or at 1.3 atm and 24% oxygen. Measurements of C-reactive protein (CRP) and markers of oxidative stress, including plasma oxidized glutathione (GSSG), were assessed by fasting blood draws collected before and after the 40 treatments. Changes in clinical symptoms, as rated by parents, were also assessed. The children were closely monitored for potential adverse effects.

Results: At the endpoint of 40 hyperbaric sessions, neither group demonstrated statistically significant changes in mean plasma GSSG levels, indicating intracellular oxidative stress appears unaffected by either regimen. A trend towards improvement in mean CRP was present in both groups; the largest improvements were observed in children with initially higher elevations in CRP. When all 18 children were pooled, a significant improvement in CRP was found ($p = 0.021$). Pre- and post-parental observations indicated statistically significant improvements in both groups, including motivation, speech, and cognitive awareness ($p < 0.05$). No major adverse events were observed.

In several domains of autism. However, since this was an open-label study, definitive statements regarding the efficacy of HBOT for the treatment of individuals with autism must await results from double-blind, controlled trials.

Rossignol, et al., 2007 *BMC Pediatrics* 7:36

Lauren W. Underwood PhD



Medical Hypotheses (2007) 68, 1208–1227

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medical hypotheses

http://intl.elsevierhealth.com/journals/mehy

Hyperbaric oxygen therapy might improve certain pathophysiological findings in autism

Daniel A. Rossignol

Summary Autism is a neurodevelopmental disorder currently affecting as many as 1 out of 166 children in the United States. Numerous studies of autistic individuals have revealed evidence of cerebral hypoperfusion, neuroinflammation and gastrointestinal inflammation, immune dysregulation, oxidative stress, relative mitochondrial dysfunction, neurotransmitter abnormalities, impaired detoxification of toxins, dysbiosis, and impaired production of porphyrins. Many of these findings have been correlated with core autistic symptoms. For example, cerebral hypoperfusion in autistic children has been correlated with repetitive, self-stimulatory and stereotypical behaviors, and impairments in communication, sensory perception, and social interaction. Hyperbaric oxygen therapy (HBOT) might be able to

circulation. Recent studies in humans have shown that stem cells can enter the brain and form new neurons, astrocytes, and microglia. It is expected that amelioration of these underlying pathophysiological problems through the use of HBOT will lead to improvements in autistic symptoms. Several studies on the use of HBOT in autistic children are currently underway and early results are promising.

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Rossignol, D. 2007 *Med Hypoth 68* 1208-1227

Lauren W. Underwood PhD

Immune globulin therapy

- Immunoglobulins are
  - produced by B cells and are also known as antibodies
  - naturally occurring in the blood plasma serum of healthy individuals.
  - neutralize and mark pathogens for antibody recognition
- There are 5 classes of immunoglobulins/antiboides
  - IgG-most prevalent; found in all body fluids
  - IgM- first type of antibody made in response to an infection
  - IgA-produced near mucous membranes and found in secretions
  - IgE-responsible for allergic reations and antibodies binding to antigens produce inflammatory sustances (histamine)
  - IgD- may be involved in cell differentiation; how they work is unclear

Lauren W. Underwood PhD

Immune globulin therapy

- Administration Routes of Immune Globulin Therapy
  - Intramuscular (IMIG)
  - Subcutaneous (SCIG)
  - Intravenous (IVIG)
- IMIG-intravenous immune globulin
  - a treatment to provide high doses of IgG
  - usually used as a replacement therapy.
  - products are derived from pooled human blood plasma.
- FDA Approved Indications
  - Primary Immune Deficiency
  - Idiopathic Thrombocytopenic Purpura
  - Kawasaki Disease
  - B-Cell Chronic Lymphocytic Leukemia
  - HIV Infection (pediatric)
  - Bone Marrow Transplantation

Lauren W. Underwood PhD

Off label use of IVIG

- Autism
- Chronic fatigue syndrome
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Clostridium difficile colitis
- Dermatomyositis and polymyositis
- Graves' ophthalmopathy
- Guillain-Barré syndrome
- Kawasaki disease
- Autism
- Muscular Dystrophy
- Inclusion body myositis
- Lambert-Eaton syndrome
- Lupus erythematosus
- Multifocal motor neuropathy
- Multiple sclerosis
- Myasthenia gravis
- Neonatal alloimmune thrombocytopenia

Lauren W. Underwood PhD

What does immune globulin therapy have to do with autism?

- Some people believe that people with autistic spectrum disorders are susceptible to immune deficiencies and that these deficiencies may produce some of the symptoms of autism
- By injecting or swallowing immune globulin, an antibody used by the immune system to identify and neutralize foreign objects like bacteria and viruses, it is believed those abnormalities can be overcome and the symptoms of autism reduced

http://www.researchautism.net/interventionitem.ikml?print&ra=19&infolevel=4

Lauren W. Underwood PhD

IVIG side effects

- usually well tolerated. Most adverse effects are mild and are usually related to the rate of infusion
- It can cause kidney failure, especially in those with a history of kidney disease, diabetes, sepsis, plasma cell disease, or volume depletion, or in those taking medications that can cause kidney damage
- carries the risk of potentially fatal transmission of blood-borne pathogens (i.e. HIV, hepatitis, etc). Pharmaceutical grade immune globulin is prepared commercially by separating immunoglobulin fractions from pooled human blood specimens. Several steps in the process are added to ensure that any live viruses or bacteria in the specimens are inactive – but there is still a risk.
- There is potentially an unknown risk of contracting variant Creutzfeldt-Jakob disease (vCJD).

Lauren W. Underwood PhD


Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics

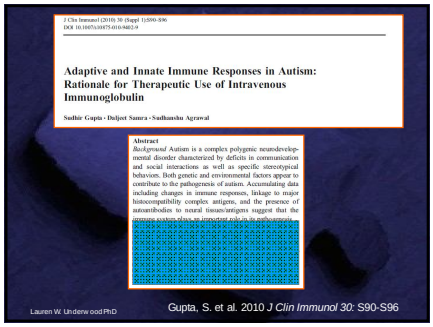
Immune Therapy in Autism: Historical Experience and Future Directions with Immunomodulatory Therapy

Michael G. Chez* and Natalie Guido-Estrada†

CONCLUSIONS

Chez and Guido-Estrada, 2010 *Neurotherapeutics: J Am Soc Exp NeuroTherapeut* 7:297-301-560

Lauren W. Underwood PhD


J Clin Immunol (2010) 30 (Suppl 1):S90–S96
DOI 10.1007/s10875-010-9402-9

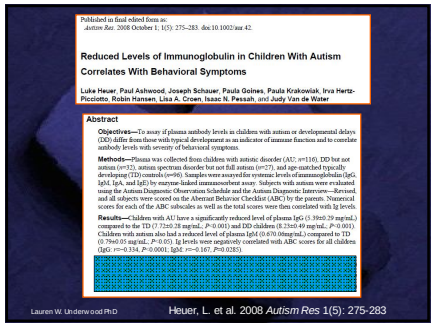
Adaptive and Innate Immune Responses in Autism: Rationale for Therapeutic Use of Intravenous Immunoglobulin

Sudhir Gupta · Daljeet Samra · Sudhanshu Agrawal

Abstract

Gupta, S. et al. 2010 *J Clin Immunol 30:* S90-S96

Lauren W. Underwood PhD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Reduced Levels of Immunoglobulin in Children With Autism Correlates With Behavioral Symptoms

Luke Heuer, Paul Ashwood, Joseph Schauer, Paula Goines, Paula Krakowiak, Irva Hertz-Picciotto, Robin Hansen, Lisa A. Croen, Isaac N. Pessah, and Judy Van de Water

Abstract

Heuer, L. et al. 2008 *Autism Res* 1(5): 275-283

Lauren W. Underwood PhD

Methyl B12-Methylcobalamin

- B12 (cobalamin) is a vitamin "family" with five unique compounds
  - a) cyanocobalamin;
  - b) hydroxycobalamin;
  - c) adenosylcobalamin;
  - d) glutathionylcobalamin;
  - e) methylcobalamin.
- Out of the B12 family, only **Methyl-B12** has the ability to activate the methionine/homocysteine biochemical pathway directly.
- It is this pathway that is responsible for the formation of homocysteine, the "crossroads" molecule that is responsible either to recycle back to methionine and SAMe or create cysteine, taurine, and glutathione-
  - **Glutathione is the body's primary intracellular antioxidant and is responsible for many detoxification reactions**
- Methyl-B12 is closely allied with the folic acid biochemical pathway. A precursor folic acid molecule must interact with the enzyme MTHFR (methyleneterahydrofolic acid) to become 5-methyltetrahydrofolic acid, the molecule that donates its methyl group to B12 so it can become Methyl-B12.

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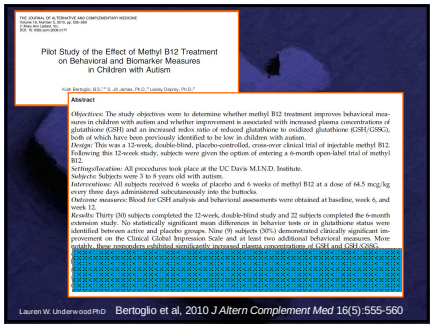
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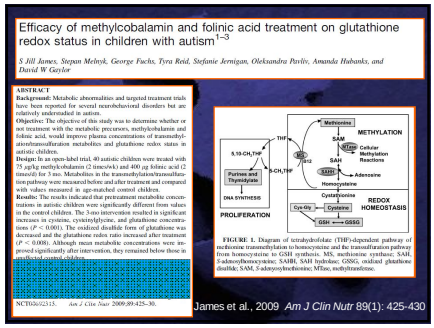
Pilot Study of the Effect of Methyl B12 Treatment on Behavioral and Biomarker Measures in Children with Autism

Kalli Bertoglio, B.S.,[1–3] S. Jill James, Ph.D.,[4] Lesley Deprey, Ph.D.,[4]

Abstract

Bertoglio et al, 2010 *J Altern Complement Med* 16(5):555-560

Lauren W. Underwood PhD


Efficacy of methylcobalamin and folinic acid treatment on glutathione redox status in children with autism[1–3]

S Jill James, Stepan Melnyk, George Fuchs, Tyra Reid, Stefanie Jernigan, Oleksandra Pavliv, Amanda Hubanks, and David W Gaylor

ABSTRACT

NCT00502515.

James et al., 2009 *Am J Clin Nutr* 89(1): 425-430

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Paradigm switch

autism is *not* a psychological condition –
it is a neuro-gastro-immunological disorder resulting from
a genetic susceptibility and
an environmental insult

Lauren W. Underwood PhD

The abnormal metabolic profile in children with autism is consistent with the abnormal genetic profile and strengthens the hypothesis that may predispose these children ***genetic susceptibility to oxidative stress and reduced methylation capacity to neurological, immunological,*** **and** ***gastrointestinal*** dysfunction that occurs with autism"

—Dr. Jill James

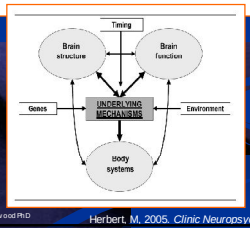
Lauren W. Underwood PhD

James et al., 2004 *Am J Clin Nutr* 80(6):1611-1617

Clinical Neuropsychiatry (2005) 2, 6, 354-379

AUTISM: A BRAIN DISORDER, OR A DISORDER THAT AFFECTS THE BRAIN?

Martha R. Herbert



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Herbert, M. 2005. *Clinic Neuropsych* 2(6): 354-379

Review

Expert Opinion

1. Introduction
2. Treatment
3. Expert opinion

Autism: an emerging 'neuroimmune disorder' in search of therapy

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Background: Autism spectrum disorders (ASDs) are neurodevelopmental disorders characterized by difficulties in communication and by repetitive and stereotypic behaviors, as well as by social impairment, attention, cognitive, and learning defects. ASDs present in early childhood and their prevalence has increased significantly to 1/150 children. Despite a number of theories, the actual reasons for this increase are still not clear. There is no reliable screening test, and no definite pathogenesis or curative therapy. Consequently, there is a major gap hampering development of effective treatments. *Objective:* To review recent publications on ASDs pathogenesis and treatment with emphasis on neuroimmune processes and new therapeutic approaches. *Methods:* Mostly original papers (652) on epidemiology, possible pathogenesis or treatment of ASDs in Medline from 1990 to May 2009 clinical trials with nonpsychotropic drugs were few and ASD characteristics varied considerably, making conclusions difficult. Psychotropic drugs are often used for stereotypic and aggressive behaviors. Unique combinations with

Lauren W. Underwood PhD

Theoharides et al., 2009 Expert *Opin Pharmacother* 10 (13):2127-2143

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NeuroToxicology

NeuroToxicology 29 (2008) 190–201

Review

How environmental and genetic factors combine to cause autism: A redox/methylation hypothesis

Richard Deth*, Christina Muratore, Jorge Benzecry, Versa-Ann Power-Charnitsky, Mostafa Waly

Abstract

Recently higher rates of autism diagnosis suggest involvement of environmental factors in causing this developmental disorder, in concert with genetic risk factors. Autistic children exhibit evidence of oxidative stress and impaired methylation, which may reflect effects of toxic exposure on sulfur metabolism. We review the metabolic relationship between oxidative stress and methylation, with particular emphasis on adaptive responses that limit activity of cobalamin and folate-dependent methionine synthase. Methionine synthase activity is required for dopamine-stimulated phospholipid methylation, a unique membrane-delimited signaling process mediated by the D4 dopamine receptor that promotes neuronal synchronization and attention, and synchrony is impaired in autism. Genetic polymorphisms adversely affecting sulfur metabolism, methylation,

"Redox/methlation hypothesis of autism"

Lauren W. Underwood PhD

Deth et al., 2008 *Neurotoxicology* 29: 190-201

A new paradigm in autism

- Autism is an environmental illness with a genetic component
- It is a complex metabolic disease, not just a developmental disability
- Autism is *treatable*, but . . .
- We must continue fighting for a cure!

Lauren W. Underwood PhD

What you can do now . . .

1. Initiate early intervention
2. Improve diet
3. Remove gluten and casein from the diet
4. Introduce supplements, one at a time
5. Stabilize intestinal dysbiosis
6. Consider advanced biomedical intervention,
   - HBOT
   - IVIG
   - methyl B12

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