Advanced Biomedical Treatments Using New Biomarkers

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Biomarker - Definition

- A characteristic that is objectively measured and evaluated as an indicator of normal biologic or pathogenic processes or pharmacological responses to a therapeutic intervention
- Binding
  - early effects such as intracellular, membrane or circulating receptor e.g. binding to ACE of ACE-Is was an early clue that the effects will be relatively prolonged than their blood level half life

Biomarker - Definition II

- ✓ Effects on activity of an intrinsic or externally induced molecule
  - Effect on an externally induced enzyme, hormone or cytokine is the effect examined e.g. inhibition of infused isoproterenol as a measure of beta blockade
- ✓ Effect on etiologic agents or anatomical features
  - infectious agent
  - pathological hallmarks of neurologic disease e.g. arteriosclerotic plaque structure

Our Preferred "Biomarkers" / Lab Tests: We must define individual needs

- **OXIDATIVE STESS**: ***Urine***: 8-OHG and when available Isoprostane, ***Blood***; Transferrin, Ceruloplasmin, Ammonia and Lactate and if available Reduced Glutathione or GSSG.
- **METHYLATION AND TRANSSULFATION: *Plasma;*** Fasting Cysteine and Methionine.
- **IMMUNOLOGICAL**: ***Urinary;*** Neopterin and Biopterin, ***Blood***; Anti-endothelial Antibodies at WUSTL, ASO and Anti-DNase B, IgG subclasses, IgM, IgA and IgE, Complete Blood Count. ***Special***; if Neopterin elevated and/or GI symptoms are present, check intestinal permeability to lactulose and mannitol. ***Urine*** tested after standard dose at timed interval.
- **HEAVY METALS**: ***Blood;*** Packed Erythrocyte Minerals and Toxic Metals, Lymphocyte Metallthionein pre/post induction ***Urinary;*** Fractionated Porphyrins and if elevated get a post chelation challenge 6 hour urine toxic metal assay.
- **Metabolic profile**: ***Blood;*** Electrolytes, Liver and Renal Chemistries.
- **Helpful**: ***Urinary*** Organic Acid Test and ***Urinary*** Oxalates.

Current and Emerging Interventions

- Behavioral, Sensory, Occupational, Speech, AIT and Physical Therapies
- Diet Modifications – Multifactorial Reasons and Effects to do this. ORGANIC if possible.
- Nutritional support: Inadequate Nutrient Intake & Pica Issues
- Dysbiosis (Gut Pathogen) treatment: Probiotics and Cultured Foods, Vancomycin, and Antifungals
- Antioxidants: Oral and IV (Vit C & rGSH)
- Immune Modifying: IVIG, IBD Rx, Allergy Type Meds, NSAIDS, Steroids, & Novel Anti-Inflammatories
- Secretin and Oxytocin
- Metal Detox: various methodologies
- Mild Hyperbaric Oxygen Therapy = HBOT

RANK: Modified CGI – Combined Parent/Clinician

Courtesy Dr Rimland, Autism Research Institute, San Diego, CA

HBOT?

Spironolactone?

Actos?

Nasal Oxytocin & Secretin?

Valtrex?

Nasal Methyl B12

		Got Worse[A]	No Effect	Got Better	Better: Worse	No. of Cases[B]
1	**Chelation**	2%	22%	76%	38::1	324
2	**Gluten- Casein-Free Diet**	3%	32%	65%	22::1	1446
3	**MethylB12**	4%	33%	63%	16::1	192
4	**Food Allergy Treatment**	3%	37%	61%	21::1	560
5	**Melatonin**	8%	30%	61%	8::1	573
6	**Digestive Enzymes**	3%	42%	56%	19::1	737
7	**Fatty Acids**	2%	42%	55%	28::1	626
8	**Diflucan**	5%	41%	55%	11::1	330
9	**Candida Diet**	3%	44%	54%	18::1	756
10	**Risperidal**	18%	28%	54%	3::1	616
11	**Feingold Diet**	2%	45%	53%	27::1	758
12	**P5P (Vit. B6)**	13%	37%	51%	4::1	213
13	**Cod Liver Oil**	3%	47%	50%	17::1	818
14	**Nystatin**	5%	46%	49%	10::1	986
15	**Secretin IV**	7%	44%	48%	7::1	333
16	**Zinc**	2%	51%	47%	24::1	1244
17	**VitB6 w/Mg**	4%	49%	47%	12::1	5780
18	**Clonidine**	21%	31%	47%	2::1	1280
19	**IVIG**	7%	51%	42%	6::1	45
20	**DMG/TMG**	7%	51%	42%	6::1	5153
21	**Secretin TD**	10%	49%	41%	4::1	132
22	**Paxil**	29%	30%	41%	1.4::1	283
23	**Prozac**	31%	32%	36%	1.2::1	1123

4 Major Areas of Biology Are Impacted by Autism

Your plan for must both define the disorders in each and as you treat you must verify the treatment is adequately causing correction of the problem.

Oxidative Stress

Methylation and Transsulfation

Immunological

Heavy Metals

Oxidative Stress must be controlled
Putting out the Fire in Autism

Increased excretion of a lipid peroxidation biomarker in autism.

Ming X, Stein TP, Brimacombe M, Johnson WG, Lambert GH, Wagner GC.
Department of Neurosciences, UMDNJ-New Jersey Medical School, Newark, 07103, USA.

Prostaglandins Leukot Essent Fatty Acids. 2005 Nov;73(5):379-84.

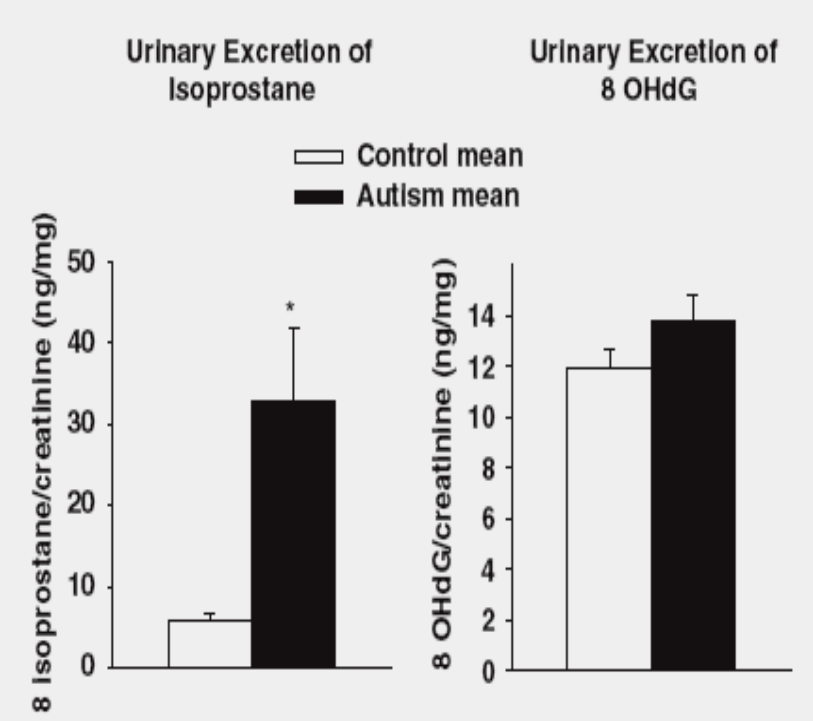
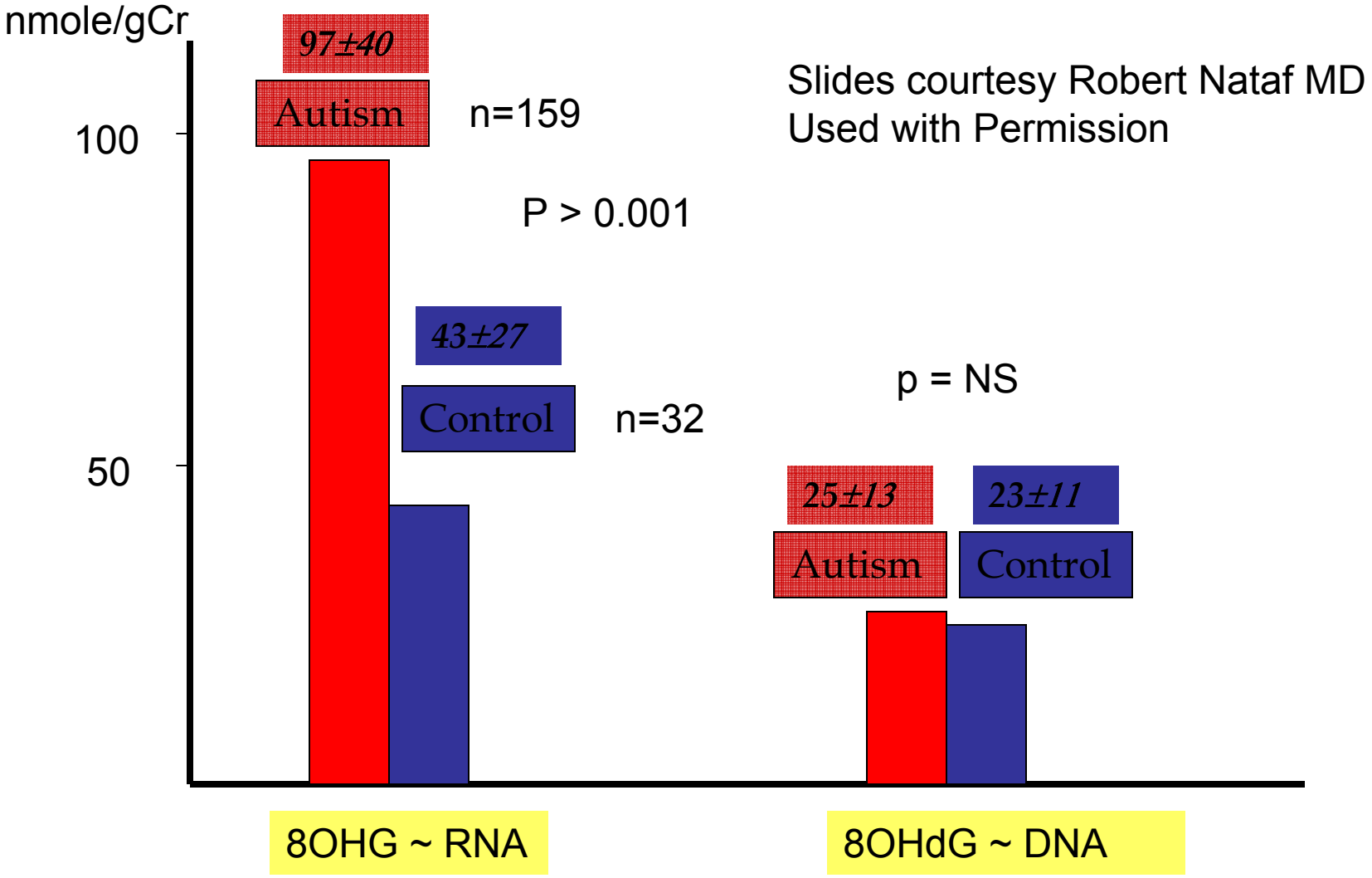
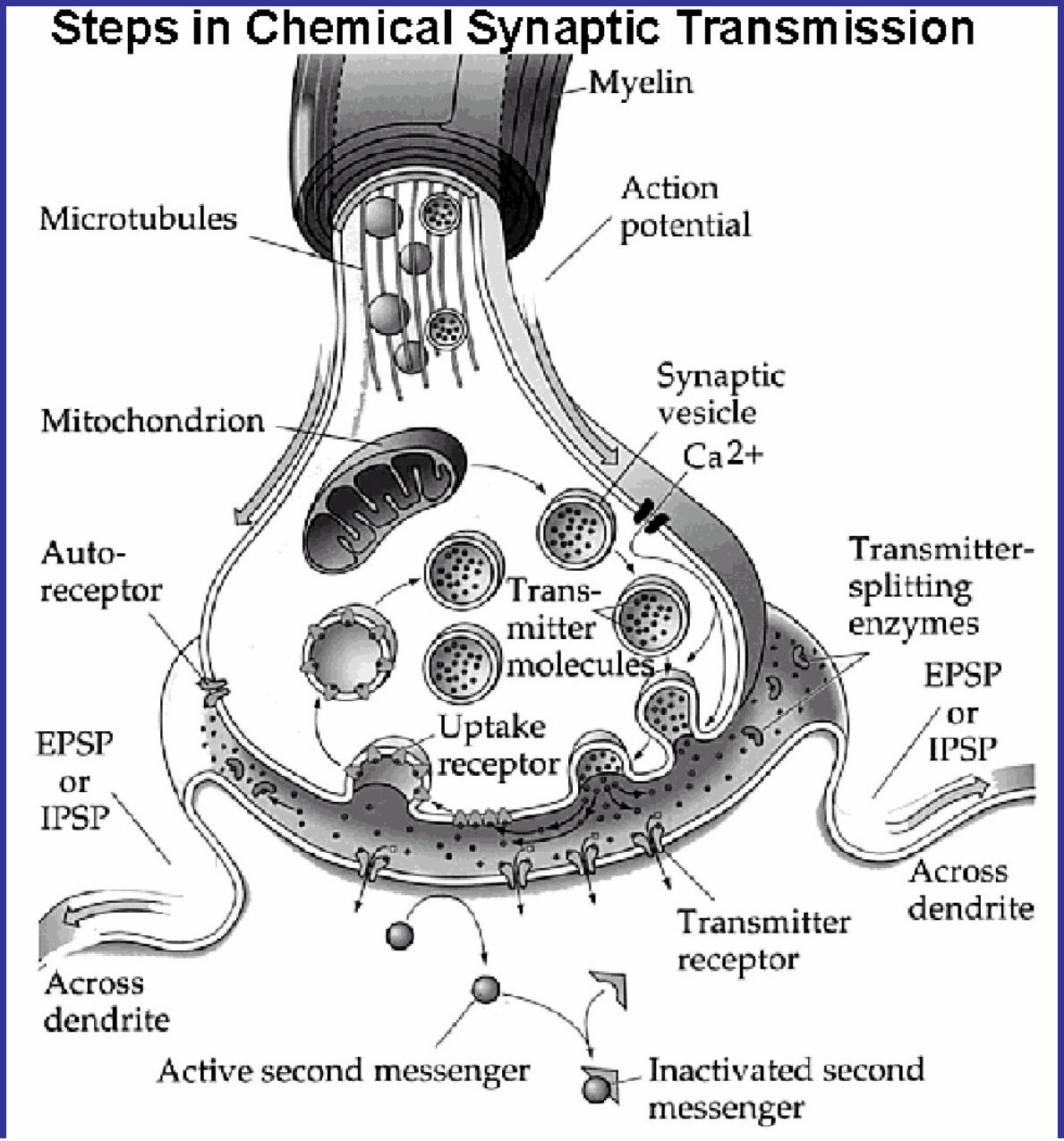


Fig. 1. Urinary excretion of isoprostane and 8-OHdG in children with autism and controls. $^{*}P < 0.05$, Student's *t*-test.

DNA and RNA Oxidative Markers preliminary results in 110 Children w/Autism (age = 2-11 years old)



Mitochondrial Insufficiency

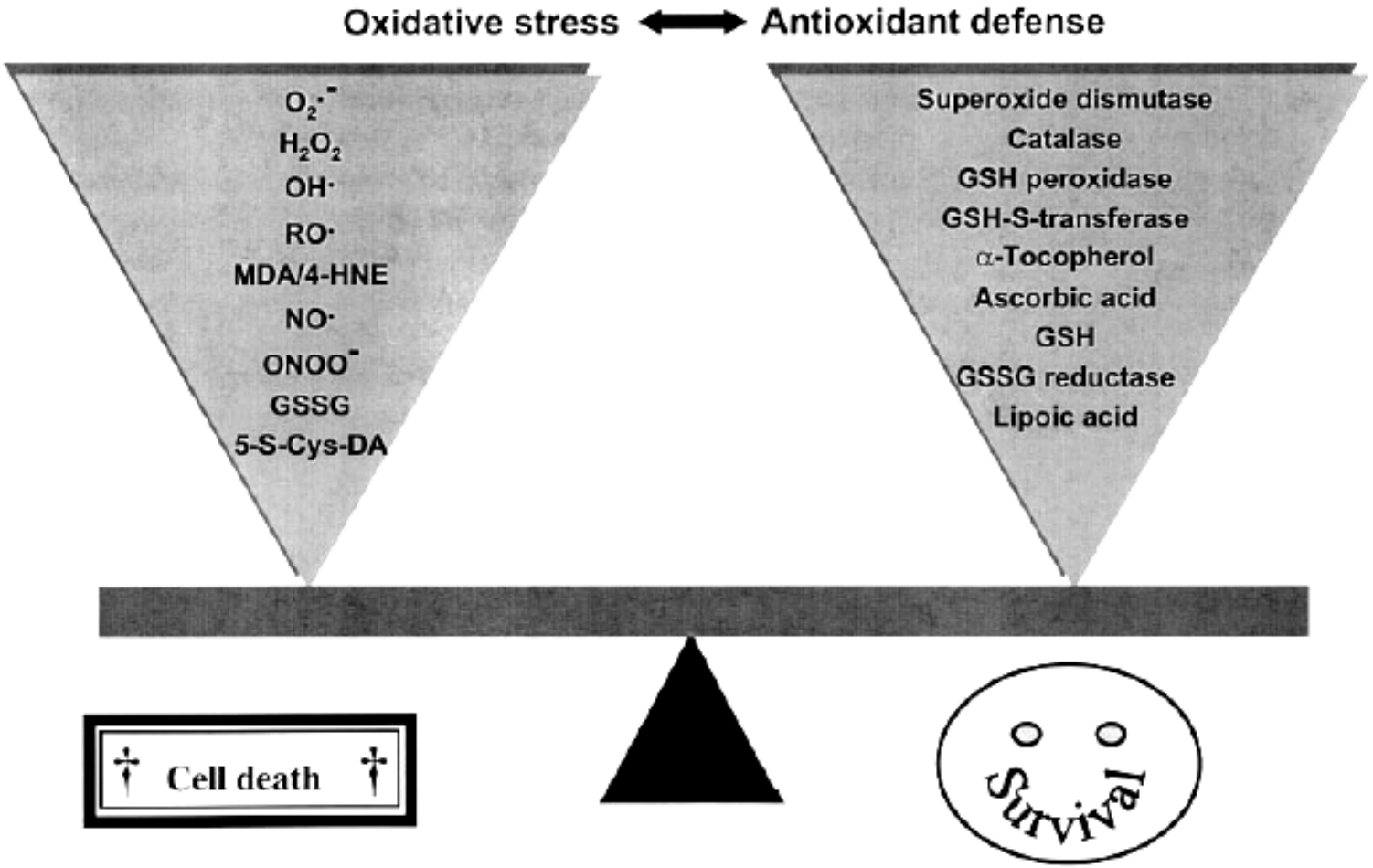


MINIREVIEW *Eur. J. Biochem.* 267, 4904–4911 (2000) © FEBS 2000

Glutathione, oxidative stress and neurodegeneration

Jörg B. Schulz, Jörg Lindenau, Jan Seyfried and Johannes Dichgans

Neurodegeneration Laboratory, Department of Neurology, University of Tübingen, Germany



Relative Carnitine Deficiency in Autism

Journal of Autism and Developmental Disorders, Vol. 34, No. 6, December 2004 (© 2004)

Pauline A. Filipek,[1,2] Jenifer Juranek,[1] Minh T. Nguyen,[1] Christa Cummings,[1] and J. Jay Gargus[1,3,4]

A random retrospective chart review was conducted to document serum carnitine levels on 100 children with autism. Concurrently drawn serum pyruvate, lactate, ammonia, and alanine levels were also available in many of these children. Values of free and total carnitine ($p < 0.001$), and pyruvate ($p = 0.006$) were significantly reduced while ammonia and alanine levels were considerably elevated ($p < 0.001$) in our autistic subjects. The relative carnitine deficiency in these patients, accompanied by slight elevations in lactate and significant elevations in alanine and ammonia levels, is suggestive of mild mitochondrial dysfunction. It is hypothesized that a mitochondrial defect may be the origin of the carnitine deficiency in these autistic children.

Significantly increased NH3 and Alanine with mild increase in Lactate = Mild Mitochondrial Dysfunction

Interventions for Oxidative Stress

- Plant Based Antioxidants: Acai (South American Berry), tops the list of berries. Barley grass may be good too.
- All chelators are antioxidants and may be getting some of their positive effects from this chemistry.
- Vitamins C (IV or Oral) and E
- Reduced Glutathione

Antioxidant ORAC/ 1 gram of whole food
Freeze dried ACAI is > 420

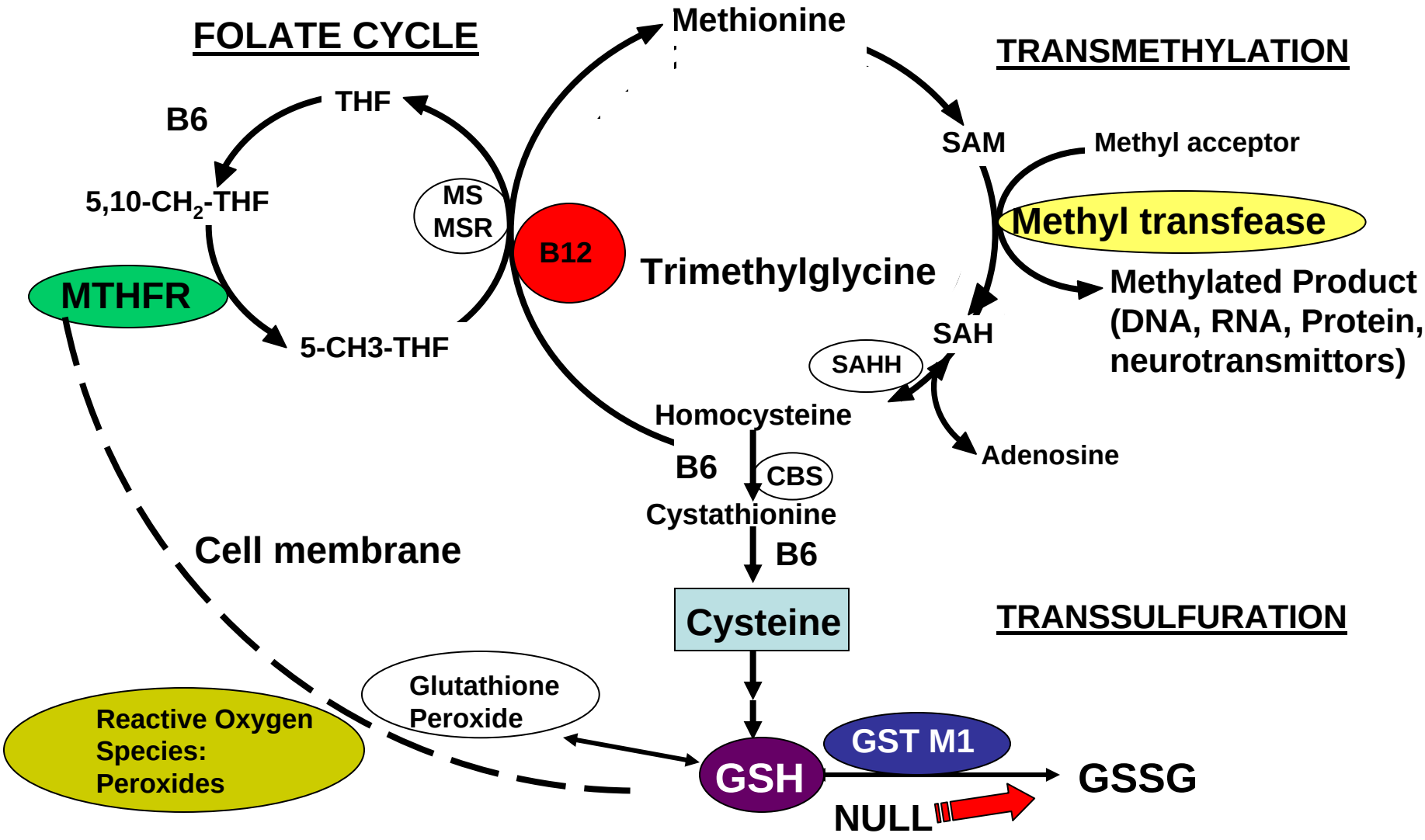
Muscadine Grape Seed**	559
Acai*	387
Goji Berry*	253
Noni*	151
Pomegranates*	105
Raspberries*	82
Blueberries*	77
Red Grapes*	74
Prunes*	57
Cherries*	67
Strawberries*	36

*Antioxidant Capacities of Foods. J. Agric. Food Chem., Vol. 52, No. 12, 2004 4027

*Wu X, Beecher GR, Holden JM, Haytowitz DB, Gebhardt SE, Prior RL, J Agric Food Chem. "Lipophilic and hydrophilic antioxidant capacities of common foods in the United States." 2004 Jun 16;52(12):4026-37

Methylation and Transsulfation change and protect molecules:
Key in RedOx as well as control of neurotransmitters and defense of metals

The Methylation and Transsulfuration Pathways Provide the Reduced Glutathione (GSH) to Repair Oxidative Damage.



Courtesy of Jill James, PhD, University of Arkansas

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

James SJ, Melnyk S, Jernigan S, Cleves MA, Halsted CH, Wong DH, Cutler P, Bock K, Boris M, Bradstreet JJ, Baker SM, Gaylor DW (Goldblatt A)

Am J Med Genet B Neuropsychiatr Genet. 2006 Aug 17

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 360 autistic children and 205 controls. The metabolic results indicated that plasma methionine and the ratio of S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH), an indicator of methylation capacity, were significantly decreased in the autistic children relative to age-matched controls. In addition, plasma levels of cysteine, glutathione, and the ratio of reduced to oxidized glutathione, an indication of antioxidant capacity and redox homeostasis, were significantly decreased. Differences 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 glutathione-S-transferase (GST M1). **We propose that an increased vulnerability to oxidative stress (endogenous or environmental) may contribute to the development and clinical manifestations of autism.**

Interventions for Methylation and Cysteine-Glutathione

- Cysteine: Tricky many children react to NAC, SAMe, Methionine
- Topical Reduced Glutathione (GSH)
- IV GSH and Vitamin C
- B6 critical to pathway
- Folic Acid, TMG or DMG, MeB12
- Remove Oxidative stress – shut downs pathway

S-adenosylmethionine (SAMe) as treatment for depression: a systematic review.

Clin Invest Med. 2005 Jun;28(3):132-9.

Williams AL et al

RESULTS: Eleven articles met initial inclusion criteria; five intervention trials, two RCTs, two reviews, one controlled clinical trial, and one meta-analysis. Using the one common outcome measure among all the intervention studies and RCTs, the Hamilton Rating Scale for Depression, direct comparison of effect sizes was made. A favourable and significant between group effect was seen.

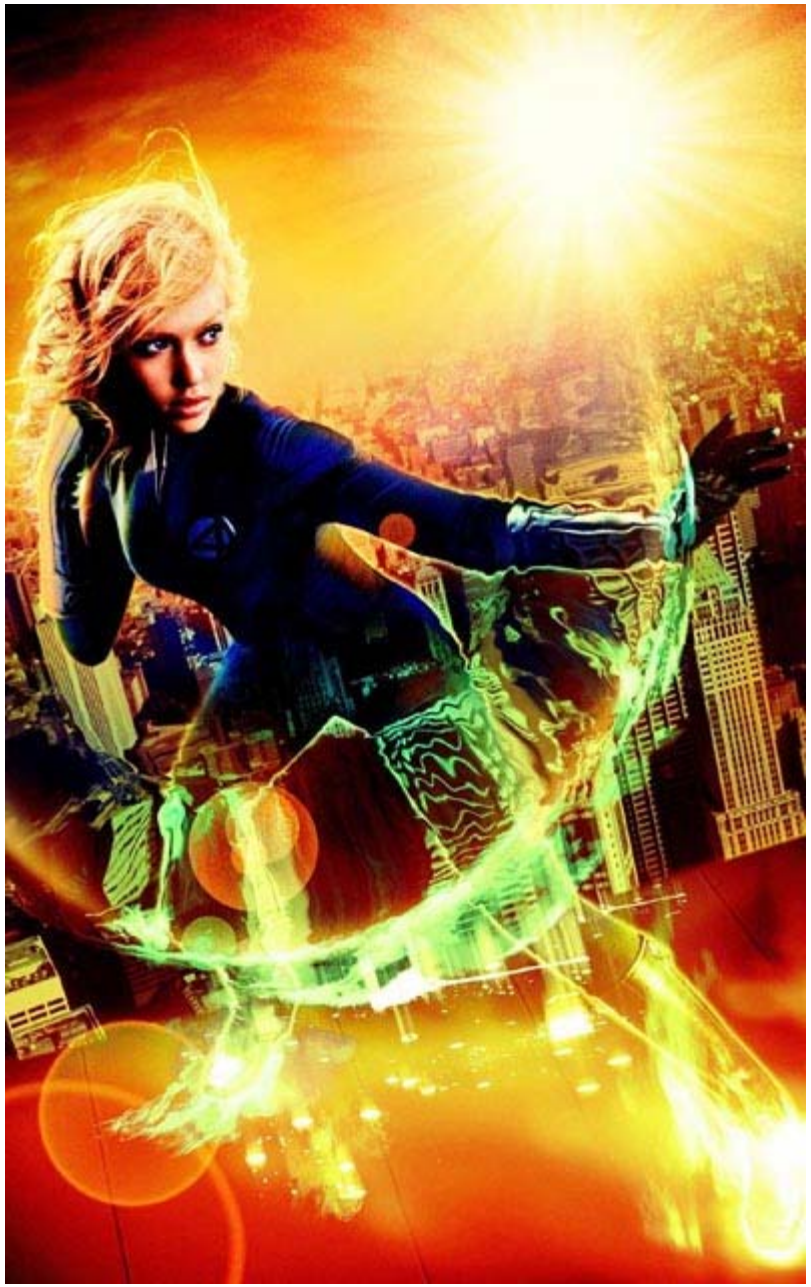
S-adenosylmethionine (SAM-e) for the treatment of depression in people living with HIV/AIDS.

BMC Psychiatry. 2004 Nov 11;4:38.

Shippy RA et al

RESULTS: Data show a significant acute reduction in depressive symptomatology, as measured by both the HAM-D and the BDI instruments.

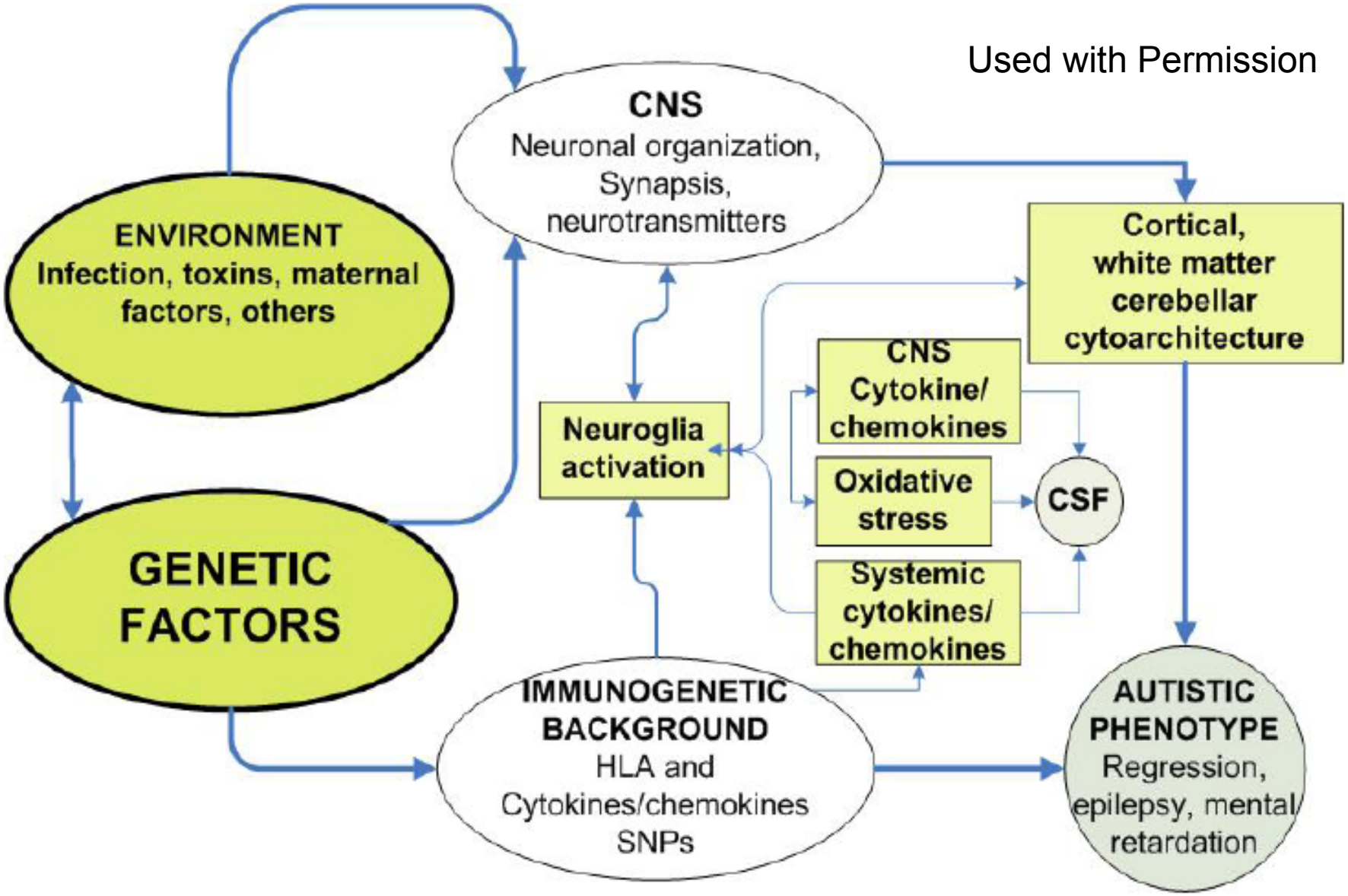
CONCLUSIONS: SAM-e has a rapid effect evident as soon as week 1 ($p < .001$), with progressive decreases in depression symptom rating scores throughout the 8 week study.



The Immunological System protects from outsiders but shouldn't see the body as the enemy

International Review of Psychiatry, December 2005; 17(6): 485–495

Immune system & Autism: An overview



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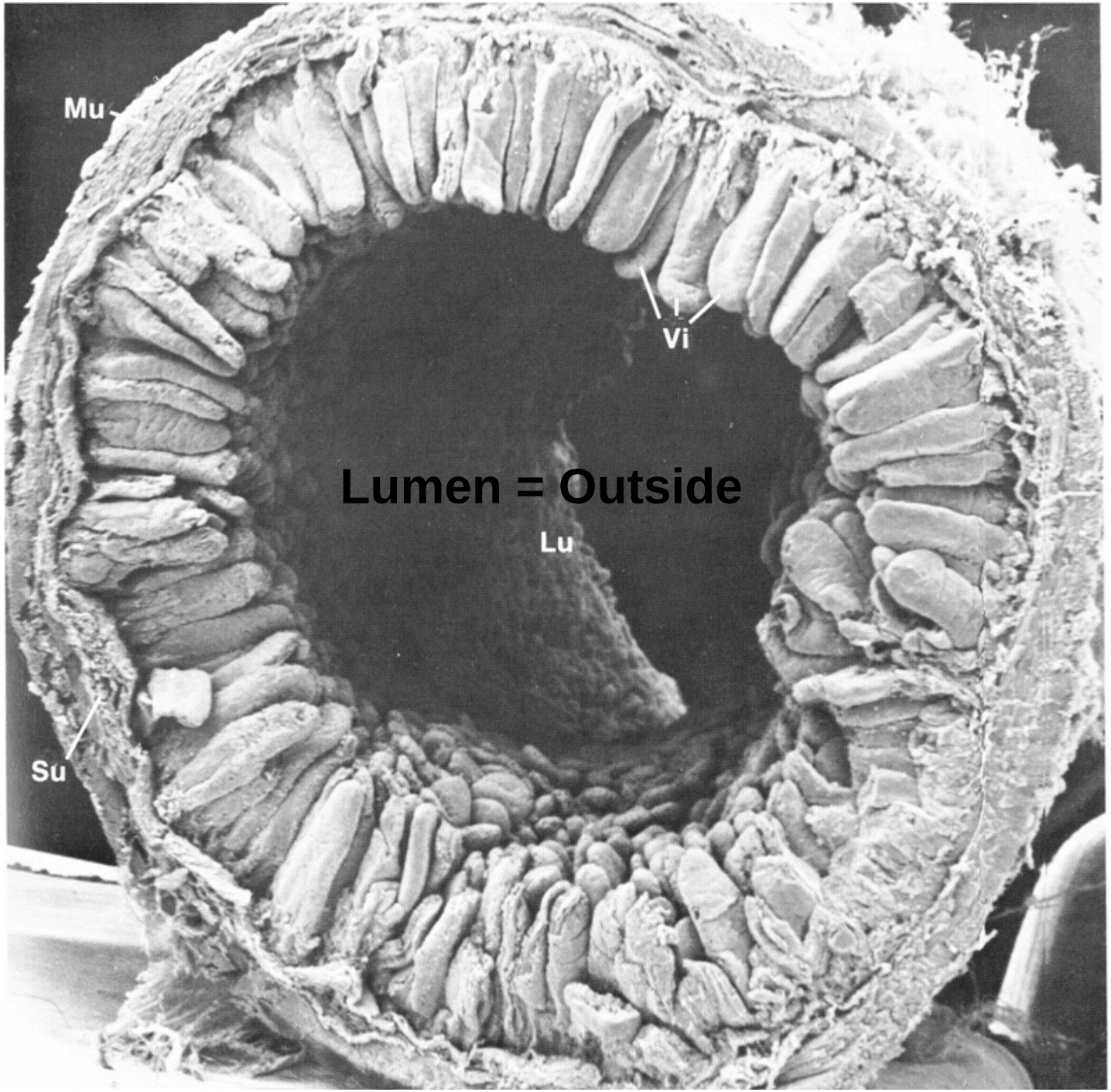
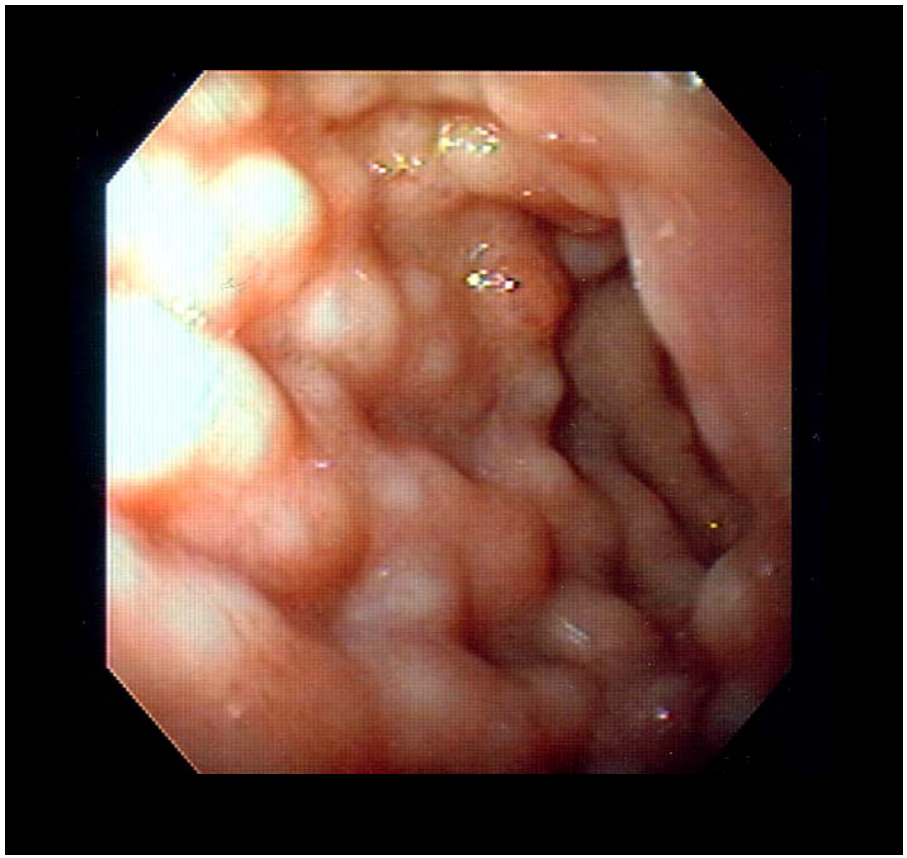
Gut (and peripheral immune system) – Brain interactions

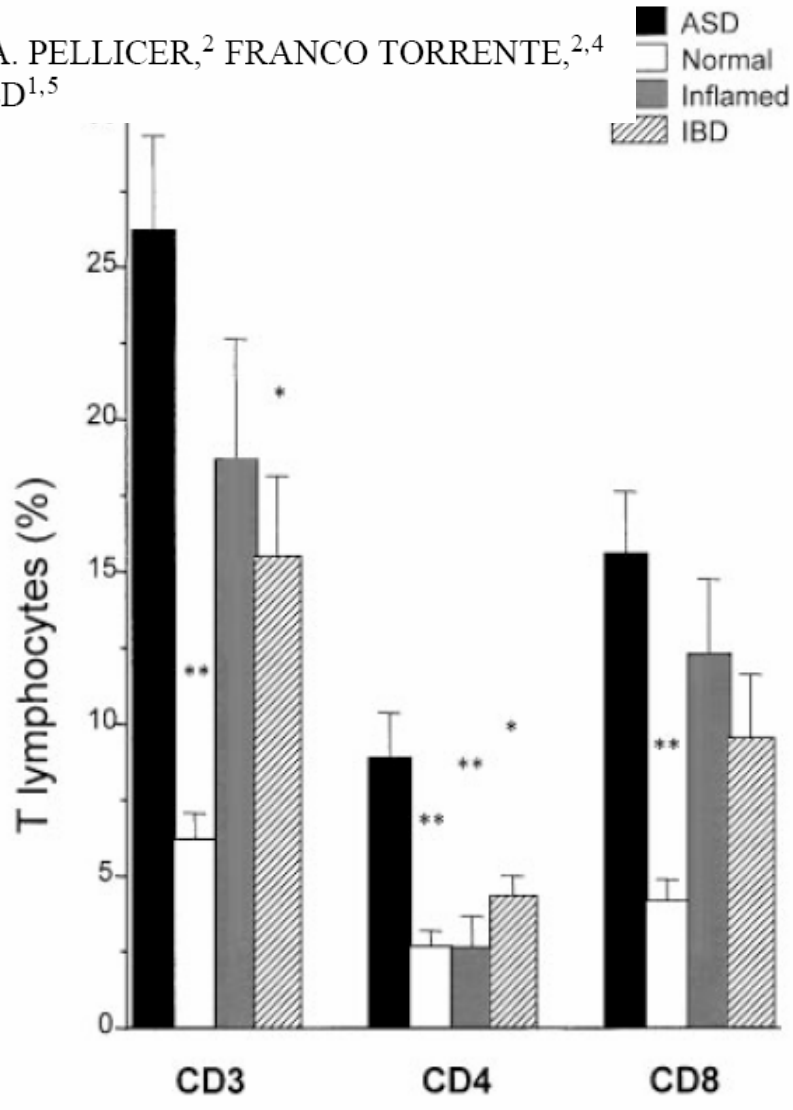

Mu
Vi
Lumen = Outside
Lu
Su

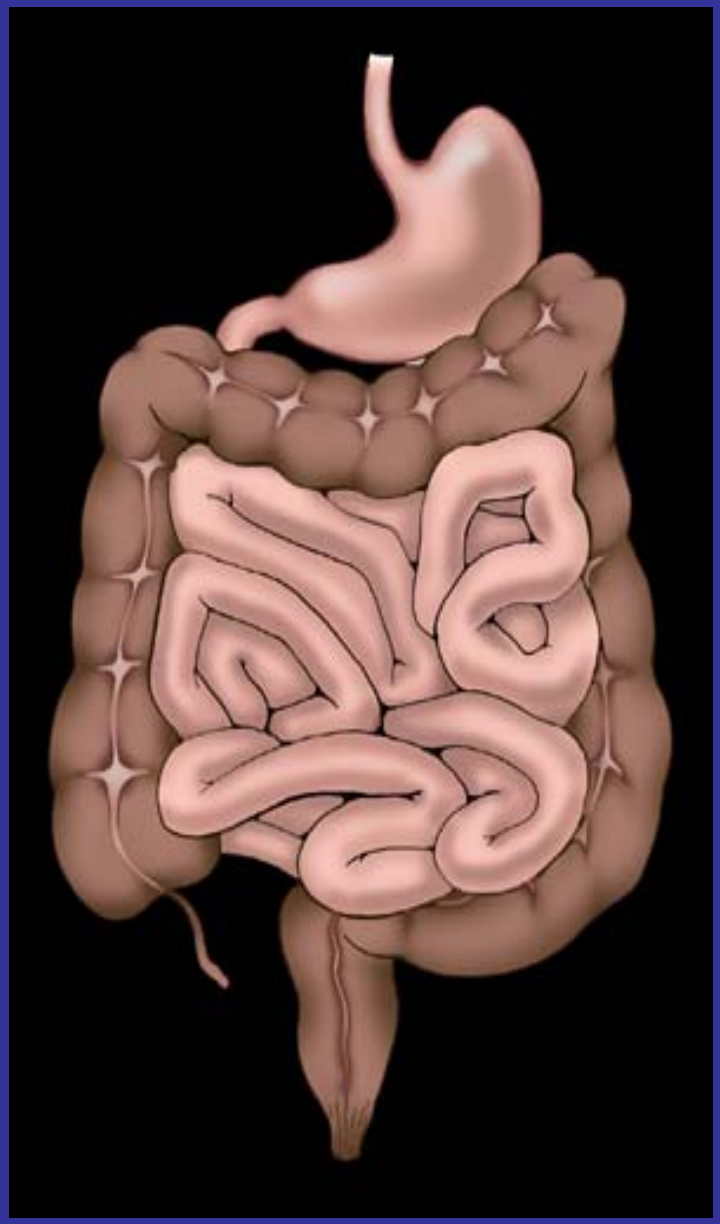
Intestinal Lymphocyte Populations in Children with Regressive Autism: Evidence for Extensive Mucosal Immunopathology

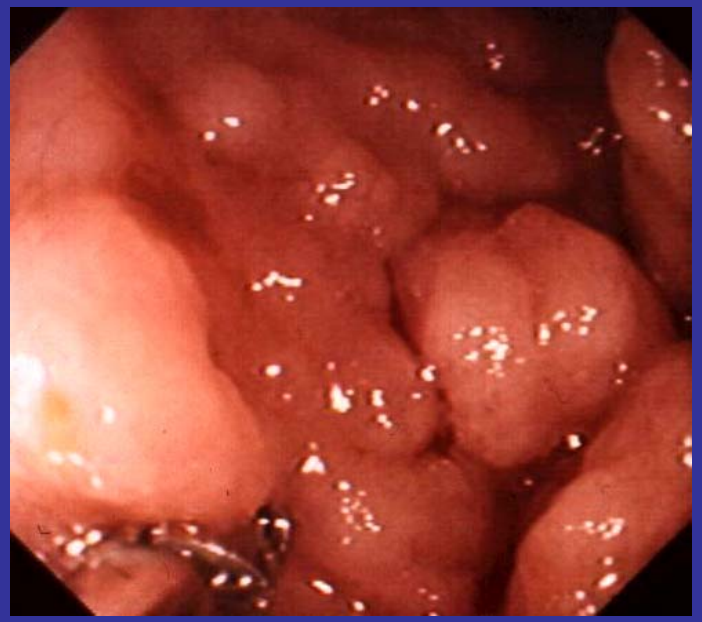
Journal of Clinical Immunology, Vol. 23, No. 6, November 2003 (© 2003)

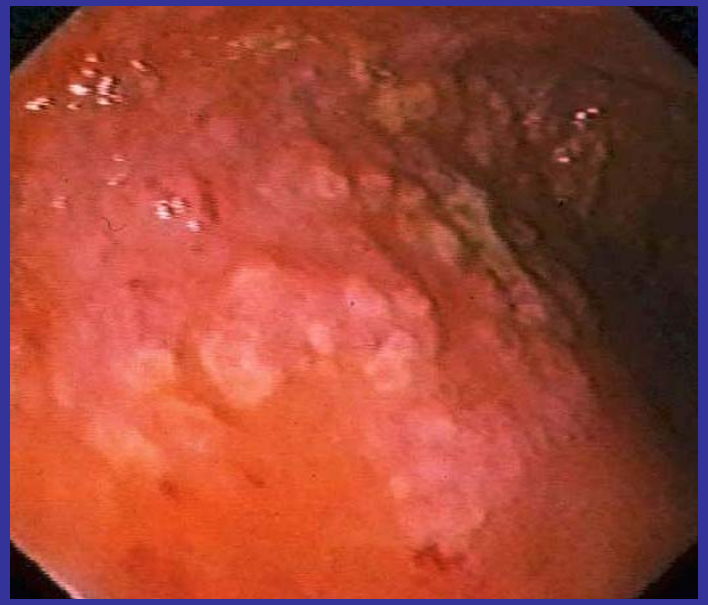
PAUL ASHWOOD,[1,2,6] ANDREW ANTHONY,[1,3] ALICIA A. PELLICER,[2] FRANCO TORRENTE,[2,4] JOHN A. WALKER-SMITH,[2] and ANDREW J. WAKEFIELD[1,5]





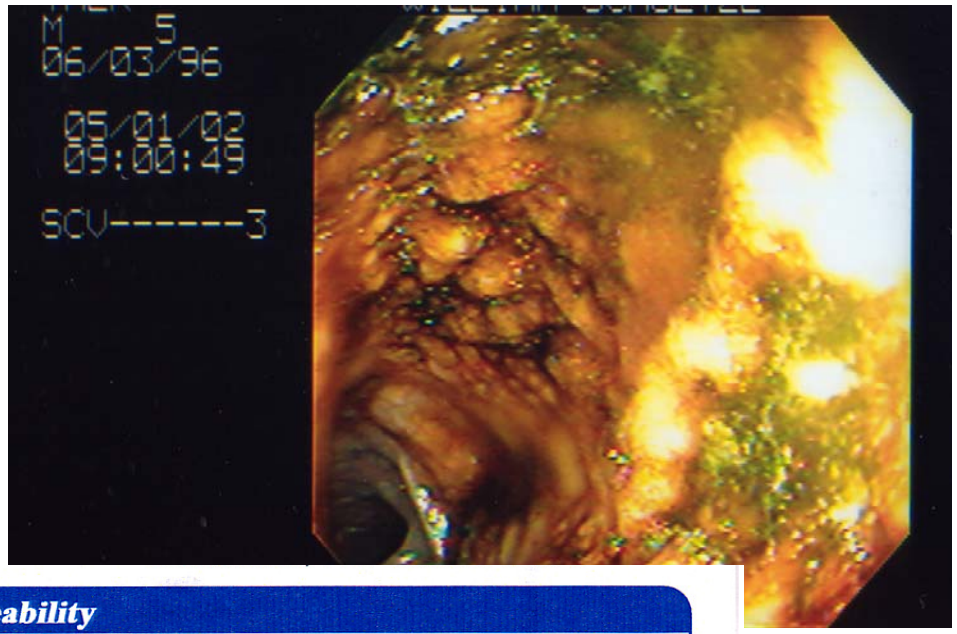


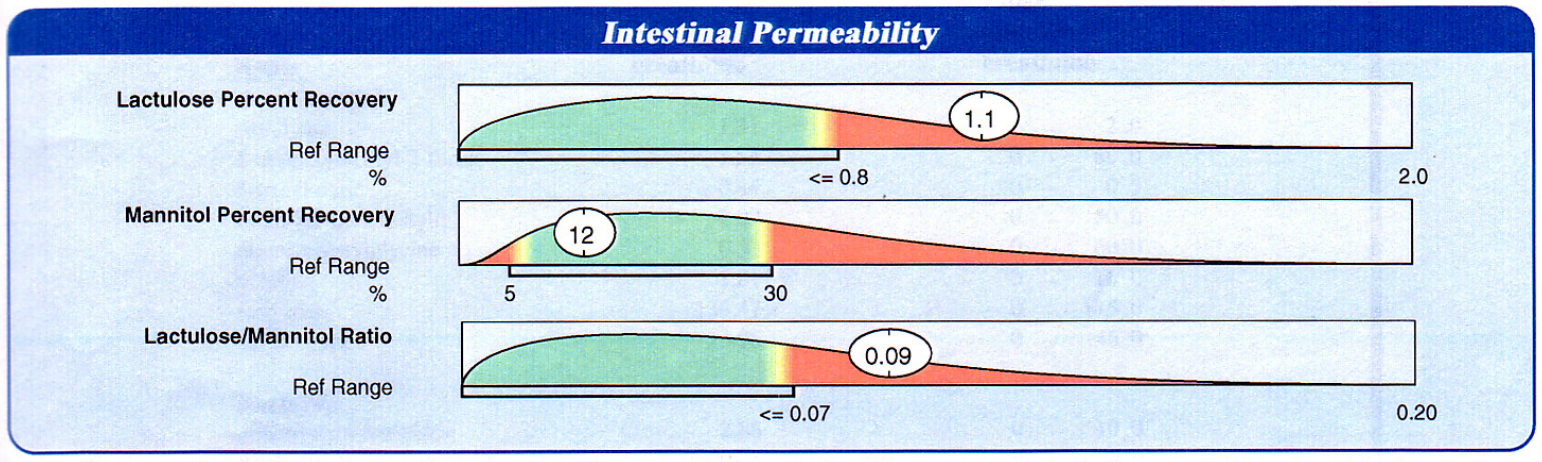




Intestinal immune changes lead to *increased intestinal permeability*

Abnormal lactulose absorption can be measured in the urine after a standard oral dose in many children with autism.
***Acta Paediatr.* 1996 Sep;85(9):1076-9.**



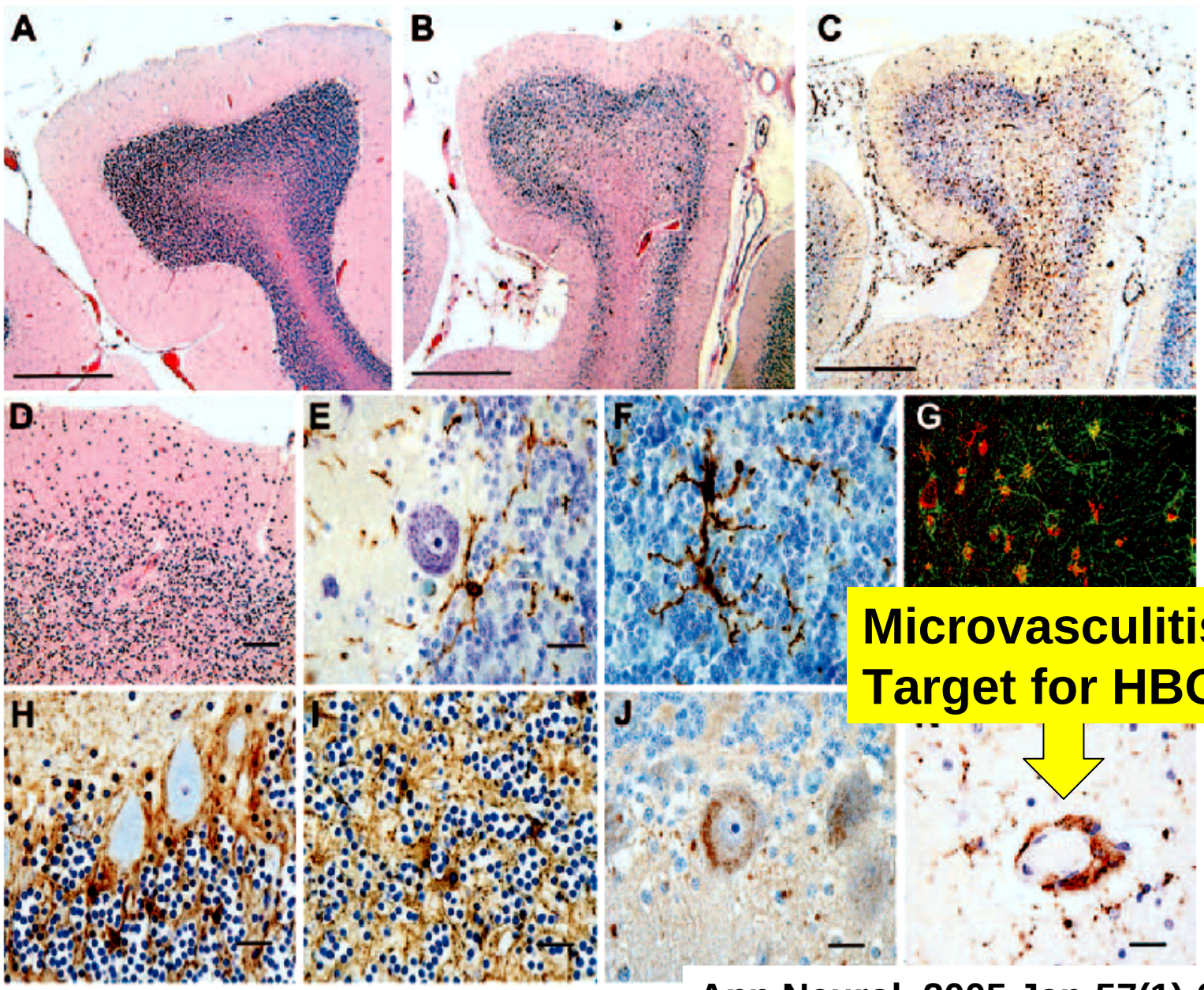


Neuroglial Activation and Neuroinflammation in the Brain of Patients with Autism

Diana L. Vargas, MD,[1,2] Caterina Nascimbene, MD,[1–3] Chitra Krishnan, MHS[1]
Andrew W. Zimmerman, MD,[1,4] and Carlos A. Pardo, MD[1,2,5]

Autism is a neurodevelopmental disorder characterized by impaired communication and social interaction and may be accompanied by mental retardation and epilepsy. Its cause remains unknown, despite evidence that genetic, environmental, and immunological factors may play a role in its pathogenesis. To investigate whether immune-mediated mechanisms are involved in the pathogenesis of autism, we used immunocytochemistry, cytokine protein arrays, and enzyme-linked immunosorbent assays to study brain tissues and cerebrospinal fluid (CSF) from autistic patients and determined the magnitude of neuroglial and inflammatory reactions and their cytokine expression profiles. Brain tissues from cerebellum, midfrontal, and cingulate gyrus obtained at autopsy from 11 patients with autism were used for morphological studies. Fresh-frozen tissues available from seven patients and CSF from six living autistic patients were used for cytokine protein profiling. We demonstrate an active neuroinflammatory process in the cerebral cortex, white matter, and notably in cerebellum of autistic patients. Immunocytochemical studies showed marked activation of microglia and astroglia, and cytokine profiling indicated that macrophage chemoattractant protein (MCP)–1 and tumor growth factor–β1, derived from neuroglia, were the most prevalent cytokines in brain tissues. CSF showed a unique proinflammatory profile of cytokines, including a marked increase in MCP-1. Our findings indicate that innate neuroimmune reactions play a pathogenic role in an undefined proportion of autistic patients, suggesting that future therapies might involve modifying neuroglial responses in the brain.

Ann Neurol. 2005 Jan;57(1):67-81



Ann Neurol. 2005 Jan;57(1):67-81

NEUROMUSCULAR DISEASE CENTER
Phone: 314-362-6981
Fax: 314-362-3752
Washington University, St. Louis, MO USA

Serum autoantibodies to brain in Landau-Kleffner variant, autism, and other neurologic disorders.

Journal of Pediatrics 1999 May;134(5):607-13. Connolly, et al

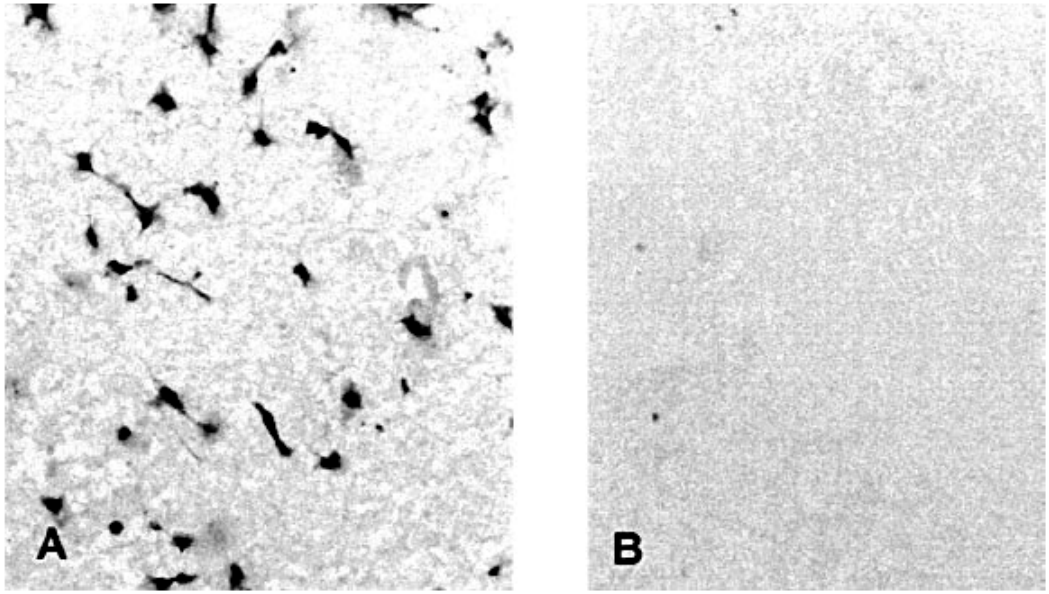


Fig 1. **A,** IgG antibodies from a child with LKSV binding to small blood vessels in human temporal lobe cortex (original magnification ×80). Immunostaining (1:100) demonstrates distinct capillary staining. **B,** Control serum shows no specific labeling.

Urinary levels of neopterin and biopterin in autism

S. Messahel[a,b], A.E. Pheasant[a,*], H. Pall[b], J. Ahmed-Choudhury[a], R.S. Sungum-Paliwal[c], P. Vostanis[c]

[a]School of Biochemistry, University of Birmingham, Edgbaston Park Road, Birmingham B15 2TT, UK
[b]Department of Neurology, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK
[c]Department of Child Psychiatry, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

Neuroscience Letters 241 (1998) 17–20

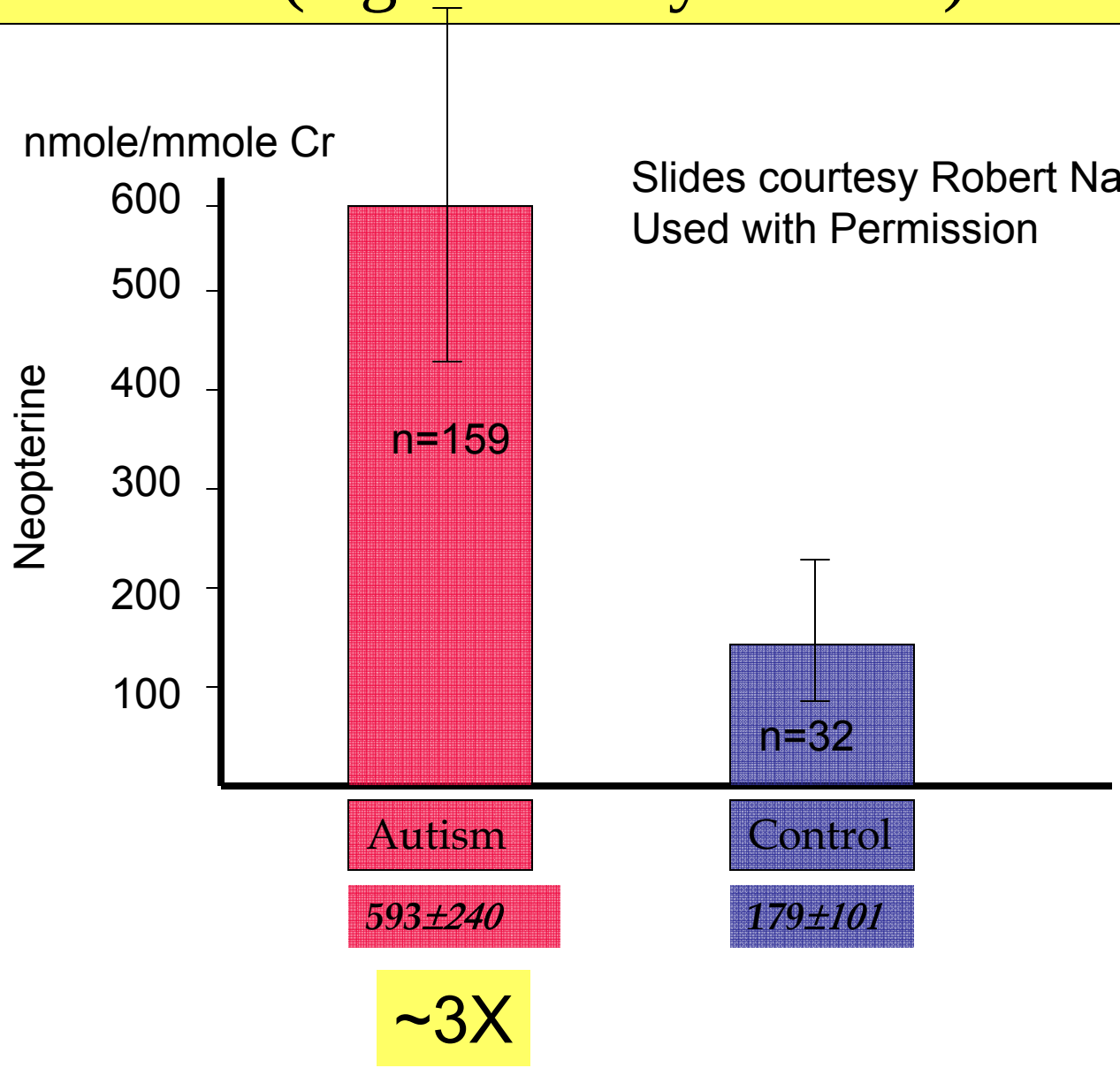
Table 1

Urinary neopterin and biopterin levels in autistic children, their siblings and control children

	Neopterin (μmol/mol creatinine)	Biopterin (μmol/mol creatinine)
Autistic children ($n = 14$)	3116 ± 686*	3691 ± 882**
Siblings ($n = 21$)	1490 ± 346	2923 ± 626**
Control children ($n = 16$)	908 ± 201	359 ± 80

Data are the mean ± SEM. Significantly different from controls: *$P < 0.01$; **$P < 0.001$.

Urinary Neopterine in Children with Autism (Age = 2-11 years old)



Slides courtesy Robert Nataf MD
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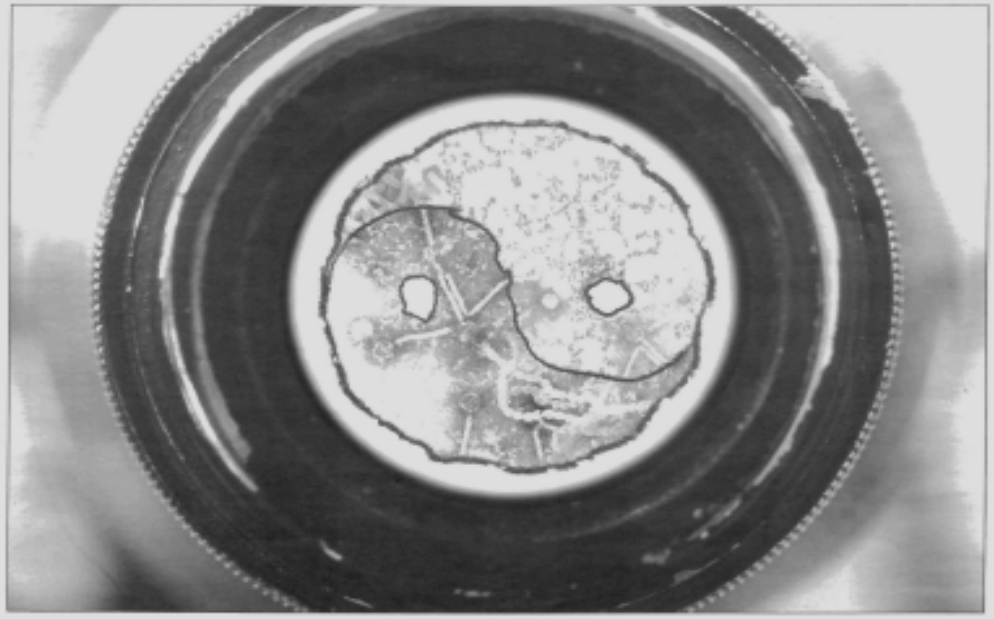
Interventions for Immune Issues

Researchers studying customized cancer vaccine [PAGE 46]



Bugs in balance

WHEN TREATED WITH AN ANTIBIOTIC FOR RECURring infections, a patient of Robert Bonakdar, MD, a family physician in San Diego, invariably confronted a round of debilitating stomach problems — bloating, upsets and diarrhea. His conundrum raised the possibility that the cure really was worse than the disease.

But all that changed when the patient also took an over-the-counter product packed with strains of good bacteria that normally populate the gut. "In this case, the patient was able to take the antibiotic and not have the diarrhea," said Dr. Bonakdar, who practices at the Scripps Center for Integrative Medicine and also heads an annual conference there. The conference brings in experts to help physicians sort through the "good, the bad and the ugly" of the booming supplement field, he said. Helpful [illegible] do their jobs more efficiently to help fend off infections.

The good bacteria in the human gut play a huge role in maintaining health. Sometimes they need a little help.

The colonies are in constant flux as major quantities bacteria are eliminated daily, and others may be killed antibiotics. One way to sustain those colonies is to inge more of the beneficial bacteria in a product known a probiotic. That's what Dr. Bonakdar's patient did.

Combating antibiotic-associated diarrhea is o of several research-supported uses for probiotic which were defined in 2001 by the World Heal Organization as "live organisms which, wh administered in adequate amounts, confer health benefit on the host."

Research in the area is growing rapidl fueled by the search for a "natural" pa to good health and further driven by t spread of antibiotic-resistant strains harmful bacteria. The quest is on find ways to help the white-hat ba

What's Broken Can Be Fixed

This photograph was taken of our son's Robert Lee Becerra's stool in June of 1999. This is what his stool looked like the first three years of his life. It was always bright yellow, slimy, no formation, pasty and gritty like sand and often had pieces of undigested food in it. The smell was horrible and Robert would strain hard with each bowel movement.

After a year long process this is what his stool looks like now at age 4. We began by first taking wheat (gluten) and dairy (casein) products out of his diet. Then we began treating the yeast in his intestine. We started with Nystatin and Diflucan. We maintain it now daily with acidophilus in very high amounts. We give him Ultra Green which is a phytonutrient and lots of olive oil and grapeseed oil everyday. We added several vitamins and minerals. We began treatments of transdermal secretin and IVIG (intravenous immune gamma globulins). We recently added bovine colostrum and today we see nice, well formed, normal colored and smelling stools. Robert does not strain any more at all while having a bowel movement.

Lilia Becerra 4-20-00

Available online at www.sciencedirect.com
ScienceDirect
Behavioural Brain Research 176 (2007) 149–169
BEHAVIOURAL BRAIN RESEARCH
www.elsevier.com/locate/bbr

Research report

Neurobiological effects of intraventricular propionic acid in rats: Possible role of short chain fatty acids on the pathogenesis and characteristics of autism spectrum disorders

Derrick F. MacFabe[a,*], Donald P. Cain[b], Karina Rodriguez-Capote[c], Andrew E. Franklin[d], Jennifer E. Hoffman[b], Francis Boon[d], A. Roy Taylor[d], Martin Kavaliers[b], Klaus-Peter Ossenkopp[b]

[a] *The Kilee Patchell-Evans Autism Research Group, Departments of Psychology and Psychiatry, Division of Developmental Disabilities, University of Western Ontario, Social Science Centre, Room 7252, London, Canada N6A 5C2*

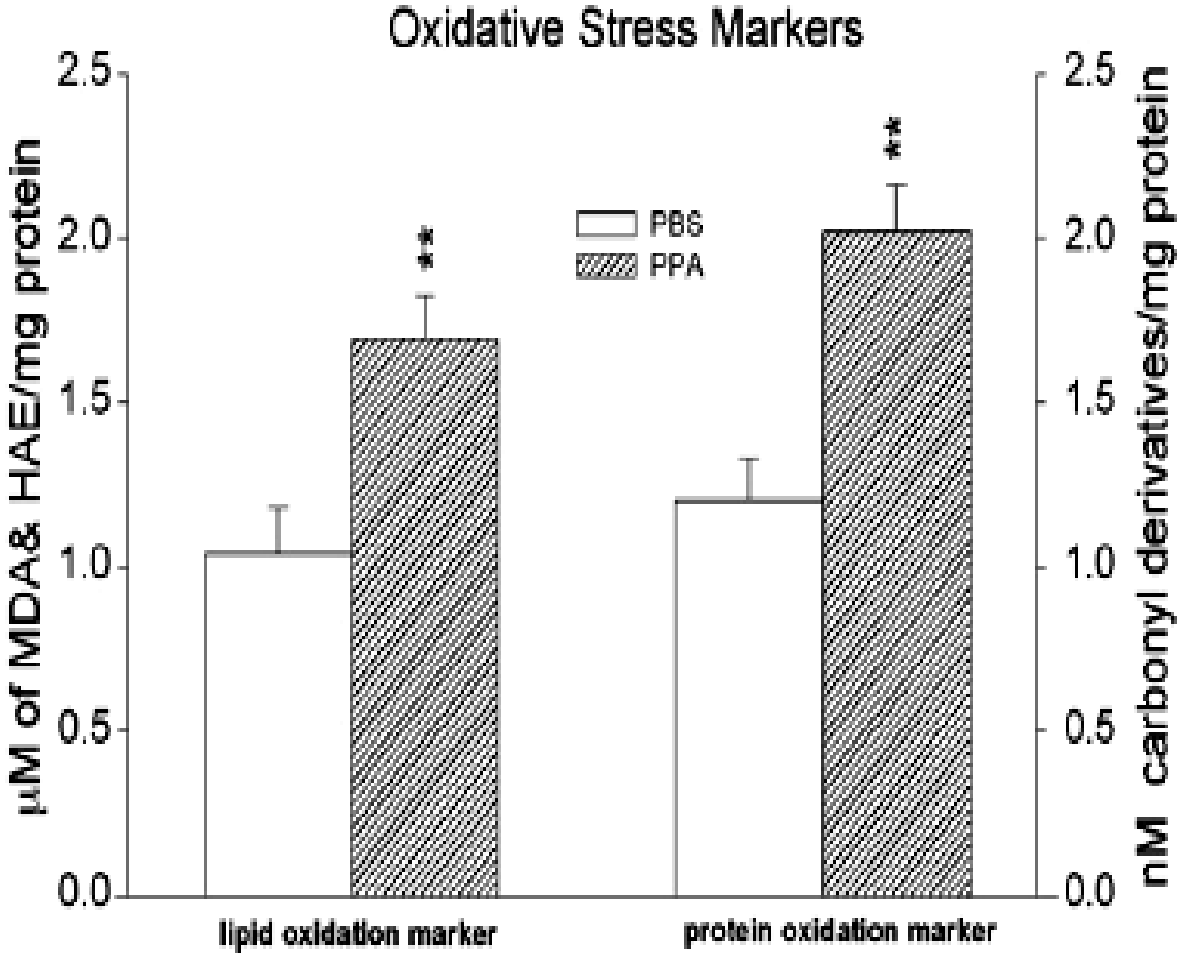


Fig. 9. Group mean (±S.E.M.) levels of lipid (left *Y*-axis) and protein (right *Y*-axis) oxidation produced after PPA or PBS treatment twice daily for seven consecutive days. $^{*}p < .05$; $^{**}p < 0.01$. MDA: malonaldehyde; HNE: 4-hydroxy-2,3-nonenal.

APPLIED AND ENVIRONMENTAL MICROBIOLOGY, Nov. 2004, p. 6459–6465 Vol. 70, No. 1
0099-2240/04/$08.00+0 DOI: 10.1128/AEM.70.11.6459–6465.2004

Real-Time PCR Quantitation of Clostridia in Feces of Autistic Children

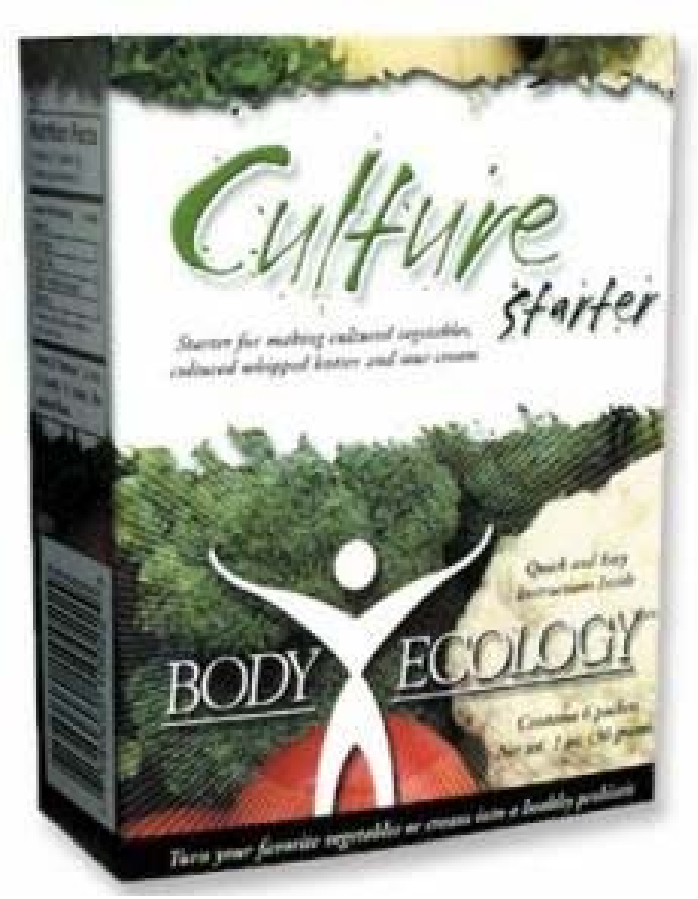
Yuli Song,[1]* Chengxu Liu,[1] and Sydney M. Finegold[2,3,4]

Research Service[1] and Infectious Diseases Section,[2] VA Medical Center West Los Angeles, and Department of Medicine[3] and Department of Microbiology, Immunology, and Molecular Genetics,[4] UCLA School of Medicine, Los Angeles, California

Received 11 February 2004/Accepted 27 June 2004

Based on the hypothesis that intestinal clostridia play a role in late-onset autism, we have been characterizing clostridia from stools of autistic and control children. We applied the TaqMan real-time PCR procedure to detect and quantitate three *Clostridium* clusters and one *Clostridium* species, *C. bolteae*, in stool specimens. Group- and species-specific primers targeting the 16S rRNA genes were designed, and specificity of the primers was confirmed with DNA from related bacterial strains. In this procedure, a linear relationship exists between the threshold cycle (C_T) fluorescence value and the number of bacterial cells (CFU). The assay showed high sensitivity: as few as 2 cells of members of cluster I, 6 cells of cluster XI, 4 cells of cluster XIVab, and 0.6 cell of *C. bolteae* could be detected per PCR. Analysis of the real-time PCR data indicated that the cell count differences between autistic and control children for *C. bolteae* and the following *Clostridium* groups were statistically significant: mean counts of *C. bolteae* and clusters I and XI in autistic children were 46-fold ($P = 0.01$), 9.0-fold ($P = 0.014$), and 3.5-fold ($P = 0.004$) greater than those in control children, respectively, but not for cluster XIVab (2.6×10^8 CFU/g in autistic children and 4.8×10^8 CFU/g in controls; respectively). More subjects need to be studied. The assay is a rapid and reliable method, and it should have great potential for quantitation of other bacteria in the intestinal tract.

Cultured Food
Lactobacillus Most Important



www.bodyecologydiet.com GOOD INFO

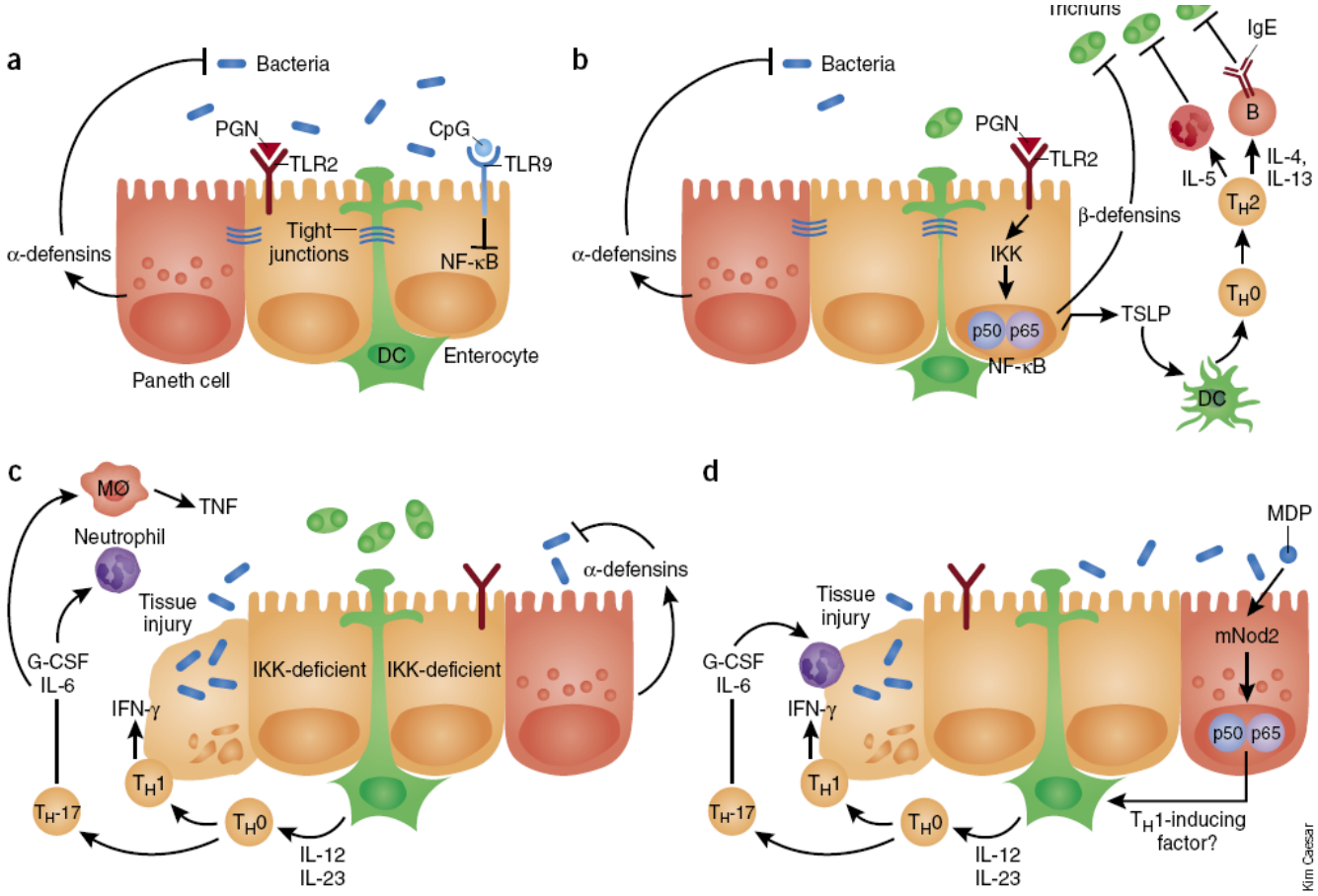
Cultured Vegetables

Epithelial NF-κB maintains host gut microflora homeostasis

NATURE IMMUNOLOGY VOLUME 8 NUMBER 5 MAY 2007

Yinon Ben-Neriah & Marc Schmidt-Supprian

Epithelial NF-κB preserves the integrity of the gut epithelial barrier and coordinates the antimicrobial actions of the innate and adaptive immune systems. Deficiency in or hyperactivation of this transcription factor results in chronic inflammatory bowel disease.



Brief Report: Dysregulated Immune System in Children with Autism: Beneficial Effects of Intravenous Immune Globulin on Autistic Characteristics[1]

J Autism Dev Disord. 1996 Aug;26(4):439-52.

Sudhir Gupta,[2] Sudeepta Aggarwal, and Cathy Heads
Division of Basic and Clinical Immunology, University of California, Irvine

DISCUSSION

In this preliminary study a marked abnormality of immune parameters was observed in children with autism when compared to age-matched controls. This included abnormalities of various lymphocyte subsets and serum levels of various immunoglobulin classes and subclasses. Furthermore, intravenous immunoglobulin treatment resulted in improved autistic features.

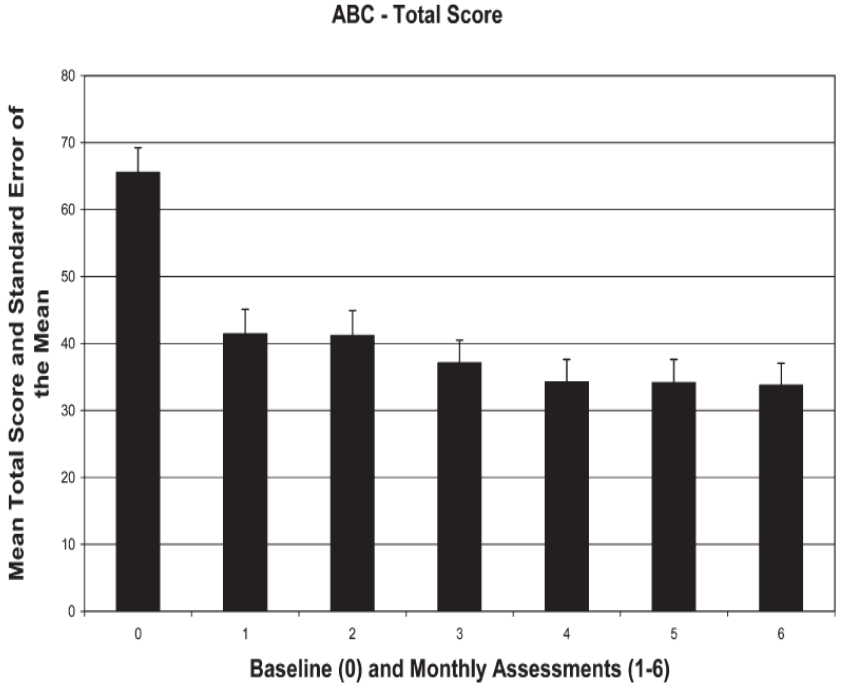
50% responded markedly – verbal communication with Prof. Gupta related an 80% recovery rate if 18 monthly treatments completed (unpublished). Not all studies as favorable --- subgroups??

Improvement in children with autism treated with intravenous gamma globulin

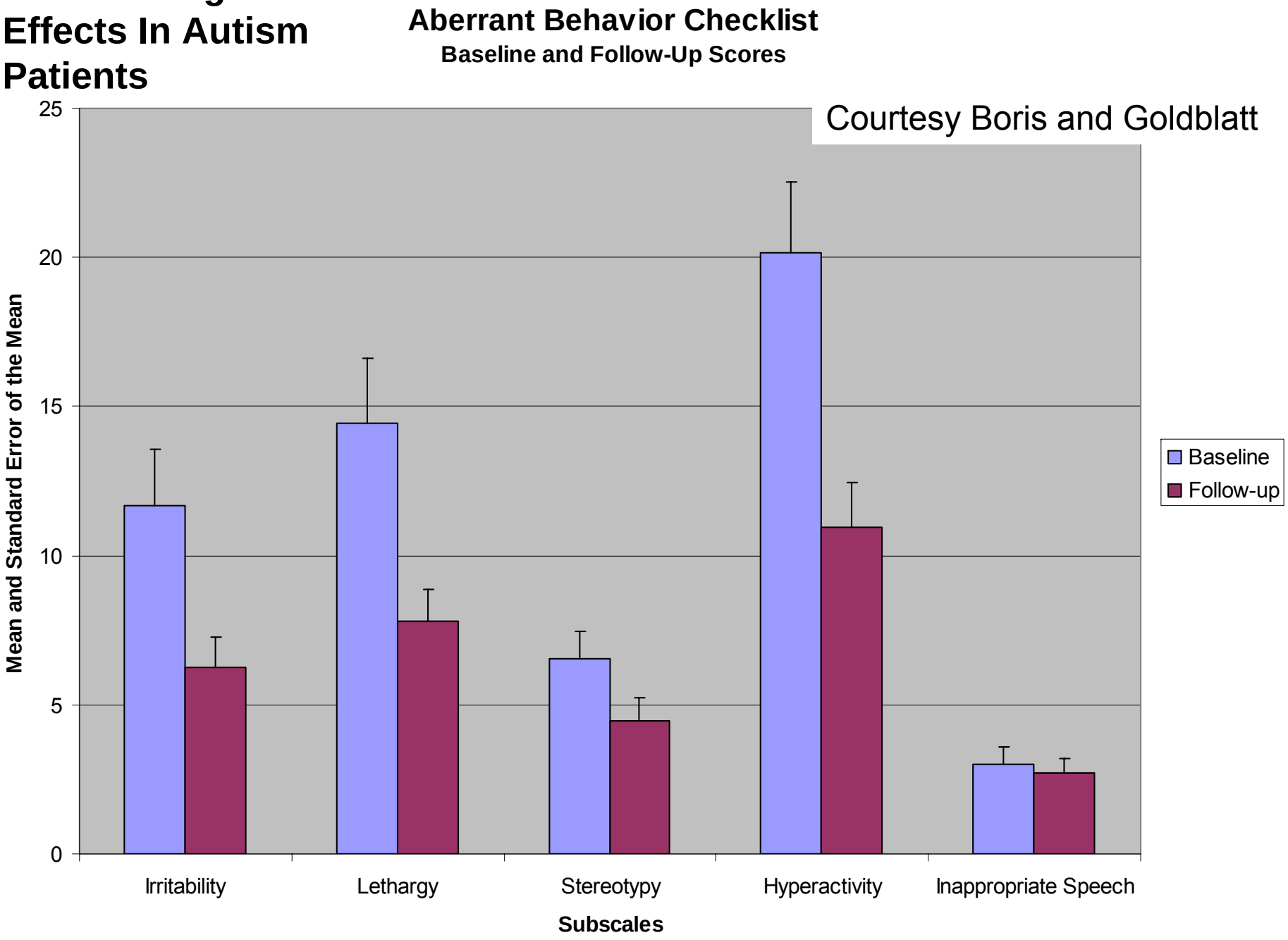
Journal of Nutritional & Environmental Medicine, December 2006; 15(4): 1–8
Taylor & Francis
Taylor & Francis Group

MARVIN BORIS, MD[1], ALLAN GOLDBLATT, PA-C[2] &
STEPHEN M. EDELSON, PHD[3]

[1]*New York University School of Medicine, New York, New York, USA,* [2]*Truro College, New York, New York, USA, and* [3]*Autism Research Institute, 4182 Adams Ave, San Diego, CA 92116, USA*



ACTOS Pioglitazone Effects In Autism Patients



Important Note: No Safety Studies in Children with Actos (**Pioglitazone**)

Medical Hypotheses (2006) x, xxx–xxx

ELSEVIER

medical hypotheses

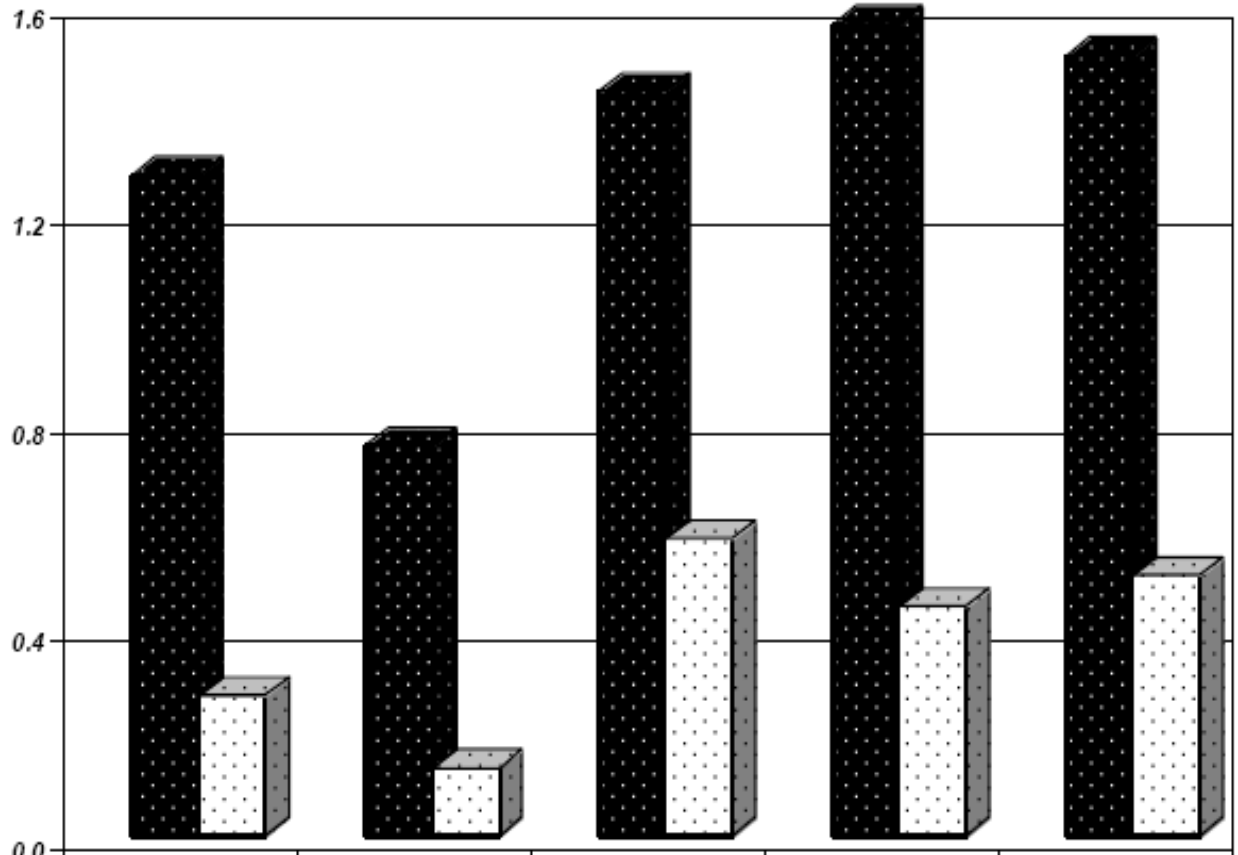
http://intl.elsevierhealth.com/journals/mehy

Spironolactone might be a desirable immunologic and hormonal intervention in autism spectrum disorders

James Jeffrey Bradstreet [a], Scott Smith [a], Doreen Granpeesheh [b], Jane M. El-Dahr [c], Daniel Rossignol [d,*]

Summary Multiple studies now demonstrate that autism is medically characterized, in part, by immune system dysregulation, including evidence of neuroglial activation and gastrointestinal inflammation. This neuroglial process has further been characterized as neuroinflammation. In addition, a subset of autistic children exhibit higher than average levels of androgens. Spironolactone is an aldosterone antagonist and potassium-sparing diuretic with a desirable safety profile. It possesses potent anti-inflammatory and immune modifying properties that might make it an excellent medical intervention for autism spectrum disorders. Furthermore, spironolactone possesses potent anti-androgen properties that might further enhance its appeal in autism, particularly in a definable subset of hyperandrogenic autistic children. One case report is briefly reviewed demonstrating objective clinical improvements in an autistic child after spironolactone administration. Additional research in controlled trials is now needed to further define the risks and benefits of spironolactone use in children with autism.

Figure 1: Changes in the ABC subset scores pre- and post-spironolactone at a dose of 2 mg/kg daily for 4 weeks



	Irritability	Lethargy	Stereotypy	Hyperactivity	Inappropriate Speech
Pre Spironolactone	1.27	0.75	1.43	1.56	1.50
Post Spironolactone	0.27	0.13	0.57	0.44	0.5

Language Gains in the 1st Case

- Pre- and post-administrations of the Peabody Picture Vocabulary Test III by the same psychologist (DG) were scored independently by another psychologist employed by (DG). These demonstrated a receptive language gain of 21 months in this same four week period, indicating an increase in vocabulary greater than one standard deviation at either age level.

Spironolactone: Safety and Tolerability

- Spironolactone is also commonly prescribed as an adjunct in the treatment of precocious puberty.
- In a six year study using spironolactone in 10 boys (ages 2.3 to 5.6 years) with precocious puberty, no serious side-effects were noted despite relatively high doses of spironolactone (average 5.7 mg/kg/day).
- No Change in electrolytes were noted.
- 50% of aggressive boys had significant reduction in negative symptoms.

J Clin Endocrinol Metab. 1999 Jan;84(1):175-8.

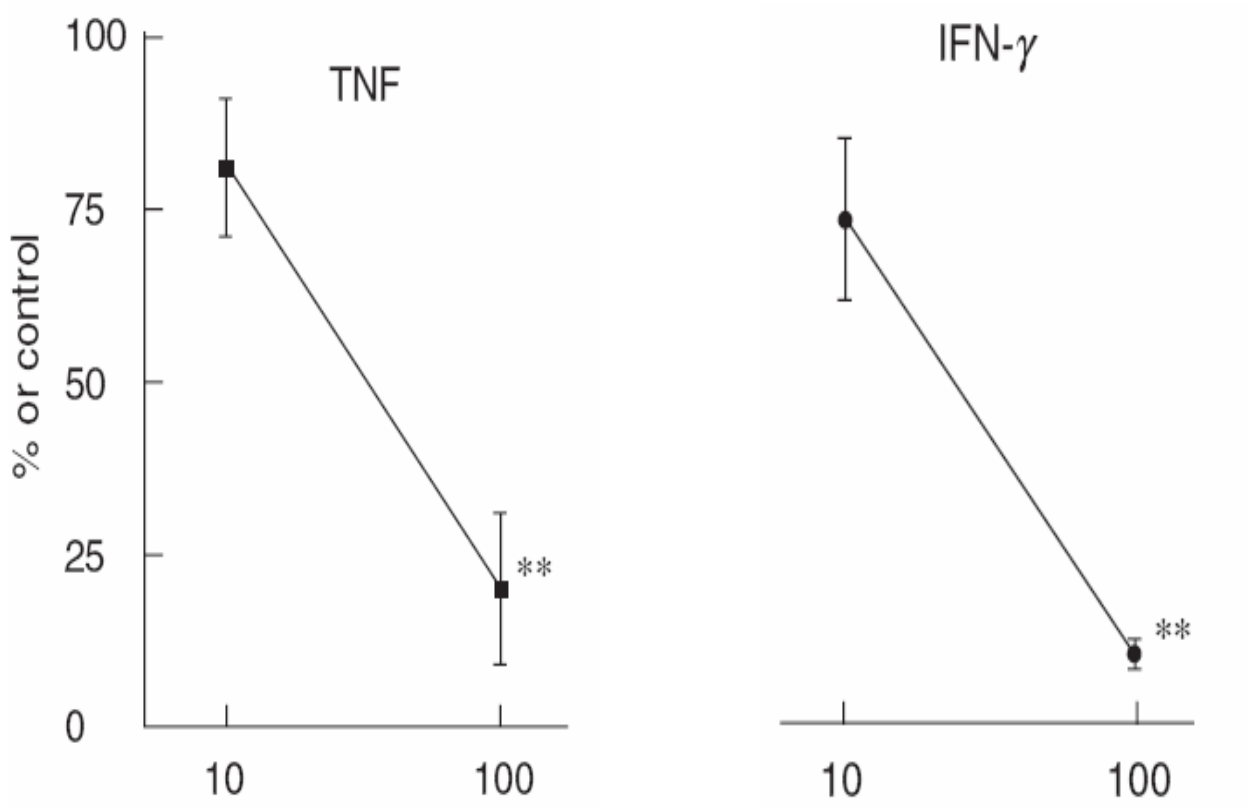
Spironolactone: Lack of Toxicity

- It is considered safe for children when used in typical doses (1-3 mg/kg/day) [Ann Pharmacother. 2005 May;39(5):823-8. Epub 2005 Apr 5.], although the official FDA literature state that a safe range has not been established for children.
- Despite this fact, the oral LD50 of spironolactone is greater than 1,000 mg/kg in mice, rats, and rabbits [Pfizer, Inc.].
- Further, a study in rats, dogs, and monkeys receiving spironolactone daily for up to two years, at doses frequently in excess of 100 times the recommended human dose, demonstrated no evidence to suggest that spironolactone is tumorigenic or carcinogenic [J Environ Pathol Toxicol. 1978 May-Jun;1(5):641-60.]

Spironolactone inhibits production of proinflammatory cytokines, including tumour necrosis factor-α and interferon-γ, and has potential in the treatment of arthritis

Clin Exp Immunol 2003;**134**:151–158

K. BENDTZEN*, P. R. HANSEN†, K. RIENECK* & THE SPIRONOLACTONE/ARTHRITIS STUDY GROUP‡ *Institute for Inflammation Research, Rigshospitalet National University Hospital, Copenhagen, Denmark, and †Department of Cardiology P, Gentofte l, Hellerup, Denmark



Int. Arch. Arbeitsmed. 33, 329—334 (1974)

Protection by Spironolactone and Different Antidotes against Acute Organic Mercury Poisoning of Rats

Kornélia Lehotzky

State Institute of Occupational Health, Department of Applied Toxicology, Budapest
(Head: Prof. M. Timár)

Received June 20, 1974 / Accepted August 22, 1974

Summary. Investigations carried out at our laboratory have shown that BAL (dimercaptopropanol) can be used, with some restrictions, in the treatment of organic mercury poisoning. Depending on the radical of the poison, the antidote has a variable effect although it has no therapeutic use at all in acute intoxication with methoxy-ethyl-mercury-chloride (MEMC). Similarly, neither D-penicillamine, nor sodium-formaldehyde-sulfoxylate proved to be effective antidotes, but treatment with estrogenic hormone could protect the renal failure induced by MEMC. The life-saving effect of spironolactone (the hormonally inactive steroid) was estimated against acute poisoning induced by six different organic mercury compounds on rats. Spironolactone proved to be effective in the case of MEMC when administered prior to poisoning.

International Journal of Pediatric Otorhinolaryngology (2003) 67, 837–840

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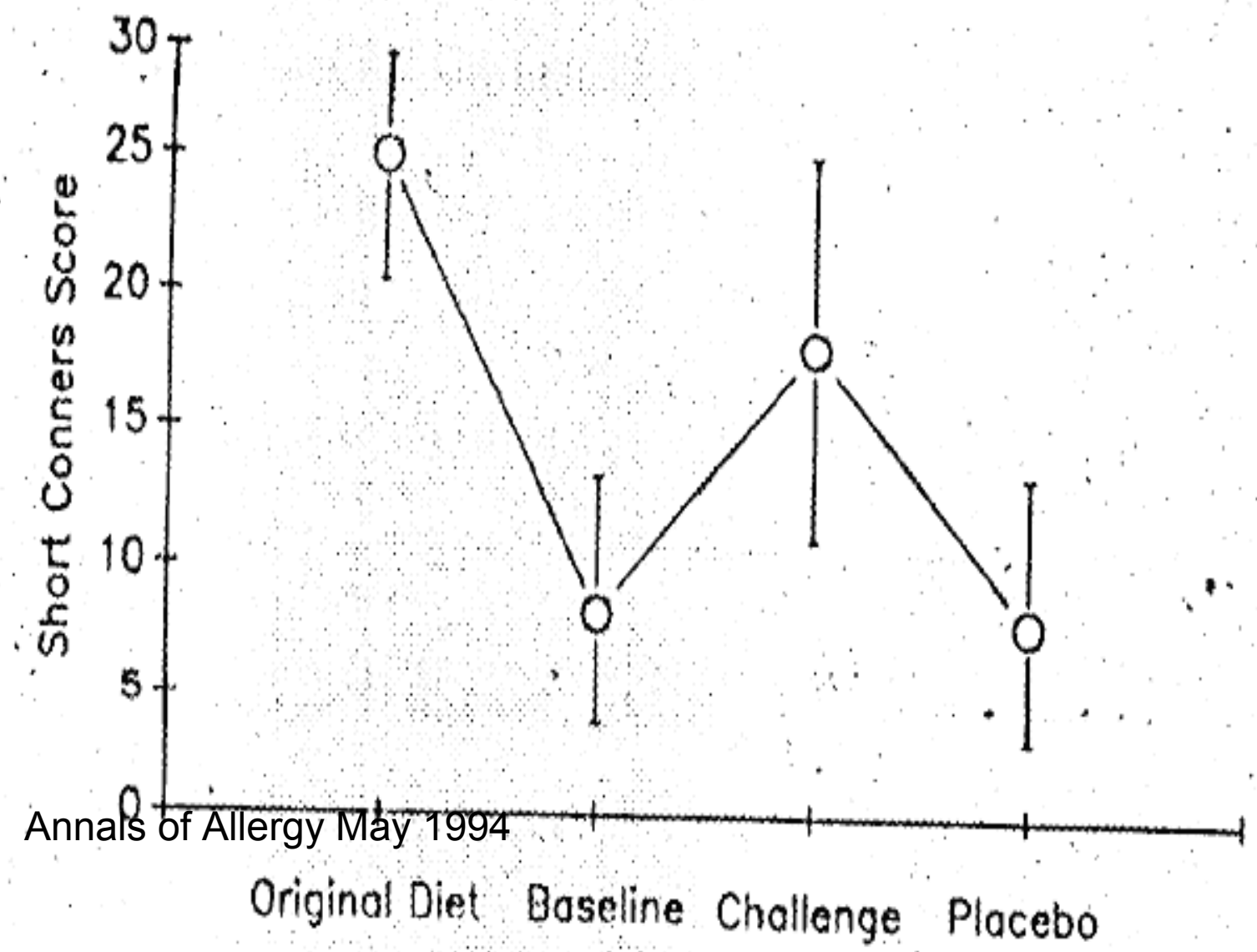
International Journal of Pediatric Otorhinolaryngology

www.elsevier.com/locate/ijporl

PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections—an uncommon, but important indication for tonsillectomy

Christine Heubi, Sally R. Shott*

Department of Pediatric Otolaryngology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229, USA



Annals of Allergy May 1994

Figure 2. Average short Conners' score for all patients.

Journal of Nutritional & Environmental Medicine (March 2004) 14(1), 47–54

Taylor&Francis
healthsciences

CLINICAL RESEARCH

Pollen Exposure as a Cause for the Deterioration of Neurobehavioral Function in Children with Autism and Attention Deficit Hyperactive Disorder: Nasal Pollen Challenge

MARVIN BORIS MD AND ALLAN GOLDBLATT PA

Allergy and Immunology, 77 Froehlich Farm Blvd, Woodbury, New York 11797, USA

Immune Intervention

- Diet: elimination, rotate, decrease artificial, & organic
- CULTURED FOODS PROBIOTICS
- Immune Balance: Complex> IVIG, Medications (IBD Drugs), Singulair, Oral Cromolyn (Gastcrom), Low Dose Naltrexone, Steroids, Actos, Celebrex, Minocin and **Spironolactone**
- PANDAS: IVIG, ATB, Tonsillectomy???
- Combinations: May be very beneficial but are complex.
- **Goal is a BALANCED Immune system, not overly suppressed.**

Heavy metals like mercury and lead must be removed while protecting the required nutrient minerals: Zinc, Selenium, etc

A Case-Control Study of Mercury Burden in Children with Autistic Spectrum Disorders

Jeff Bradstreet, M.D.
David A. Geier, B.A.
Jerold J. Kartzinel, M.D.
James B. Adams, Ph.D.
Mark R. Geier, M.D., Ph.D.

Journal of American Physicians and Surgeons Volume 8 Number 3 Summer 2003

ABSTRACT

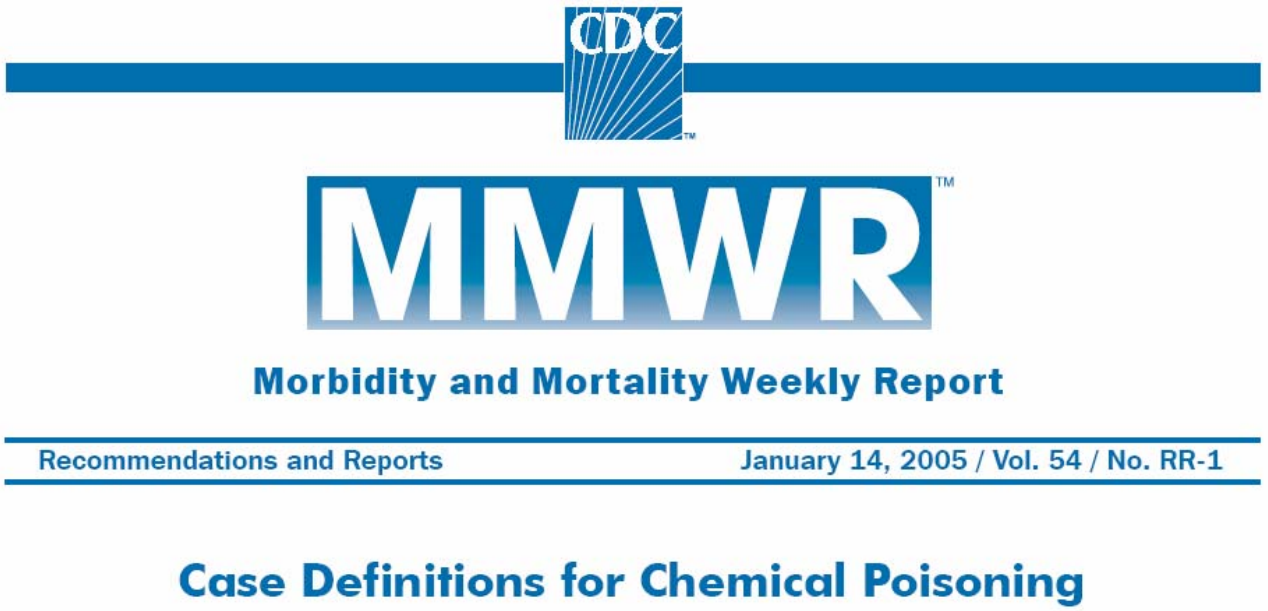
Large autism epidemics have recently been reported in the United States and the United Kingdom. Emerging epidemiologic evidence and biologic plausibility suggest an association between autistic spectrum disorders and mercury exposure.

This study compares mercury excretion after a three-day treatment with an oral chelating agent, meso-2,3-dimercaptosuccinic acid (DMSA), in children with autistic spectrum disorders and a matched control population. Overall, urinary mercury concentrations were significantly higher in 221 children with autistic spectrum disorders than in 18 normal controls (Relative Increase (RI) = 3.15; $P < 0.0002$). Additionally, vaccinated cases showed a significantly higher urinary mercury concentration than did vaccinated controls (RI = 5.94; $P < 0.005$). Similar urinary mercury concentrations were observed among matched vaccinated and unvaccinated controls, and no association was found between urinary cadmium or lead concentrations and autistic spectrum disorders.

The observed urinary concentrations of mercury could plausibly have resulted from thimerosal in childhood vaccines, although other environmental sources and thimerosal in Rh_o(D) immune globulin administered to mothers may be contributory.

Regardless of the mechanism by which children with autistic spectrum disorders have high urinary mercury concentrations, the DMSA treatment described in this study might be useful to diagnose their present burden of mercury.

Population Type	Number of Boys	Number of Girls	Mean Age in Years (Range)	Mean Urinary Mercury (mcg/ g) creatinine (Range)
Cases	183	38	6.25 (3 to 15)	4.06 ± 8.59 (0 to 58.65)
Controls	14	4	8.85 (3 to 16)	1.29 ± 1.54 (0 to 6.2)



- "Confirmed" cases: no epidemiology is required because laboratory testing is considered adequate when present.
- Confirmatory evidence for adults is listed as a blood mercury level > 10 mcg/L

Modeling Vaccine Exposure @ 2 Months –
Presented to the IOM 2004, Bradstreet

- So, in a single compartment partition, a 5 kg child receiving 50mcg of Hg in 2 month vaccines = 10mcg/L if equally distributed in the body.
- Actual first phase partition is at least 1.3 X higher since Hg does not partition to bone very much.
- Infants are 5-10 X more sensitive to Hg (IOM transcript, 2001)

Subclinical effects of prenatal methylmercury exposure on cardiac autonomic function in Japanese children.

Int Arch Occup Environ Health. 2006 May;79(5):379-86. Epub 2005 Dec 20.

Murata K, **Sakamoto M**, **Nakai K**, **Dakeishi M**, **Iwata T**, **Liu XJ**, **Satoh H**

Department of Environmental Health Sciences, Akita University School of Medicine, 010-8543, Akita, Japan, winestem@med.akita-u.ac.jp.

Conclusions: Despite the potential limitations involved in the retrospective study, **these findings suggest that prenatal methylmercury exposure (median of estimated maternal hair mercury at parturition, 2.24 mug/g) may be associated with reduced parasympathetic activity and/or sympathovagal shift**.

Reduced cardiac parasympathetic activity in children with autism.

Brain Dev. 2005 Oct;27(7):509-16
Ming X, et al

Department of Neuroscience, New Jersey Medical School, UMDNJ, Newark, 90 Bergen Street, DOC 8100, NJ 07103, USA. mingxu@umdnj.edu

Many of the clinical symptoms of autism suggest autonomic dysfunction. **results suggest that there is low baseline cardiac parasympathetic activity with evidence of elevated sympathetic tone in children with autism whether or not they have symptoms or signs of autonomic abnormalities.**

Environ Health Perspect. 2005 Oct; 113(10): 1376–1380.

Maternal Fish Consumption, Hair Mercury, and Infant Cognition in a U.S. Cohort

Emily Oken,[1] Robert O. Wright,[2,3] Ken P. Kleinman,[1] David Bellinger,[4,5] Chitra J. Amarasiriwardena,[3] Howard Hu,[3,5] Janet W. Rich-Edwards,[1,6] and Matthew W. Gillman[1,7]

[1]Department of Ambulatory Care and Prevention, Harvard Medical School and Harvard Pilgrim Health Care, Boston, Massachusetts, USA; [2]Department of Pediatrics, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts, USA; [3]Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA; [4]Department of Neurology, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts, USA; [5]Department of Environmental Health, [6]Department of Epidemiology, and [7]Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts, USA

After adjusting for participant characteristics using linear regression, higher fish intake was associated with higher infant cognition. **However, an increase of 1 ppm in mercury was associated with a decrement in VRM score of 7.5** (95% CI, –13.7 to –1.2) points. VRM scores were highest among infants of women who consumed > 2 weekly fish servings but had mercury levels ≤1.2 ppm. **Higher fish consumption in pregnancy was associated with better infant cognition, but higher mercury levels were associated with lower cognition.** Women should continue to eat fish during pregnancy but choose varieties with lower mercury contamination.
(MY TAKE JUST TAKE EFA SUPPLEMENTS!)

EHP Vol 6, 2006: Online 21 June 2006

ehp Environmental Health PERSPECTIVES

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

Gayle C. Windham, Lixia Zhang, Robert Gunier, Lisa A. Croen, Judith K. Grether

Division of Environmental and Occupational Disease Control, California Department of Health Services, Richmond, CA; Impact Assessment Inc, La Jolla, CA; and Kaiser Permanente Medical Care Program Division of Research, Oakland, CA

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.

Results: 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 mercury *(highest odds ratio)*, cadmium, nickel, trichloroethylene, and vinyl chloride.**

Conclusions: **Our results suggest a potential association between autism and estimated metal concentrations**, and possibly solvents, in ambient air around the birth residence, requiring confirmation and more refined exposure assessment in future studies.

ELSEVIER

Health & Place 12 (2006) 203–209

HEALTH & PLACE

www.elsevier.com/locate/healthplace

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

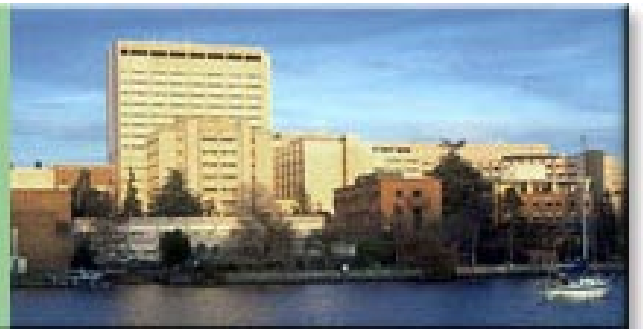
Raymond F. Palmer[a,*], Steven Blanchard[b], Zachary Stein[a], David Mandell[c], Claudia Miller[a]

[a]*University of Texas Health Science Center, San Antonio Department of Family and Community Medicine,*

The association between environmentally released mercury, special education and autism rates in Texas was investigated using data from the Texas Education Department and the United States Environmental Protection Agency. A Poisson regression analysis adjusted for school district population size, economic and demographic factors was used. There was a significant increase in the rates of special education students and autism rates associated with increases in environmentally released mercury. On average, for each 1000 lb of environmentally released mercury, there was a 43% increase in the rate of special education services and a 61% increase in the rate of autism. The association between environmentally released mercury and special education rates were fully mediated by increased autism rates. This ecological study suggests the need for further research regarding the association between environmentally released mercury and developmental disorders such as autism. These results have implications for policy planning and cost analysis.

Department of **Environmental and Occupational Health Sciences**

University of Washington
School of Public Health
and Community Medicine



James S Woods Ph.D.
Research Professor of Environmental and Occupational Health Sciences,
Toxicology Program

Prof Woods is one of the leading innovators in the assessment of mercury toxic effects through the use of porphyrin measurements and genotyping.

A cascade analysis of the interaction of mercury and coproporphyrinogen oxidase (CPOX) polymorphism on the heme biosynthetic pathway and porphyrin production.

Toxicol Lett. 2006 Feb 20;161(2):159-66. Epub 2005 Oct 7.

Heyer NJ, Bittner AC Jr, Echeverria D,Woods JS.

Battelle Centers for Public Health Research and Evaluation, 1100 Dexter Avenue N, Suite 400, Seattle, WA 98109, USA.

After controlling for precursor porphyrin concentrations, we demonstrated that 5-CP and 4-CP are independently associated with Hg concentration, while atypical keto-isocoproporphyrin is associated only with the CPOX4. These findings lend further **support to the proposed utility of urinary porphyrin changes as a biomarker of exposure and potential toxicity in subjects with mercury exposure**. Additionally, these findings demonstrate the successful application of a computational model for characterizing complex metabolic responses and interactions associated with both toxicant exposure and genetic variation in human subjects.

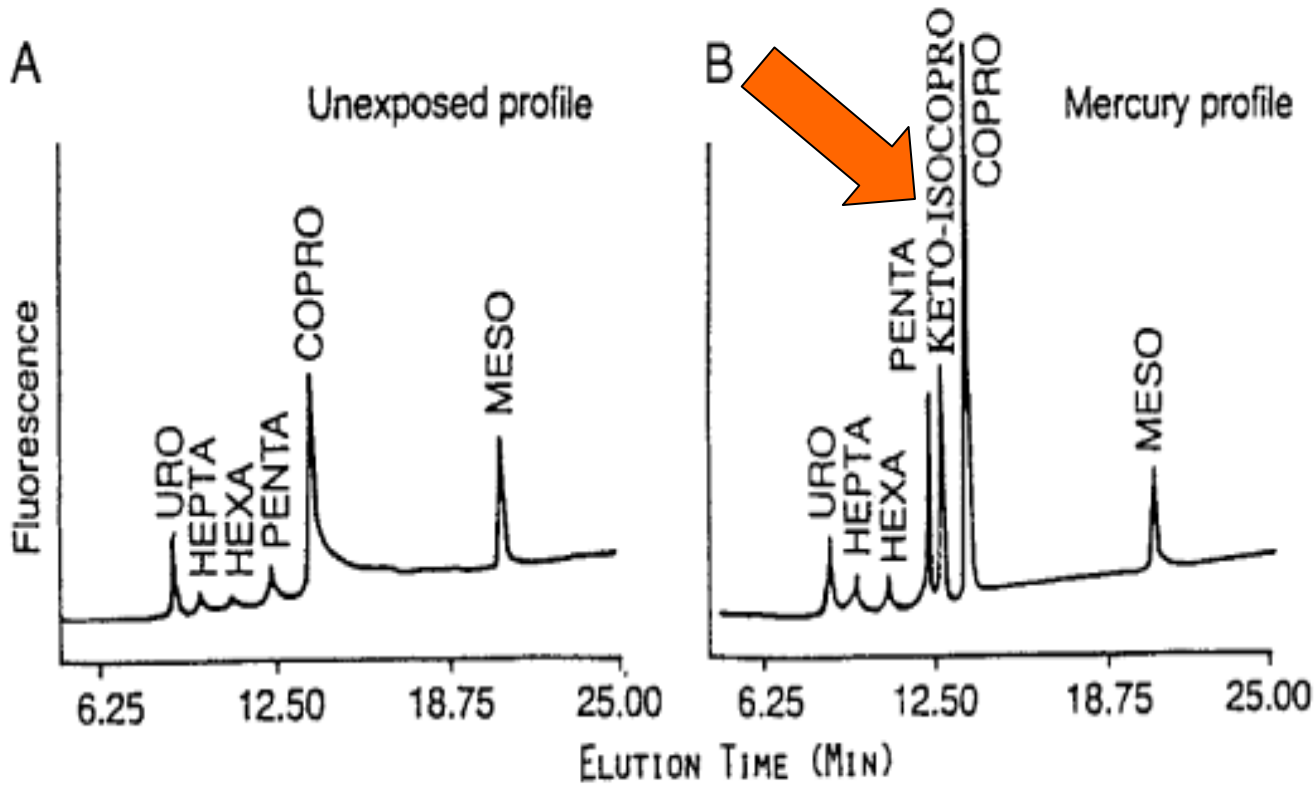


Fig. 1. HPLC urinary porphyrin profiles from: (A) unexposed and (B) mercury-exposed subjects. Abscissa is elution time in minutes. Ordinate is relative porphyrin concentration in fluorescence units. Porphyrins were measured as described in Methods. URO = uroporphyrin, HEPTA = hepta-carboxyporphyrin, HEXA = hexa-carboxylporphyrin, PENTA = pentacarboxylporphyrin, COPRO = coproporphyrin, KETO-ISOCOPRO = ketoisocoproporphyrin, MESO = mesoporphyrin (an internal standard).

THE ATYPICAL KETO-ISOCOCPROPHYRIN = PRECO IN NATAF STUDY

Porphyrinuria in Childhood Autistic Disorder: Implications for Environmental Toxicity

Robert Nataf a, Corinne Skorupkab, Lorene Ametb, Alain Lama, Anthea Springbettc, Richard Lathed
Laboratoire Philippe Auguste, Paris, France

Toxicol Appl Pharmacol. 2006 Jun 15; [Epub ahead of print]

The atypical molecule precoproporphyrin, a specific indicator of heavy metal toxicity, was also elevated in autistic disorder, N=106 ($p<0.001$) but not significantly in Asperger's N=11. A subgroup with autistic disorder was treated with oral dimercaptosuccinic acid (DMSA) N= 11, with a view to heavy metal removal. There was a significant ($p=0.002$) drop in urinary porphyrin excretion following DMSA. These data implicate environmental heavy metal toxicity in childhood autistic disorder.

Interventions for Heavy Metals

Chelation is the #1 biomedical intervention for autism at this time

RULE: Chelators are ALWAYS chelated when in a wet environment.

Chelators Chelate!

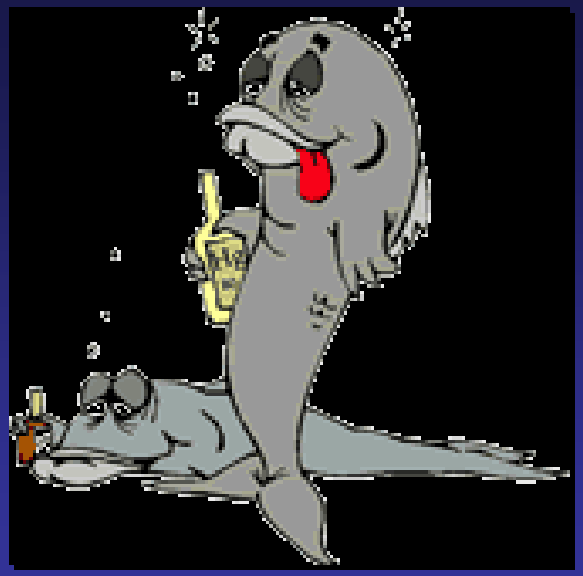
Parents and Clinicians have Reported a 76% Favorable Response Rate to Chelation of Heavy Metals – *ARI Survey*

http://www.autismwebsite.com/ari/treatment/form34q.htm

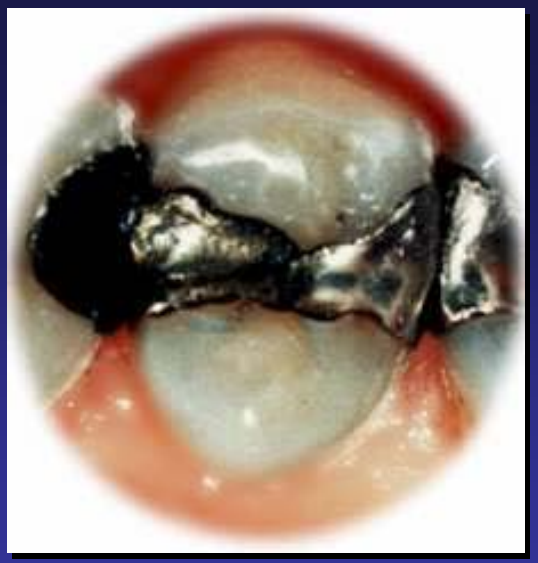
Can the available medical literature support these observations?

&

Why the Mercury Story – Debate – War Won't Be Going Away Anytime Soon Despite the Majority of the Thimerosal – Autism Epidemiology Not Showing a Link



Heavy Metal Detoxification



Requires Expert Medical Supervision, Informed Consent, a Logical Toxicological Exposure History, Appropriate Lab Data, Good Renal Function, Compatible Physical Findings, and Proper Micronutrient Support

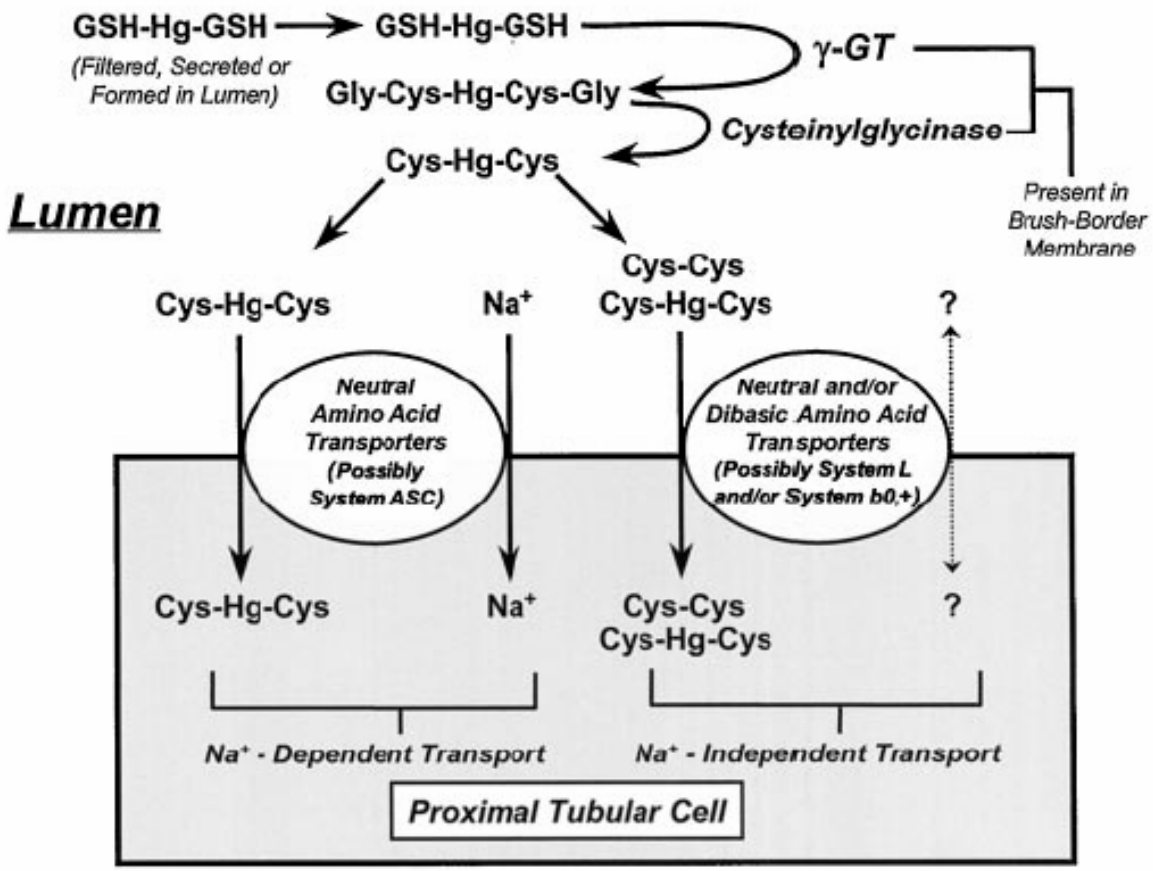
0031-6997/113/5201-0113$03.00/0
PHARMACOLOGICAL REVIEWS
Vol. 52, No. 1
Printed in U.S.A.

Molecular Interactions with Mercury in the Kidney

RUDOLFS K. ZALUPS[1]

Division of Basic Medical Sciences, Mercer University School of Medicine, Macon, Georgia

This paper is available online at http://www.pharmrev.org



Common Chelators in Use: All are off-label uses unless specific toxic criteria met

- **DMSA**: (Succimer) FDA approved for children with lead intoxication. Only 20% absorbed orally. No IV form. Suppositories well tolerated
- **DMPS**: (Dimaval) Not licensed in the US, but available legally via compounding pharmacies. More reactive than DMSA. IV form available. 50% absorbed orally. Suppositories well tolerated and effective. Considered better Hg chelator.
- **CaNa2 EDTA**: (Calcium Disodium Edetate) Licensed for Lead. Poorly absorbed orally. IV or Suppository.
- **D-Penicillamine**: 5-15 mg/kg per day – issues with safety. Check CBC and LFTs frequently – rashes – allergy. INTERESTING: also used in autoimmune disease.

Potential Side-Effects of Heavy Metal Chelators: Generally Well Tolerated Clinical Studies

- Depletion of micronutrients
- Adverse GI issues: colicky pain, gastritis, worsening of dysbiosis
- Allergy
- Rashes
- Behavioral Changes
- Anaphylaxis

Meeting Report

Role of Chelating Agents for Prevention, Intervention, and Treatment of Exposures to Toxic Metals

R.A. Goyer,[1] M.G. Cherian,[2] M.M. Jones,[3] and J.R. Reigart[4]

[1]National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709 USA; [2]University of Western Ontario, London N6A5C1 Canada; [3]Vanderbilt University, Nashville, TN 37235 USA; [4]Medical University of South Carolina, Charleston, SC 29425 USA

Chelation of Lead with D-Penicillamine

Penicillamine has been used to chelate toxic metals including copper (in Wilson's disease) as well as lead, mercury, and arsenic. It has been approved by the FDA for treatment of Wilson's disease, cystinosis, and rheumatoid arthritis but not for lead poisoning, primarily to avoid its misuse in the workplace. Nevertheless, a substantial body of experimental and clinical data exists regarding the pharmacology and utility of penicillamine in both adult and childhood lead poisoning.

*THE ONLY CHELATOR THAT READILY CROSSES THE BLOOD BRAIN BARRIER

Dose 5-15 mg/kg/day oral medication.

Precaution PENICILLIN ALLERGY

The toxicity pattern of D-penicillamine therapy. A guide to its use in rheumatoid arthritis.

Arthritis Rheum. 1980 Feb;23(2):158-64.
Kean WF, et al

One hundred and one patients with rheumatoid arthritis were followed prospectively to assess the efficacy and toxicity of therapy with D-penicillamine. After a mean total followup of 11.5 months (38 patients have completed 2 years of followup) there was a **70% overall improvement rate with 2 complete remissions.** Sixty-one patients developed 84 separate toxic reactions, 36 of which required drug withdrawal. **Skin rashes (27/84), proteinuria (15/84), low platelets (14/84), and taste abnormalities (10/84)** were the most common side effects of therapy at a mean D-penicillamine dose of 463 mg/day. The majority of toxic reactions (85%) occurred in the first 6 months, but proteinuria and thrombocytopenia were more common in the 6 to 12 month treatment period. **Previous gold toxicity was a risk factor for developing D-penicillamine toxicity (10/13).** Our observations suggest that D-penicillamine related toxicity is a major problem even at 500 mg/day, but the drug can be used with an increased safety margin after 9 months of continuous therapy.

D-Penicillamine

- Sulfur Amino Acid Side-Chain of Penicillin
- Similar to Cysteine
- Minor risk of allergy if PEN Allergy
- 5-15 mg per kg per day max dose.
- Must be aware of copper losses during chelation and monitor
- Supplement copper at 2 x RDA on D-Pen days
- Supplement Zinc

IV Chelation Details: CaNa2EDTA

- CaDisodium EDTA: our does is lower than many but our side-effects are also minimal. We limit it to 10mg/kg per dose but can dose up to 3 x weekly in serious cases. Some Docs use up to 50mg/kg.
- Preload with 2000 to 4000 mg of Vit C and usually 600 -1200 mg of reduced GSH.
- Be ready for rare but serious anaphylatoid reactions.

DMPS and “Bella”

- The literature finds little serious side-effects at dose under 3mg/kg per day.
- We limit out dose to 2mg/kg per dose.
- Usual follows IV Vit C and GSH.
- Special: we have observed both excellent chelation and often remarkable clinical response to what we call the “Bella” protocol = Vit C w/GSH > CaEDTA > DMPS

DMSA

- Typically given via oral administration.
- Check G6PD levels 1st > risk of Hemolytic Anemia
- Poor PO absorption ~ 20%
- Significant GI side-effects and dysbiosis issues
- Suppository administration may obviate the GI issues to a large extent.
- Dose up to 30mg/kg per suppository Q 3 days or 10mg/kg PO TID for up to 15 days then need a break.

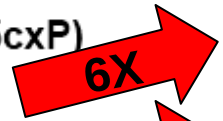
Suppository DMPS & CaEDTA

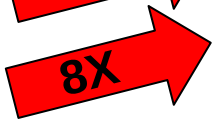
- Relatively well absorbed for DMPS ~ 50% PO and we see good effects Supp
- CaEDTA ~ 2% oral absorption (not effective) better – seemingly when given via supp
- Same rules apply to replacement of nutritional minerals: Mg, Zn, Cu, Se, are the most significantly affected by chelation.

Urinary porphyrins

HPLC-UV+Fluorescence

		(nmol)		*reference* nanomoles/gr Cr urinary	%	*Interpretation*
Uroporphyrins I &III (UP)		**15**	nmol	7-14	*1*	Slighltly increased rate
Heptacarboxy porphyrin (7cxP)		**5,1**	nmol	1,5-3,5	*0,5*	Slighltly increased rate
Hexacarboxy porphyrin (6cxP)		**0,6**	nmol	0,4-0,8	*0,0*	Average Rate
Pre 5-Carboxy-P		**1,1**	nmol			
Pentacarboxy porphyrin (5cxP)		**12,8**	nmol	1,0-2,9	*1,3*	Increased rate
Precoporphyrin (prCP)		**32,6**	nmol	2-5		Increased rate
Coproporphyrins I & III (cP)		**858**	nmol	50-80	*95*	Increased rate
prCP/UP	PrecoP/Uro ratio	**2,05**		0,3-0,6		
UP / CP	uro/copro ratio	**0,01**		0,14-0,1		





Interpretation

strongly Increased pentacarboxy, precopro and coproporphyrin
Urinary Porphyrin Profile suggestive a remarkable toxic effect on bodily physiology

URINE TOXIC METALS

DOCTOR'S DATA INC

LAB#: U051103-0454-1
PATIENT:
SEX: Male
AGE: 6

CLIENT#: 24503
DOCTOR: James Jeff Bradstreet, MD
International Autism Research
1688 W Hibiscus Blvd
Melbourne, FL 32901

POTENTIALLY TOXIC METALS

METALS	RESULT µg/g CREAT	REFERENCE RANGE	WITHIN REFERENCE RANGE / ELEVATED / VERY ELEVATED
Aluminum	< dl	< 60	
Antimony	1	< 1.5	
Arsenic	67	< 130	
Beryllium	< dl	< 0.6	
Bismuth	< dl	< 20	
Cadmium	0.6	< 2	
Lead	28	< 5	
Mercury	40	< 5	
Nickel	16	< 15	
Platinum	< dl	< 1	
Thallium	1	< 1.1	
Thorium	< dl	< 0.5	
Tin	20	< 15	
Tungsten	0.8	< 1.5	
Uranium	< dl	< 0.2	

CREATININE

	RESULT mg/dL	REFERENCE RANGE	2SD LOW 1SD LOW MEAN 1SD HIGH 2SD HIGH
Creatinine	21	25- 180	

SPECIMEN DATA

Comments:
Date Collected: 11/1/2005
Date Received: 11/3/2005
Date Completed: 11/7/2005

Method: ICP-MS
<dl: less than detection limit
Provoking Agent: IV DMPS

Collection Period: timed: 6 hours
Volume:
Provocation: POST PROVOCATIVE

Special Interventions

Nasal Oxytocin and Secretin

Intriguing Neuropeptides with low risk of side-effects if used in moderation

The Cerebellum. 2006; 5: 2–6

Taylor & Francis
Taylor & Francis Group

EDITORIAL

Secretin's role in the cerebellum: A larger biological context and implications for developmental disorders

MARTHA G. WELCH[1], ROBERT J. LUDWIG[1], MARK OPLER[3] & DAVID A. RUGGIERO[1,2]

Departments of [1]Psychiatry and [2]Anatomy, College of Physicians & Surgeons, Columbia University, and [3]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, USA

"It is more reasonable to suspect that long-range effects on stress adaptation response patterns will require continuous or serial administration of peptide combinations *(oxytocin and secretin)* over many days, in a way that more closely replicates maternal nurture mechanisms that naturally stimulate the synthesis and release of stress regulatory peptides".

Neuropsychopharmacology (2003) 28, 193–198

www.neuropsychopharmacology.org

Oxytocin Infusion Reduces Repetitive Behaviors in Adults with Autistic and Asperger's Disorders

Eric Hollander*[,1], Sherie Novotny[1], Margaret Hanratty[1], Rona Yaffe[1], Concetta M DeCaria[1], Bonnie R Aronowitz[1] and Serge Mosovich[1]

[1]*Department of Psychiatry, Seaver Autism Research Center, Mount Sinai School of Medicine, New York, USA*

Autism is a neurodevelopmental disorder characterized by dysfunction in three core behavioral domains: repetitive behaviors, social deficits, and language abnormalities. There is evidence that abnormalities exist in peptide systems, particularly the oxytocin system, in autism spectrum patients. Furthermore, oxytocin and the closely related peptide vasopressin are known to play a role in social and repetitive behaviors. This study examined the impact of oxytocin on repetitive behaviors in 15 adults with autism or Asperger's disorder via randomized double-blind oxytocin and placebo challenges. The primary outcome measure was an instrument rating six repetitive behaviors: need to know, repeating, ordering, need to tell/ask, self-injury, and touching. Patients with autism spectrum disorders showed a significant reduction in repetitive behaviors following oxytocin infusion in comparison to placebo infusion. Repetitive behavior in autism spectrum disorders may be related to abnormalities in the oxytocin system, and may be partially ameliorated by synthetic oxytocin infusion.

Neuropsychopharmacology (2003) **28,** 193–198. doi:10.1038/sj.npp.1300021

Keywords: autism; Asperger's disorder; oxytocin; peptide; obsessive–compulsive behaviors

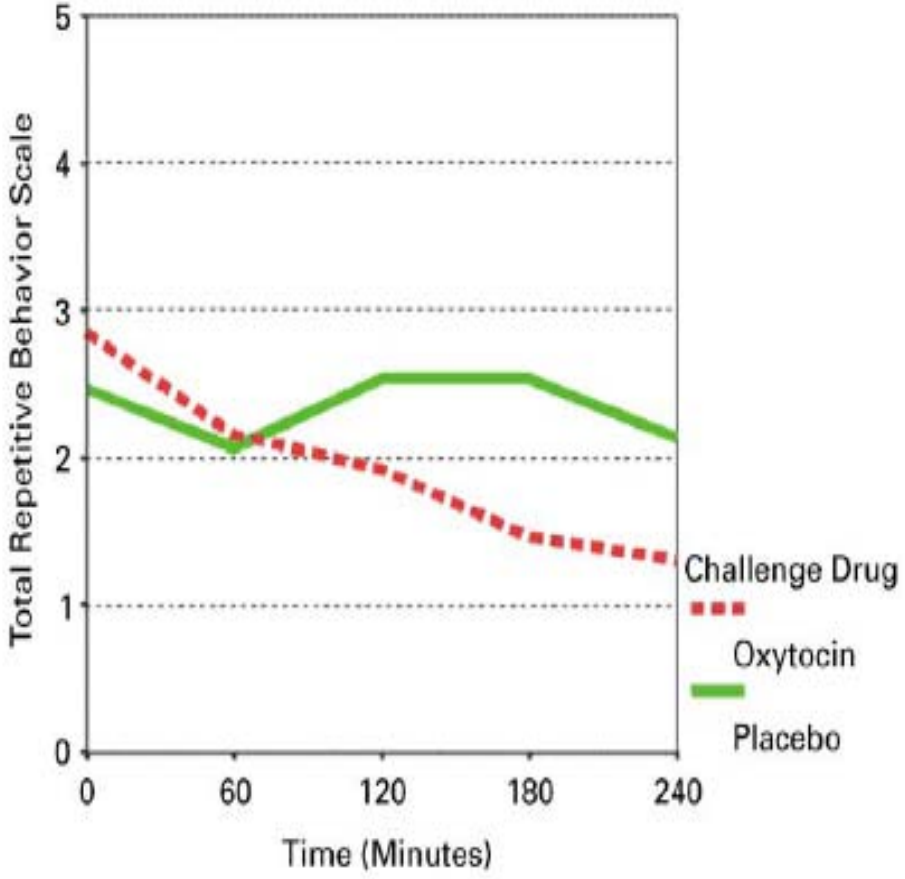


Figure 1 Effects of oxytocin vs placebo infusion on repetitive behaviors in autism spectrum disorder patients over time. Mean scores were significantly lower over time following oxytocin vs placebo ($F = 3.487$, $df = 4, 52$, $p = 0.027$).

Neuropsychopharmacology

"The initial vial of pitocin (10 u/ml) combined aseptically with a I.0 I bag of normal saline was first given at a rate of 10 ml/h. The infusion was initiated at a low rate to minimize potential side effects, and the rate gradually titrated up. Specifically, the infusion rate was titrated every 15 min by 25 ml in the first hour, 50 ml in the second hour, 100 ml in the third hour, and held constant at the maximum rate of 700 ml/h during the fourth hour."

Brief Communication

Oxytocin Modulates Neural Circuitry for Social Cognition and Fear in Humans

The Journal of Neuroscience, December 7, 2005 • 25(49):11489–11493 • **11489**

Venkata S. Mattay,[2,4] Bernd Gallhofer,[1] and Andreas Meyer-Lindenberg[2,3,4]

[1]Cognitive Neuroscience Group, Center for Psychiatry and Psychotherapy, Justus-Liebig University, D-35385 Giessen, Germany, and [2]Neuroimaging Core Facility, [3]Unit for Systems Neuroscience in Psychiatry, and [4]Clinical Brain Disorders Branch, Genes, Cognition, and Psychosis Program, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20892

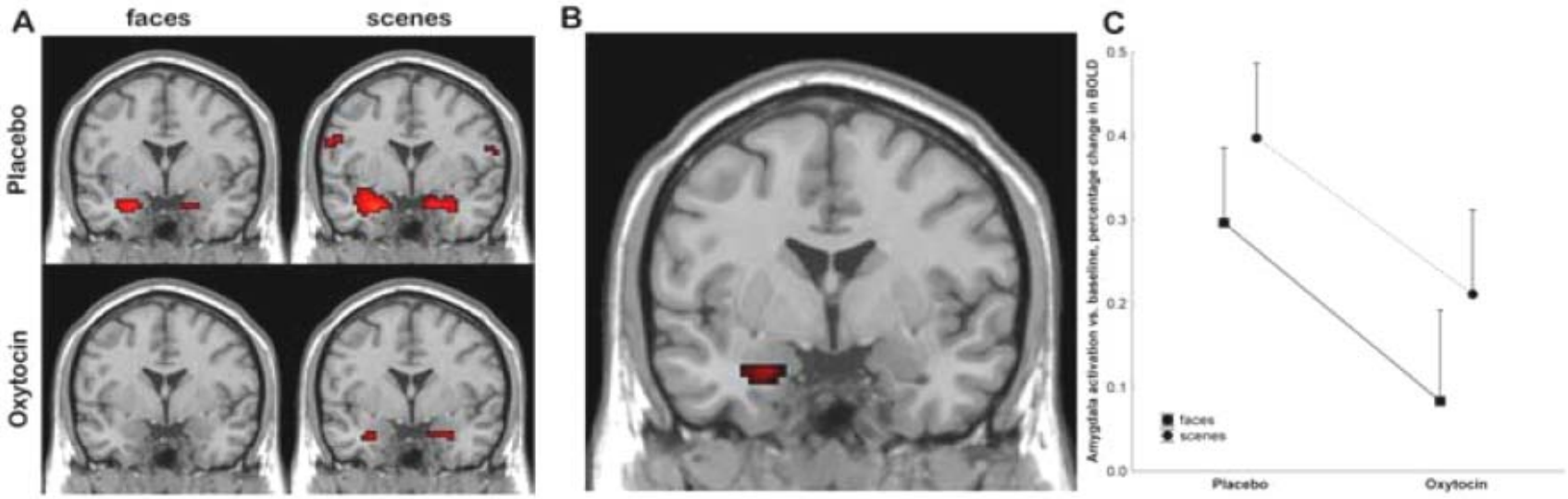


Figure 1. Oxytocin effects on amygdala activation. ***A***, Rendering on normal coronal MRI at the level of the anterior commissure (in neurological orientation: the brain left is on the viewer's left). The response to face stimuli is on the left, and the response to scene stimuli is on the right. Top, Placebo; bottom, oxytocin. See Table 2 for statistical information. ***B***, Significantly higher activation under placebo than oxytocin (main effect of drug condition). See Table 2 for statistical information. ***C***, Plot of BOLD in the amygdala ROI (ANOVA; significant main effect of drug condition: $F_{(1,56)} = 4.2$, $p = 0.045$; main effect of task and drug-by-task interaction were not significant).

ELSEVIER

Brain & Development 28 (2006) 99–103

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Administration of secretin for autism alters dopamine metabolism in the central nervous system

Yoshihiro Toda[a,*], Kenji Mori[a], Toshiaki Hashimoto[b], Masahito Miyazaki[a], Satoshi Nozaki[c], Yasuyoshi Watanabe[c], Yasuhiro Kuroda[a], Shoji Kagami[a]

[a]*Department of Pediatrics, School of Medicine, University of Tokushima, 3-18-15, Kuramoto-cho, Tokushima-shi, Tokushima 770-8503, Japan*
[b]*Department of Education for the Disabled, Naruto University of Education, 748 Nakajima, Takashima, Naruto-cho, Naruto-shi, Tokushima 772-8502, Japan*
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Received 20 October 2004; received in revised form 25 May 2005; accepted 25 May 2005

Hyperbaric oxygen therapy may improve symptoms in autistic children

Med Hypotheses. 2006;67(2):216-28. Epub 2006 Mar 22.

Daniel A. Rossignol [a,b,*], Lanier W. Rossignol

[a] *Blue Ridge Medical Center, 4038 Thomas Nelson Highway, Arrington, VA 22922, USA*
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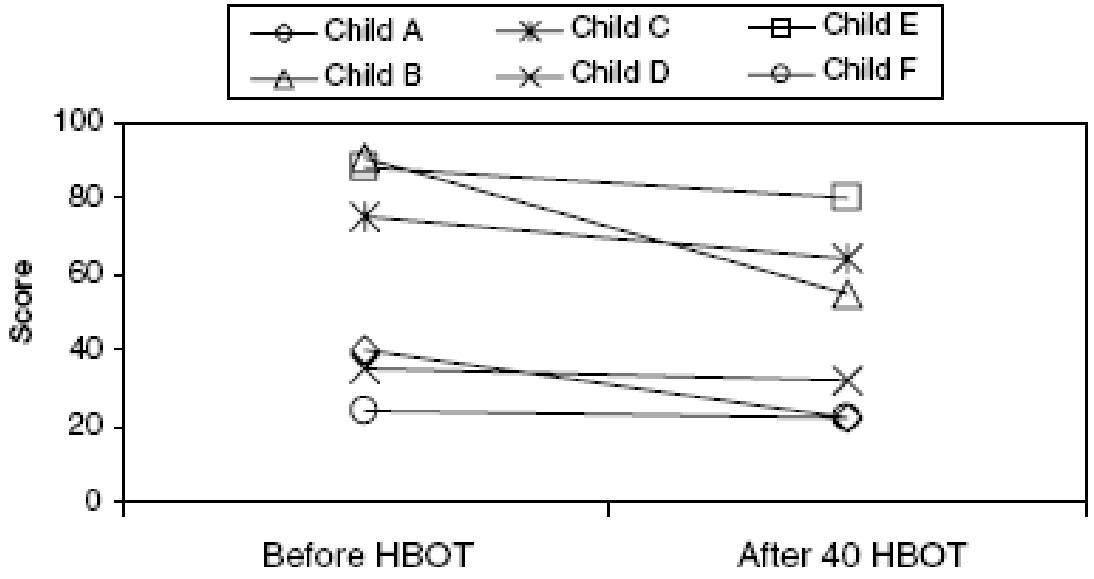
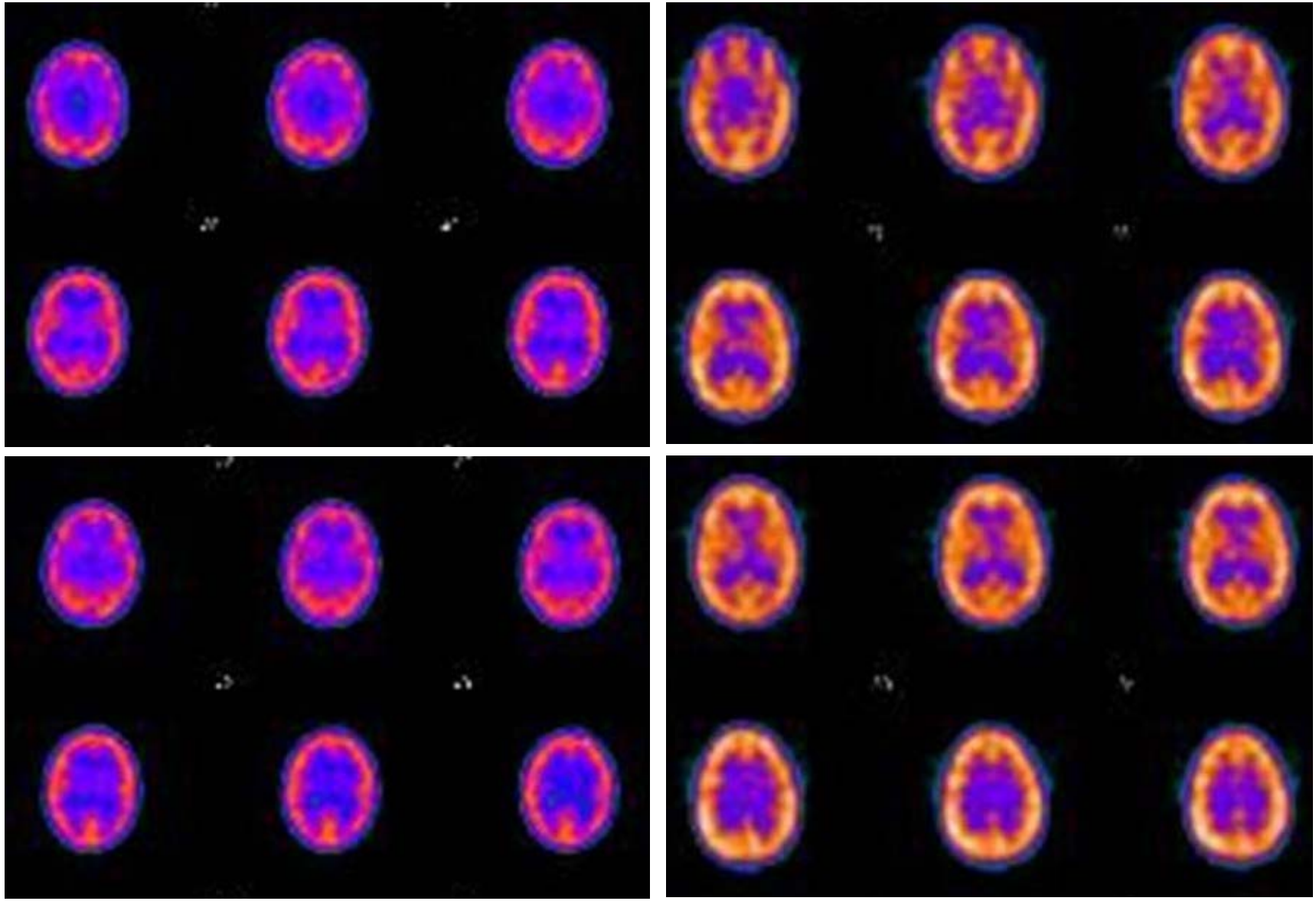


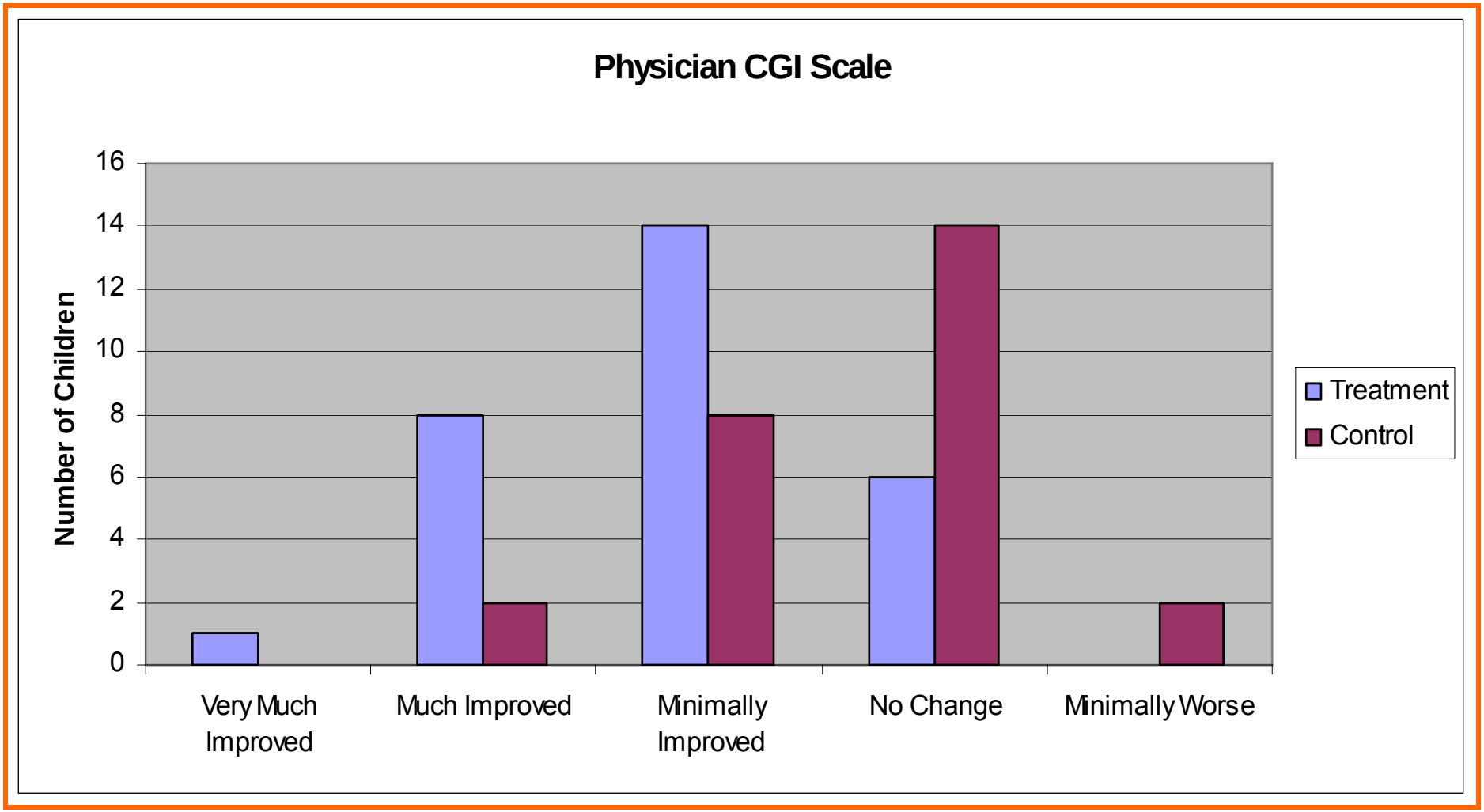
Figure 1 ATEC scores for all children.

HBOT Study #1

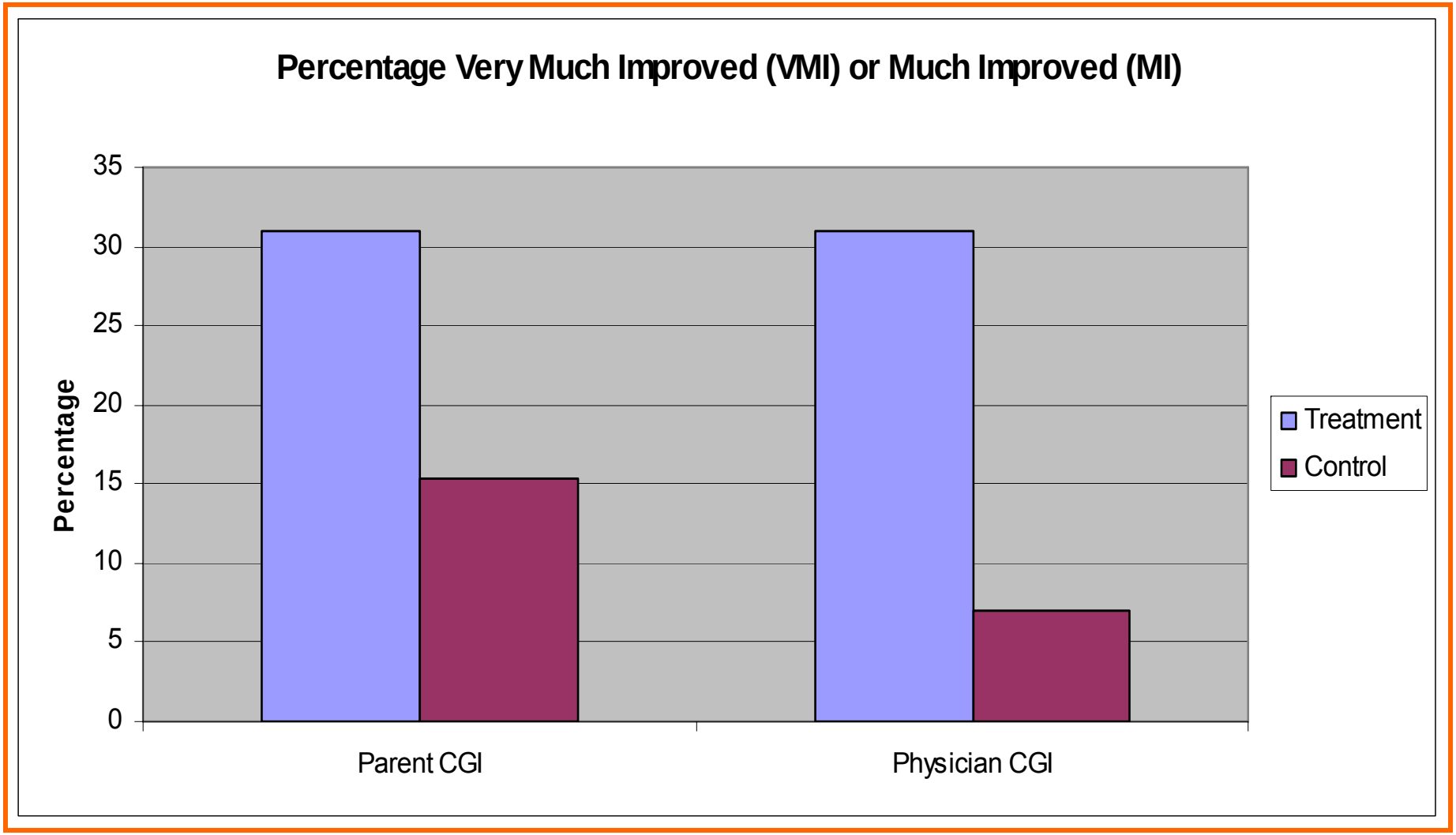
- 6 Centers
- Randomized prospective double-blind controlled study
- Blinded therapists, physicians, and parents evaluated children with several checklists

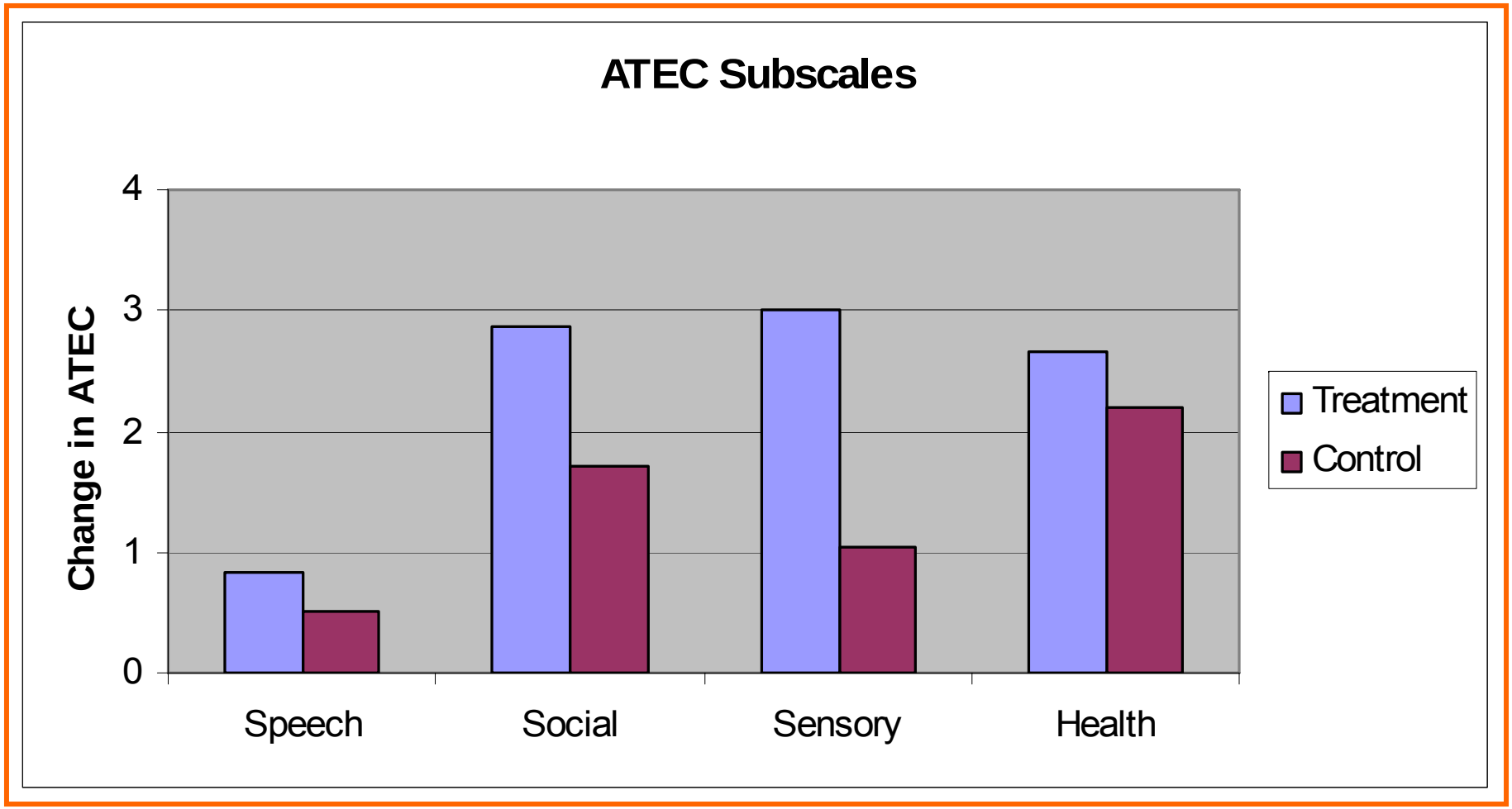
HBOT 1.3 ATA, 24% Oxygen: 4 year old child




Physician CGI Scale
Number of Children
16
14
12
10
8
6
4
2
0
Very Much Improved
Much Improved
Minimally Improved
No Change
Minimally Worse
Treatment
Control

$$p = 0.0007$$


Percentage Very Much Improved (VMI) or Much Improved (MI)
Percentage
35
30
25
20
15
10
5
0
Parent CGI
Physician CGI
Treatment
Control


ATEC Subscales
Change in ATEC
4
3
2
1
0
Speech
Social
Sensory
Health
Treatment
Control

HBOT Study #2

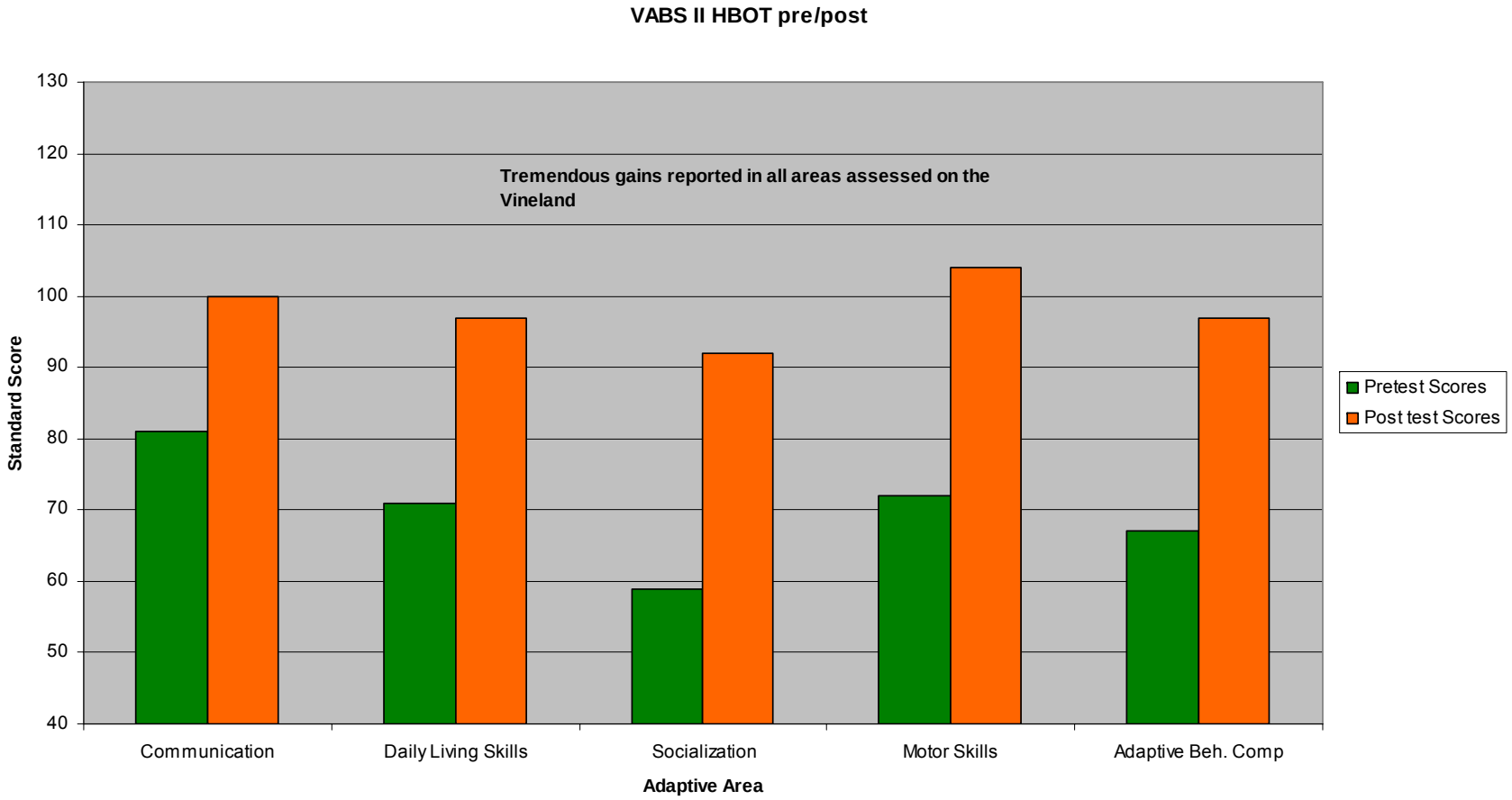
CARD and ICDRC

Numerous Outcome Measures,
True Blinded Controlled Study

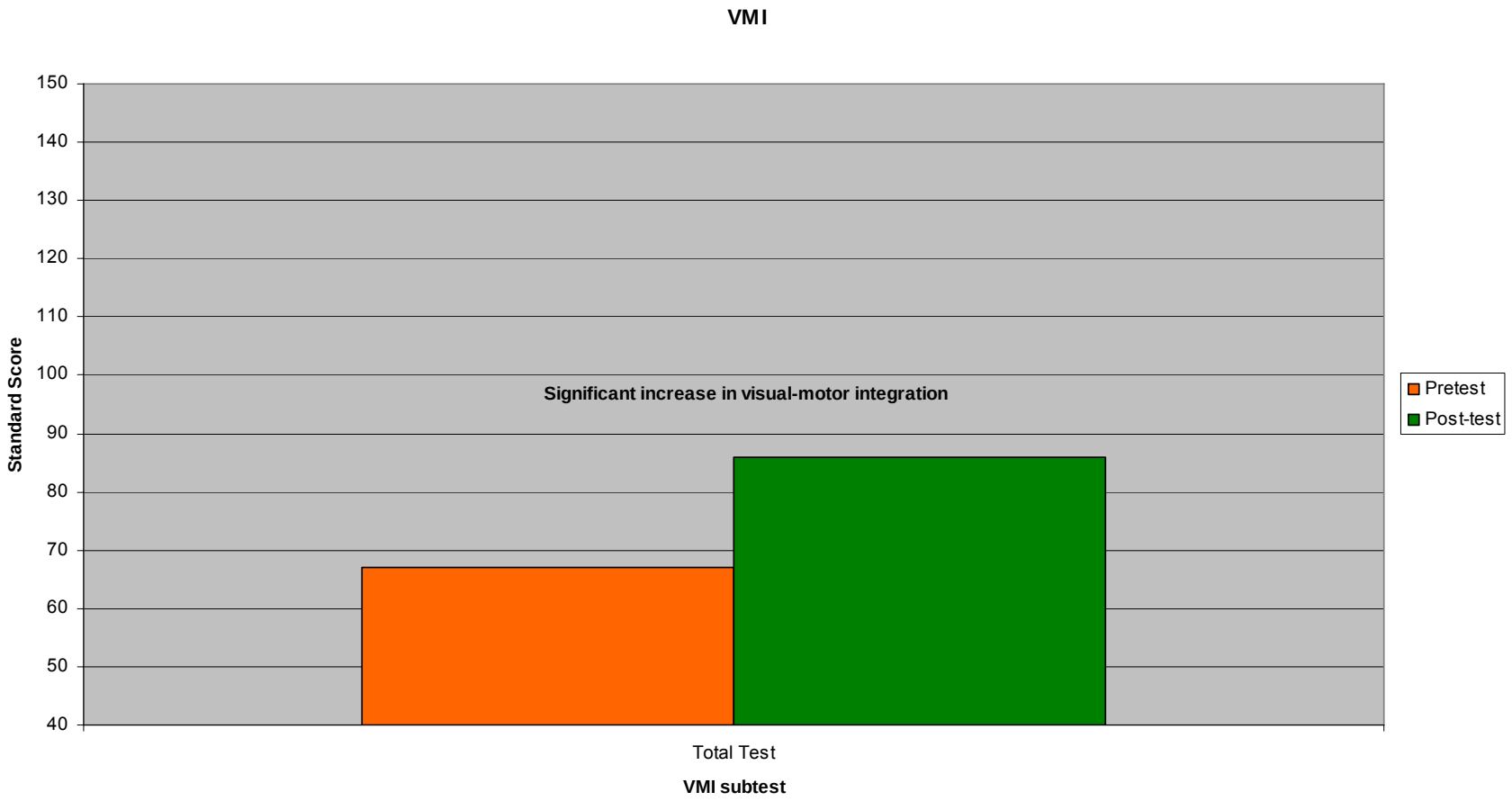
HBOT
Case Presentation

- 3-year-old male
- Completed 80 cycles (dives) in 14 weeks
- Mother reported significant gains language, social skills, and daily living skills.
- Examiner also noted a significant increase in verbalizations (**from single words to multi-clause sentences**)
- Ritualistic behaviors remained but were better at conclusion of the study.

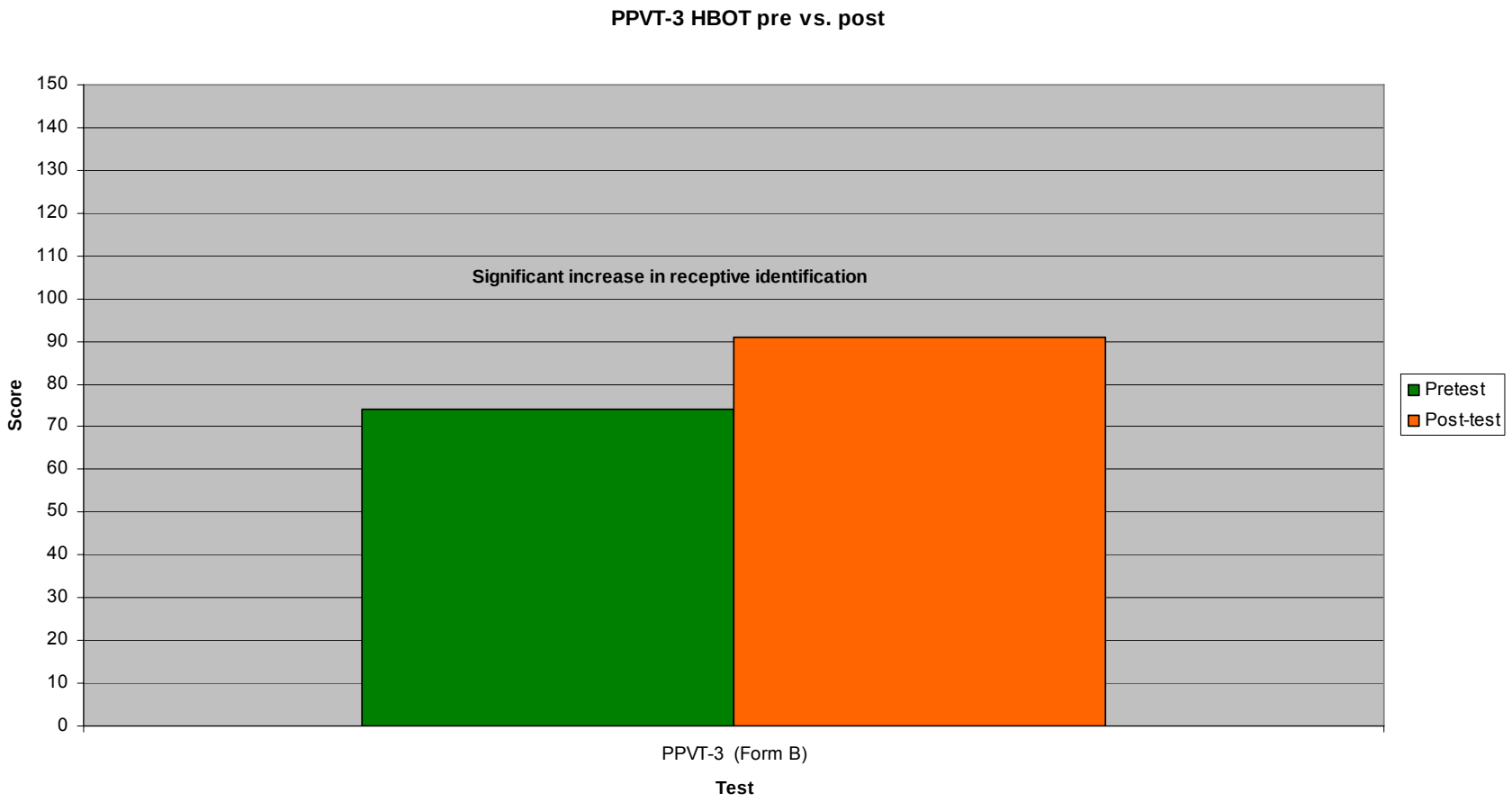
Vineland 2
Higher is better



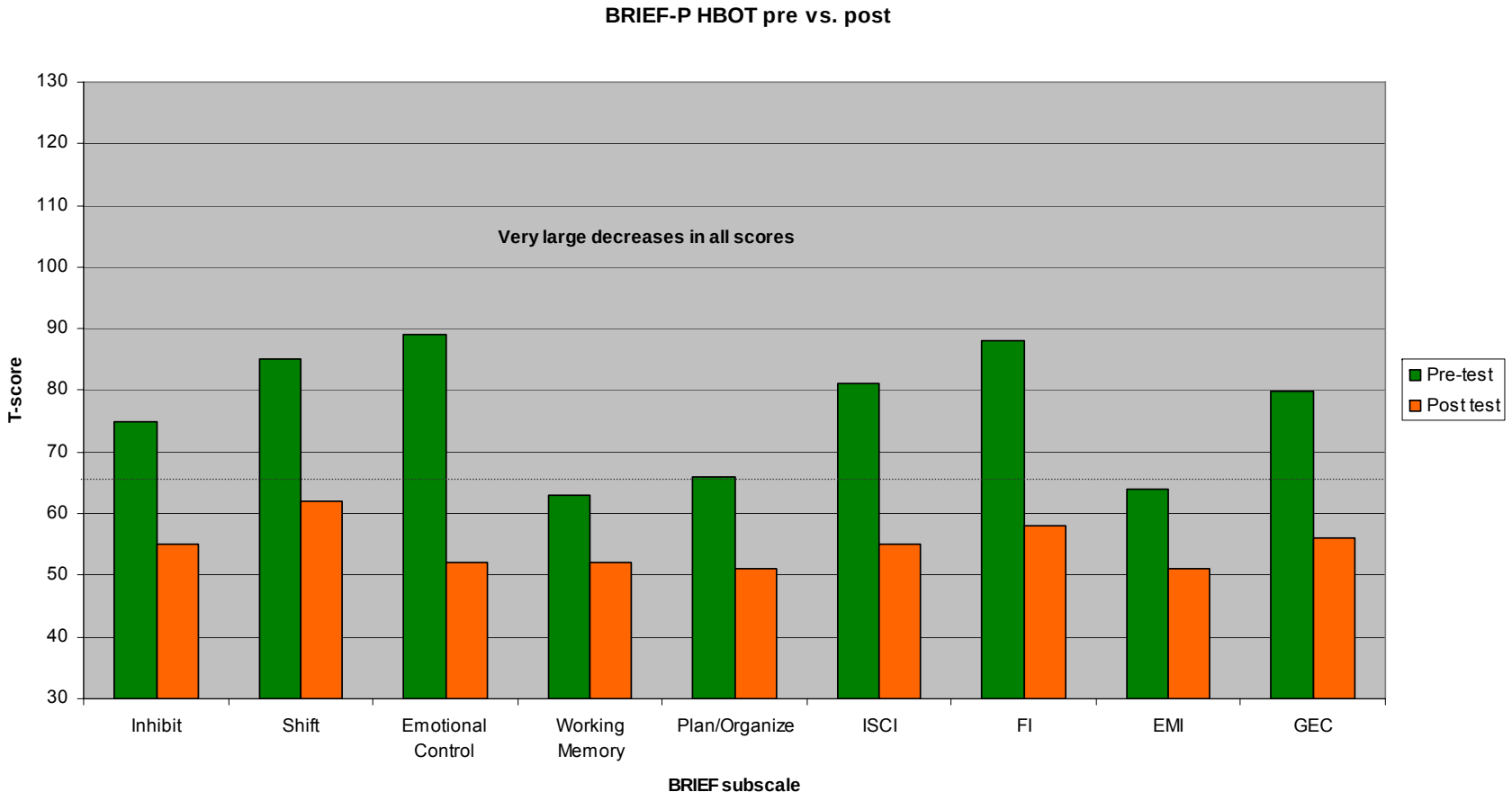
Visual Motor Integration
Higher is better



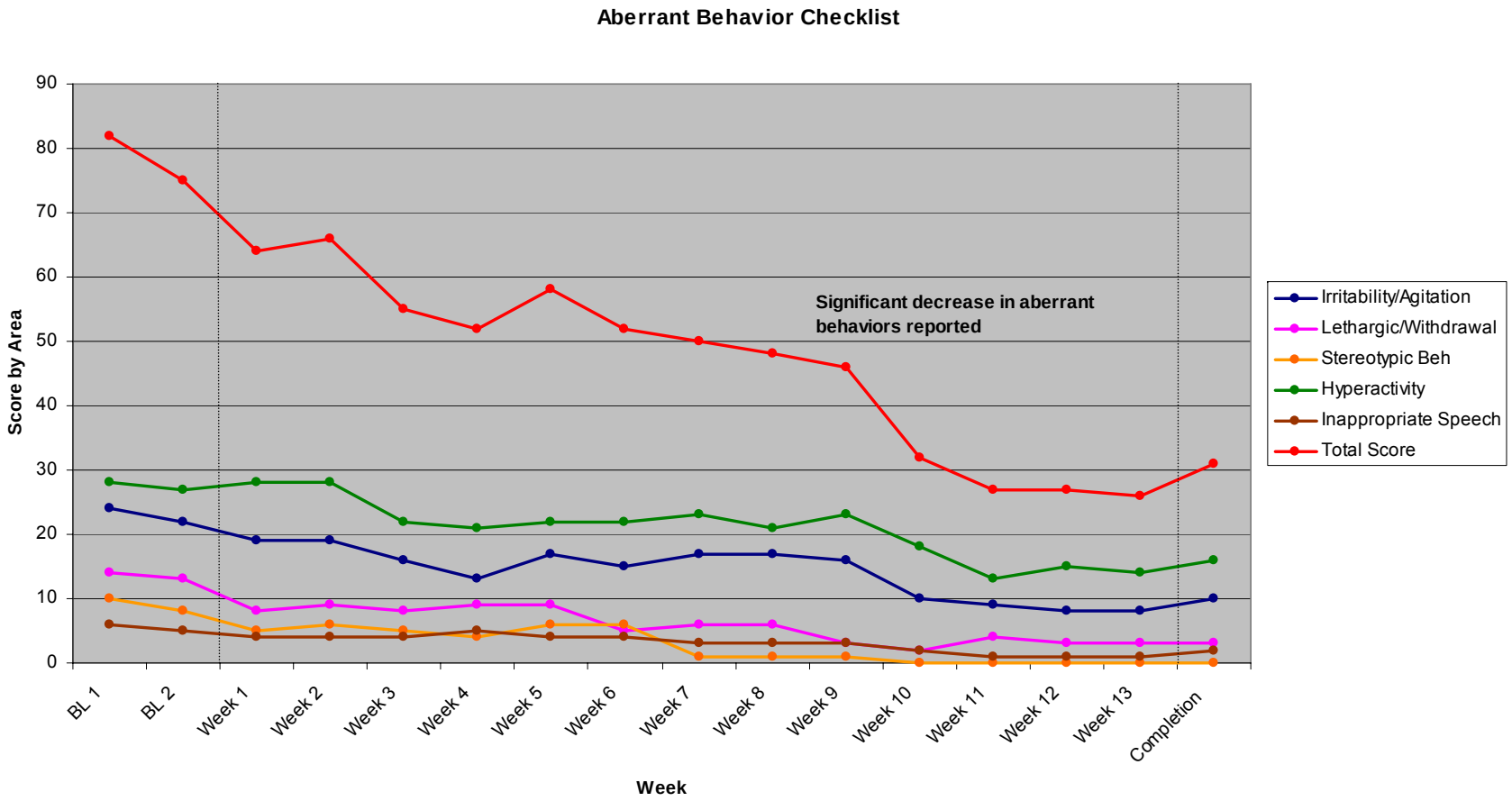
Peabody Picture Vocab T-3
Higher is better



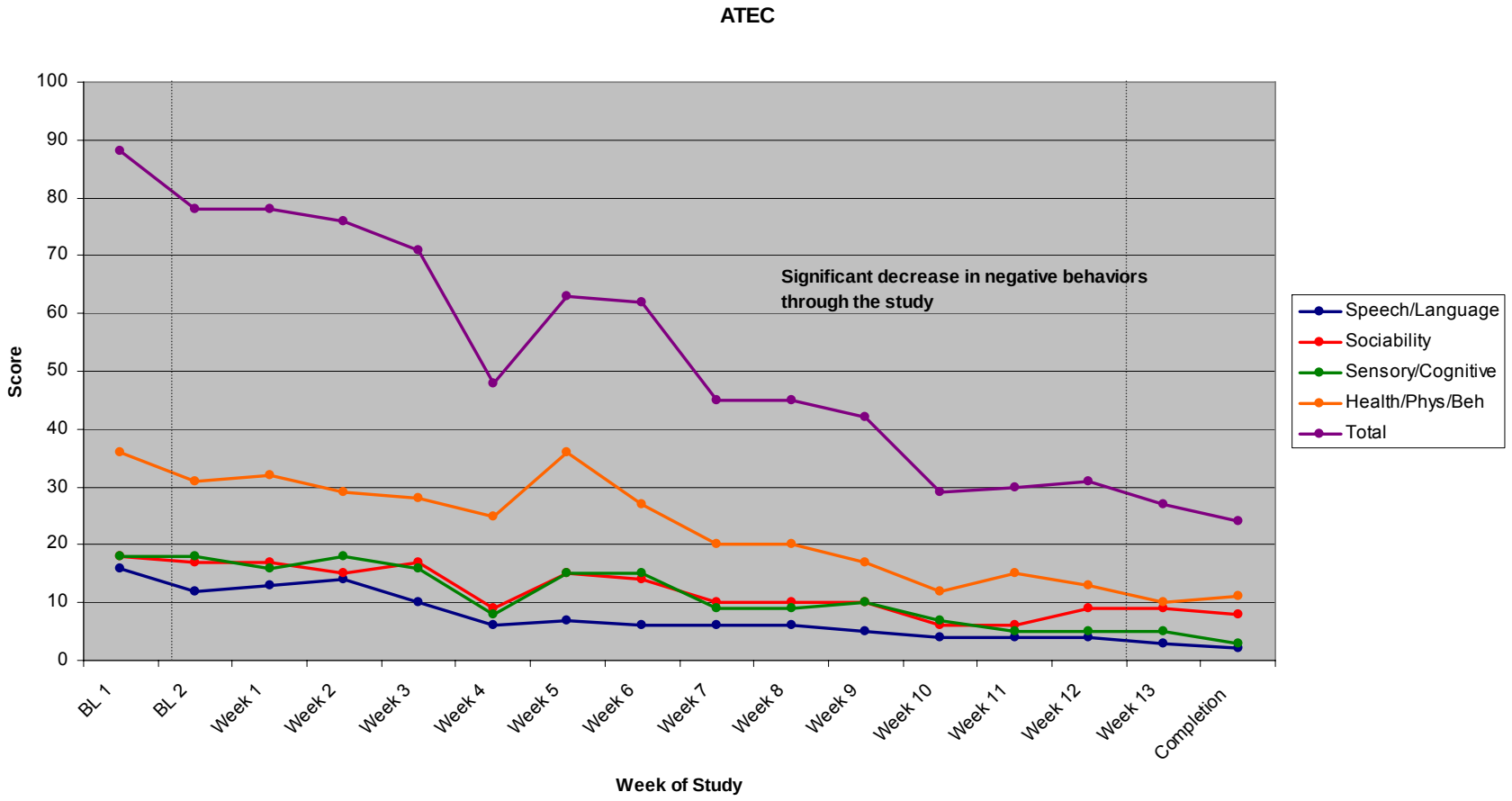
BRIEF – Executive Function
Lower means better



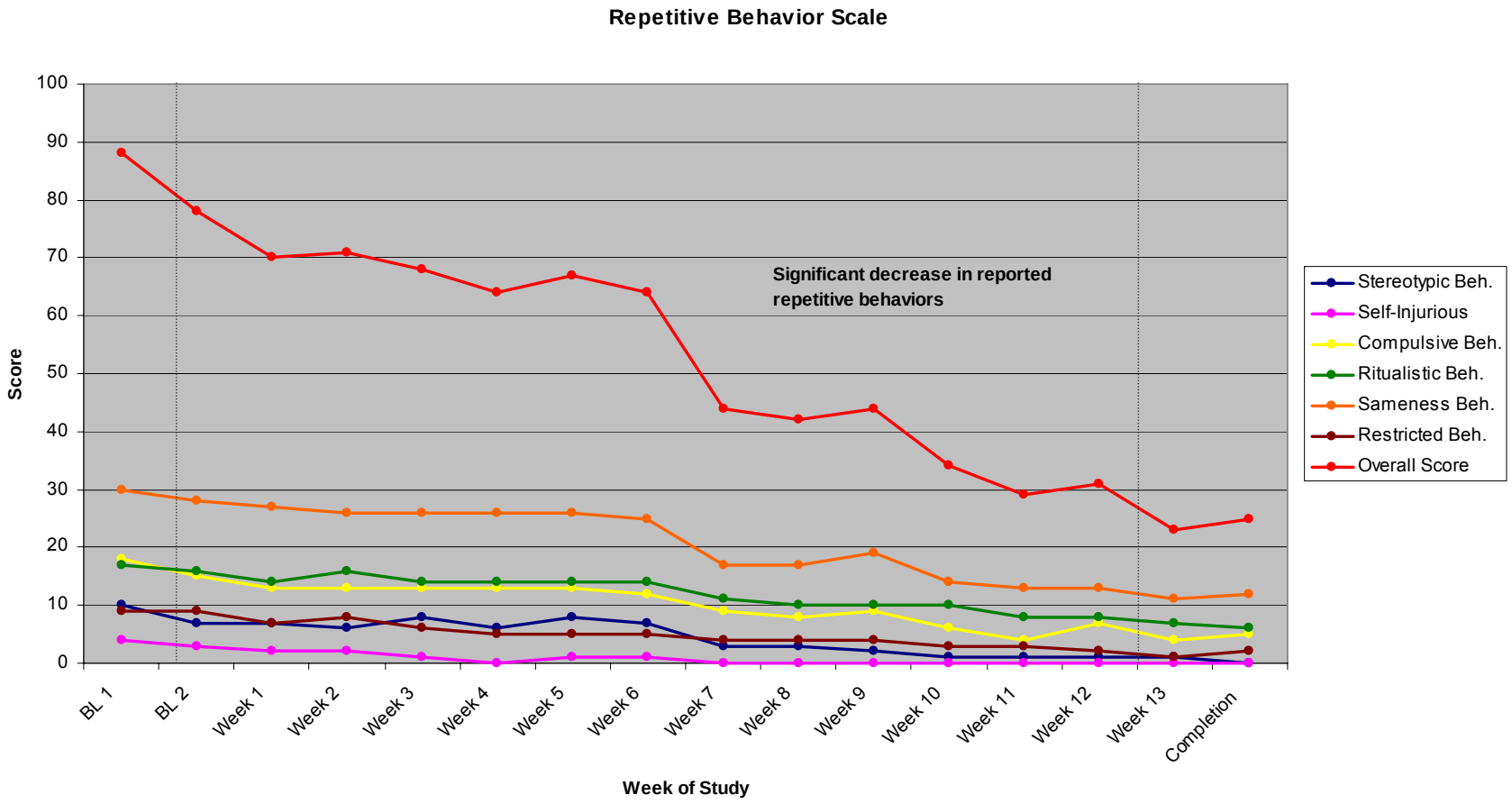
Aberrant Behavior Checklist
Lower is better



ATEC
Lower is better



Repetitive Behaviors
Lower is better



Summary

- By use of biomarkers and selected interventions children can be defined and monitored during interventions.
- Chelation is a likely significant intervention
- Immune interventions help many children
- Dysbiosis – gut pathogens are critical to remove.
- Oxidative Stress is dangerous and must be corrected by antioxidant supplements
- HBOT appears affective in at least some children
- Novel Treatments: Secretin/Oxytocin and others may help some children.