

Dietary Therapies in Autism: Modulating Metabolism and Microbiome to Shift a Dynamic Encephalopathy

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TRANSCEND Research Program

Pediatric Neurology

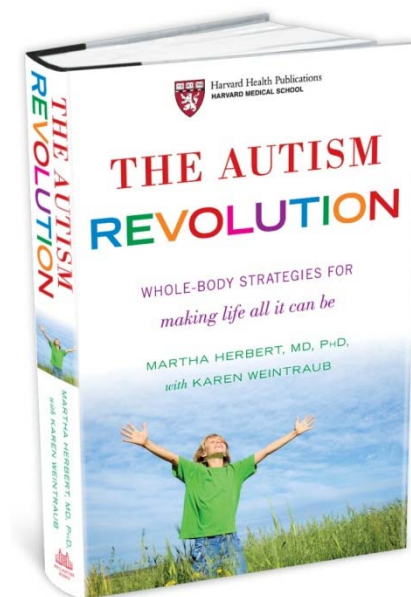
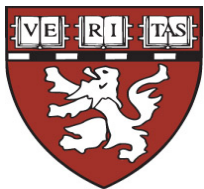
Martinos Center for Biomedical Imaging

Massachusetts General Hospital

Harvard Medical School

www.transcendresearch.org

www.AutismRevolution.org



www.AutismRevolution.org
www.autismWHYandHOW.org

Slides prepared with assistance from Kelly Barnhill MBA, CN, CCN,
Director of Nutrition, Johnson Center, and Nutrition Coordinator, Autism Research Institute

Autism: Beyond Gene-Brain-Behavior-Hopeless

Behavioral/psychiatric definition

1. Impaired social interaction
2. Impaired social communication
3. Markedly restricted repertoire of activities and interests

But also wide array of neurological and somatic features

- Sensory overload
- Social behavior issues
- Sleep problems
- Sensorimotor glitches
- Speech issues
- Stereotypies
- Seizures
- Stress

AND

**GI (diarrhea, constipation, malabsorption, dysbiosis),
Immune, Endocrine, Skin, Bone density loss, More** ²

Drop in Infectious and Rise in Chronic Immune-related disorders

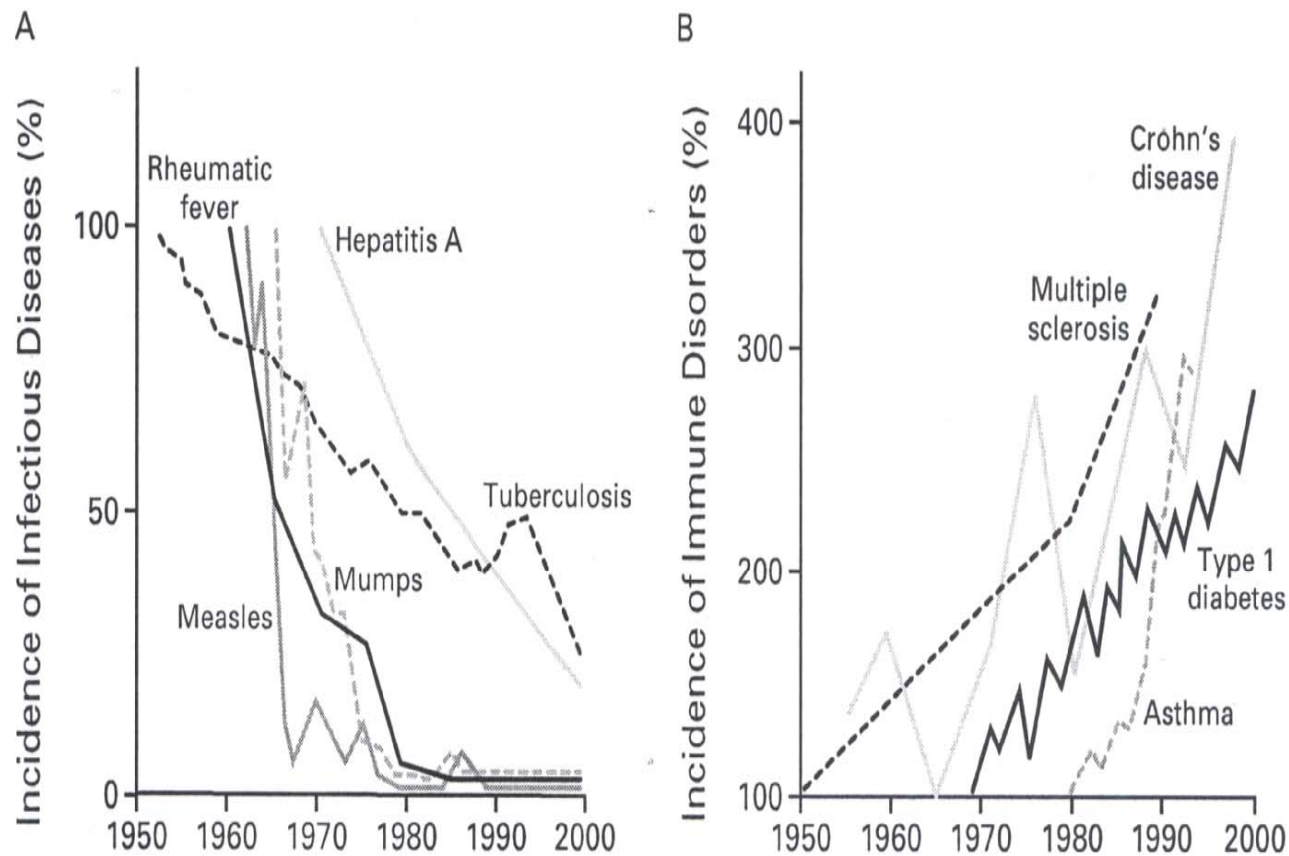


Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Joussemet et al.¹² In Panel B, data on immune disorders are derived from Swarbrick et al.,¹⁰ Dubois et al.,¹³ Tuomilehto et al.,¹⁴ and Pugliatti et al.¹⁵

Rise in Autism Prevalence v. Other Major Chronic Conditions in US

Autism

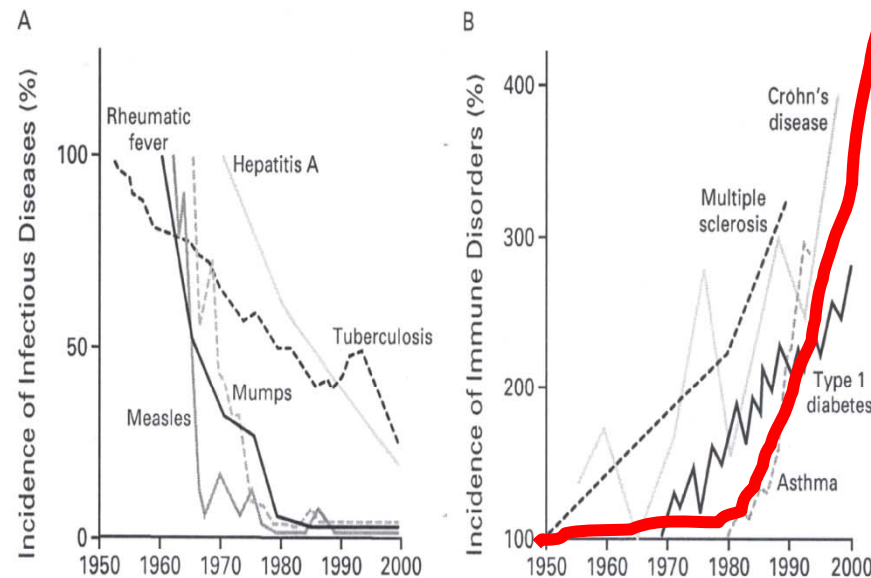
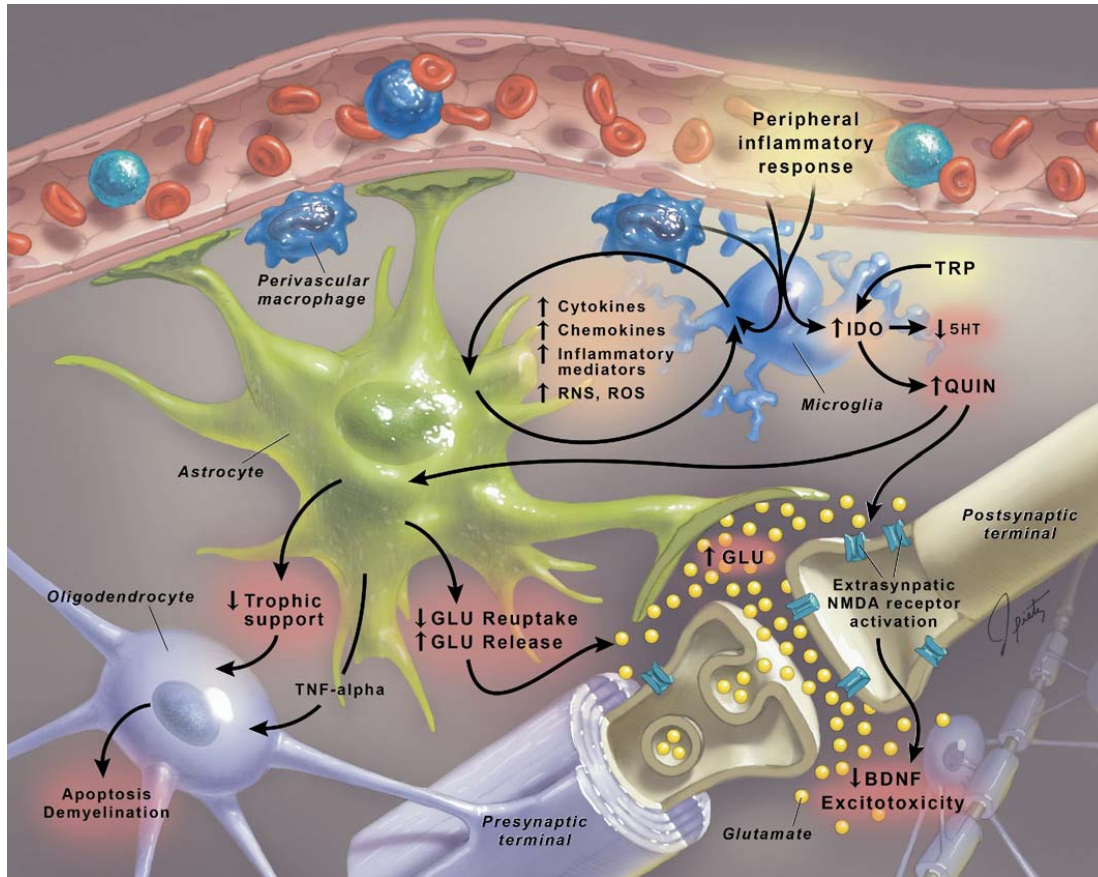


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Brain cells in inflammation

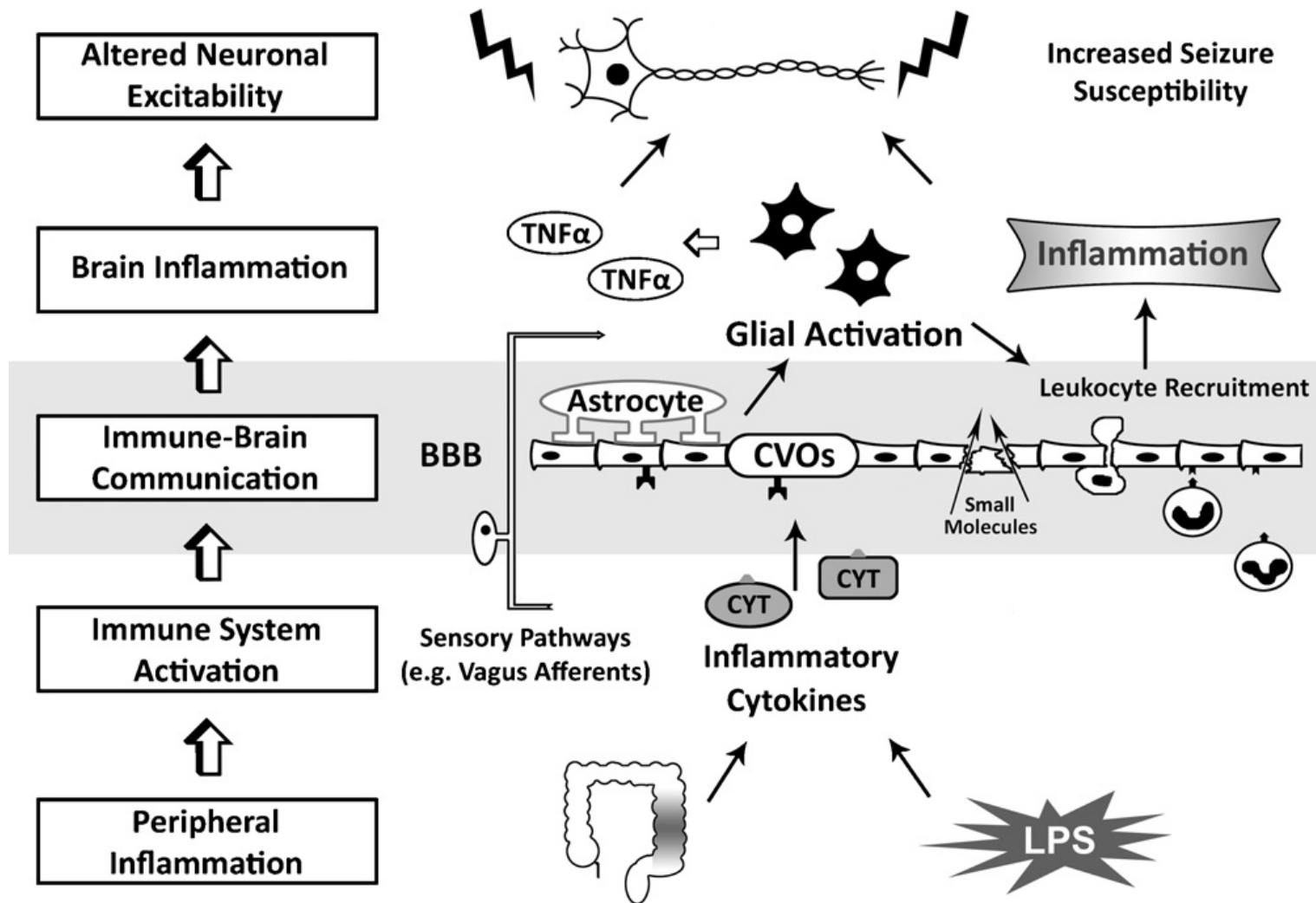


- Excitatory chemicals created by activated glial cells
- Normal housekeeping functions of glial cells get neglected
- Chronic inflammation can cause damage
- Chronic inflammation is irritating and promotes excitotoxicity

Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression.

Miller et al., BIOL PSYCHIATRY 2009;65:732–741

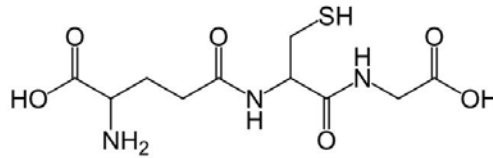
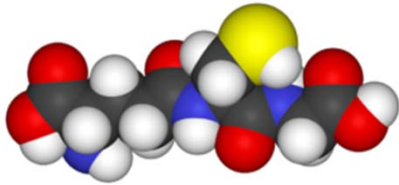
Gut-Brain-Immune Continuum



Autism as a “Perfect Storm” Situation

- Possible genetic vulnerability
- Environmental challenges
 - Poor food quality
 - Toxicants
 - Weakened immune systems
 - Compromised microbiome
 - Stress
- ➔ De novo mutations, genomic instability

GLUTATHIONE PROTECTS CELLS from environmental stress, but is often low in ASD (and many other chronic conditions)



Made in the liver from
three amino acids:
**Glutamate + Cysteine +
Glycine**

- **GLUTATHIONE is vital for detoxification**
 - Mops up toxins and free radicals
- The body's most potent anti-oxidant
- **The most abundant antioxidant in the BRAIN**
- ***Final common pathway:***
 - **Depleted by thousands of toxins, oxidative stress, infection, inflammation and nutrient-poor diet**

**New Open Access
Journal of Microbial Health and Disease:
Special Autism Issue-2012**

Genomic Instability:

**Should autism be considered a canary bird telling
that Homo sapiens may be on its way to
extinction?**

By Olav Albert Christophersen

Also,

***Autism and Microbiome article
by Derrick MacFabe***

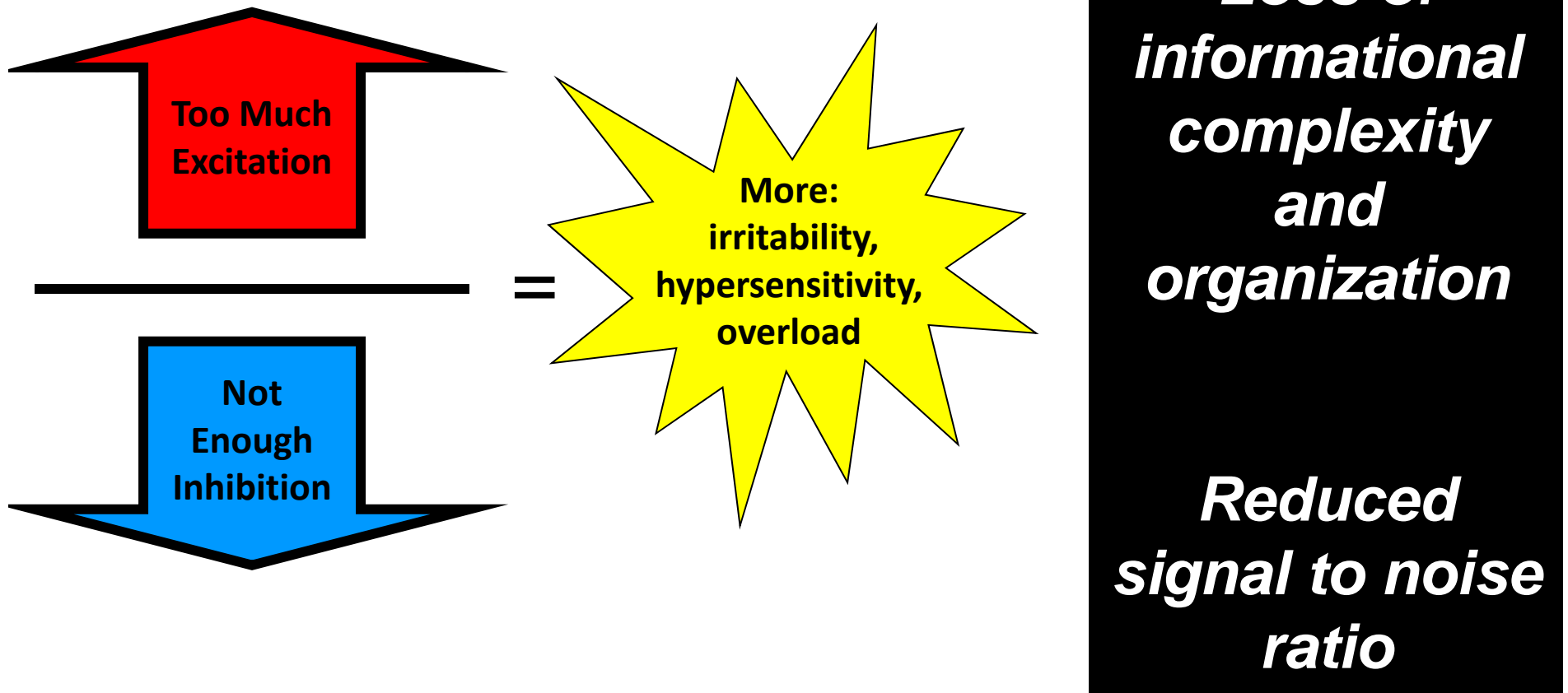
<http://www.microbecolhealthdis.net/index.php/mehd/article/view/19008>

<http://www.microbecolhealthdis.net/index.php/mehd/issue/current>

A FINAL COMMON PATHWAY?

Model of autism: Increased ratio of
excitation / inhibition in key neural systems

Rubenstein & Merzenich, *Genes, Brain and Behavior* (2003) 2: 255-267



Autism before the diagnosis

- **Common infant/toddler history of**
 - **Infant colic / diarrhea**
 - **Multiple ear or other infections in infancy with many courses of antibiotics**
 - **Self-restricted diets**
 - **Eczema**
 - **Food allergies**
 - **“Green Poop”**
 - **Poop that burns through furniture**
- **Prospective Multisystem High Risk Infant study**
- **Emerging Preconception/infancy prevention programs**

Is Autism a Brain Disorder? – OR – A Disorder that AFFECTS THE BRAIN?

FROM

**Gene-Brain-Behavior
Static Encephalopathy**

- **In this model, dietary therapy seems frivolous and delusional**

TO

**Whole Body-Brain Systems
Dynamic Encephalopathy**

- **In this model, dietary therapy seems plausible and potentially powerful**

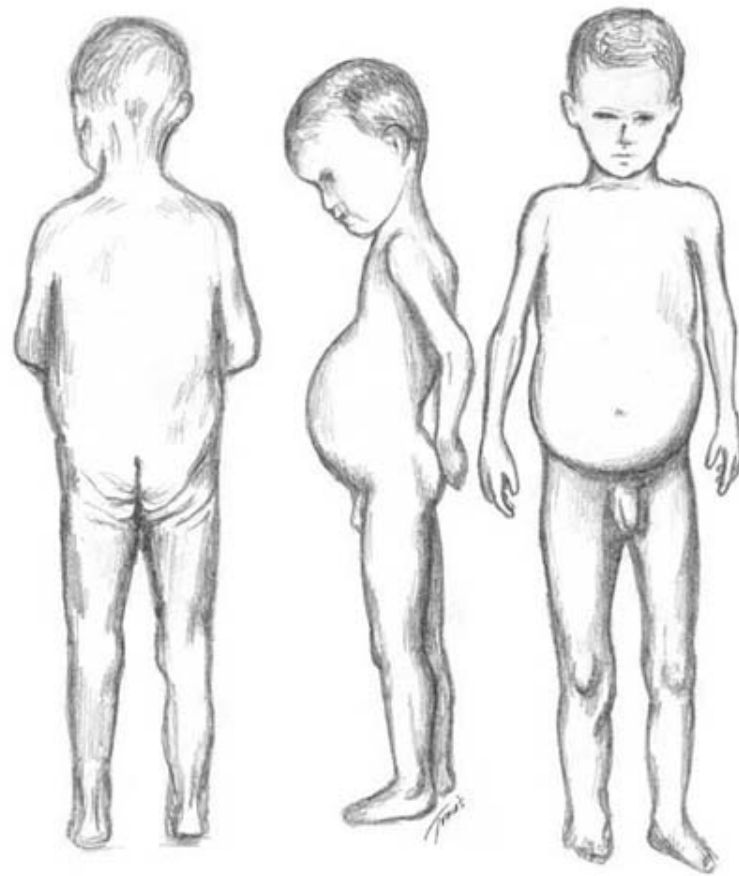
Herbert, "Autism: A Brain Disorder or a Disorder that Affects the Brain, 2005, available under publications on www.marthahebert.org

Dietary Intervention, Parent Reported Results:

From Autism Research Institute, Spring 2009:

- **GFCF** (Gluten-free and Casein-free): **66% improved**
- **SCD:** **69% improved**
- **Feingold Diet:** **56% improved**
- **Rotation Diet:** **51% improved**
- **This clinical phenomenology challenges us to look closely.**

Body habitus seen in autism suggestive of potentially diet-responsive GI disturbance



Pain-based behavior: pressure on abdomen





Krigsman





The Every Day of Some Autisms

What we need:
Clinical labs that will
detect and report
pertinent gut
pathogens



Mechanisms by which body systems might impact brain in autism

- **Metabolism**
 - Inborn errors; acquired metabolic glitches – environment/diet caused impairment of vital processes
- **Immune activation**
 - Altered cytokines
- **Microbiome**
 - Altered gut microbial ecology with altered metabolic, immune or neurochemical impacts
- **Alteration of gut-blood or blood-brain barrier**
 - Zonulin/gluten
- **Neurochemical**
 - Neurotransmitters, neuropeptides
- **Neural (e.g. vagal afferents)**

Examples of metabolic problems where treatment has impacted the “autism”

- Modulation of autism severity by treatment in cases of documented metabolic disorder was reviewed by Page in 2000 (Page 2000) and some more examples have since been reported. Autistic symptoms are reduced
- in **Smith-Lemli-Opitz** syndrome by **cholesterol treatments** (Natowicz M 2004; Aneja/Tierney).
- in **PKU** by a **low phenylalanine diet**, (Gillberg and Coleman 2000);
- in hyperuricosuric autism by a low purine diet with or without allopurinol (Coleman N 1989, Gillberg and Coleman 2000, Page and Moseley 2002);
- in patients with **low CSF bipterin** by **bipterin supplementation** (Fernell et al. 1997);
- in some **hypocalcinuric** autistic patients by calcium supplementation, (Coleman N 1989);
- in some patients with **lactic acidemia** by **thiamine and/or ketogenic diet** (Coleman N 1989), in cerebral folate deficiency by folinic acid supplementation (Moretti et al. 2005, Ramaekers and Blau 2004),
- By **correction of oxidative stress and methylation abnormality** profiles through intervention with **methylcobalamin, folinic acid and trimethylglycine** was accompanied by qualitative clinical improvement (James et al. 2004
- By **high-dose vitamin C** (Dolske et al. 1993).

Microbiome changes in ASD

- Lots of research in the pipeline
 - Differences in organisms e.g. Clostridia
 - Missing classes of organisms
 - Rare bugs not typically found
- *Stay tuned....*

Experience, Evidence, Heterogeneity and Study Design Issues

- **Autism is not one thing**
- **The behaviors are probably an “emergent feature” of a physiologically profoundly disrupted system**
- **Lumping is not a good research strategy**

Sugar-free diet

- **This is not a diet as such but an observation that sugar can be a big problem:**
 - **Rashes, yeast infections, itchiness**
 - **Explosive behaviors**
 - **Inattention**
 - **Craving for and overconsumption of nutrient-poor junk foods**
- **One common thread across most dietary therapies in autism is strict avoidance of sugar**

Gluten-Free, Casein-Free Diet (GFCF)

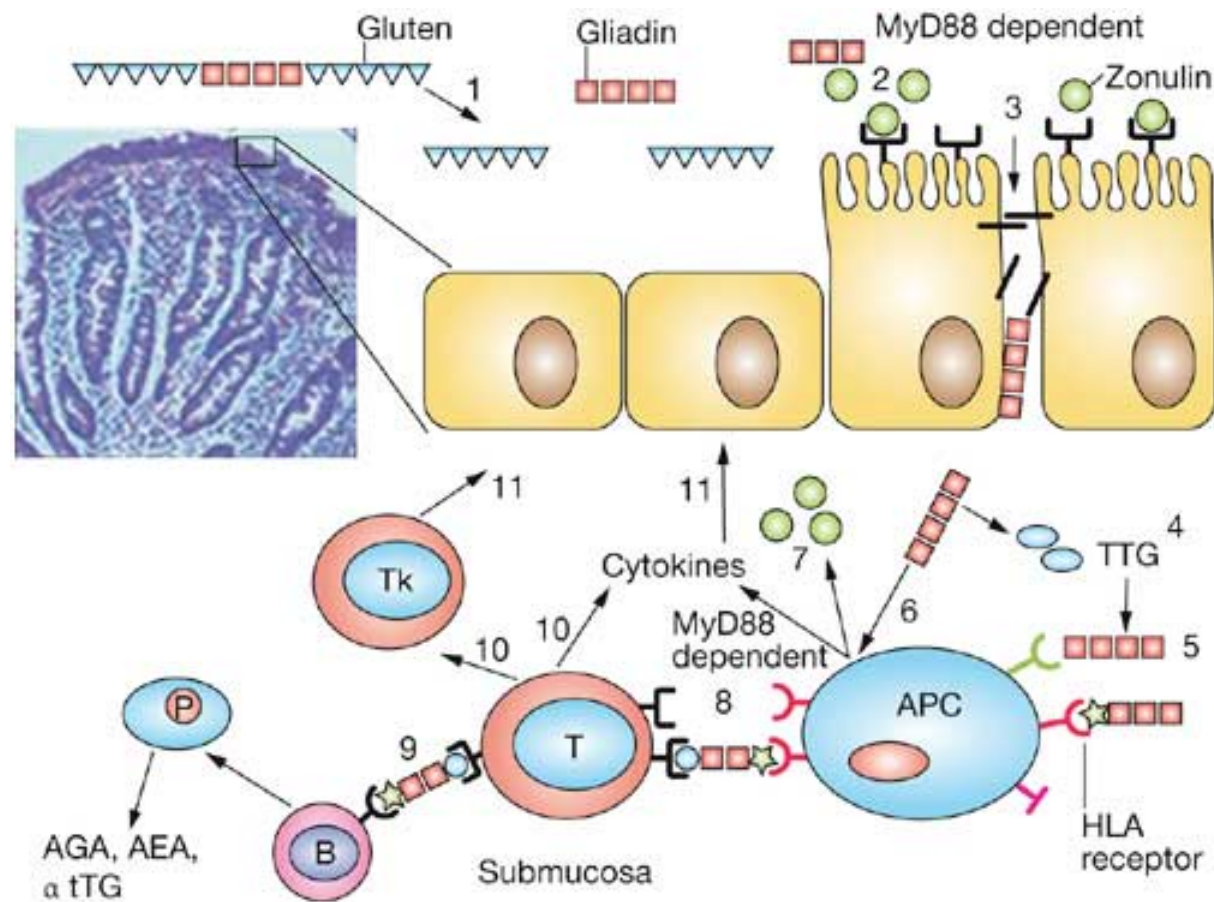
- **What it involves:**
 - Removal of ALL foods containing any trace of gluten or casein
- **When to use it**

Gluten & milk cravings	Silly, OCD, self-injury
GI: constipation, diarrhea	High pain tolerance
Poor focus & eye contact	Sensory, stims
- **Observed clinical phenomenology**
 - Improvement, sometimes rapid, sometimes gradual
 - Gradual or abrupt decompensation with re-exposure
 - Return of difficult behaviors, poorer attention span
 - Explosive behavior may return abruptly
 - Seizures

GFCF: possible mechanisms

- **Opioid peptides**
 - P Shattock: Sunderland Polytech University, Sunderland, England, 1990: Role of neuropeptides in autism and their relationships with classical neurotransmitters, Shattock et al, Brain Dysfunction; vol. 3, n°5-6, pp. 328-345; 1990.
 - K Reichelt: Gluten and milk proteins and autism: dietary intervention effect on behavior and peptide secretion. Reichelt et al, J Appl Nutr, vol 42:1-11; 1990.
- **“Leaky Gut” or Intestinal Permeability**
 - Immune/autoimmune consequences
- **Microbiome alterations**

Figure 1 Proposed role of abnormal intestinal permeability in the pathogenesis of celiac disease



Fasano A and Shea-Donohue T (2005) Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases *Nat Clin Pract Gastroenterol Hepatol* **2**: 416–422
doi:10.1038/ncpgasthep0259

“Should we all be gluten-free?”

- **Issues of altered agricultural practices that**
 - **Increase gluten content, alter gluten content of food**
 - **Failure to ferment gluten as in traditional harvesting and preparation practices**
 - **Alter protein sequence in casein**
- **Association of gluten with many autoimmune and neurological diseases**
- **Tendency to rely far too much on gluten**
- **Family members of children on GFCF who also go “GFCF” often feel a lot better**

Research

- **Mixed research but much of the research is considered methodologically flawed by advocates of diet**
 - **Choice of foods**
 - **Not enough time – need 6+ months on diet**
 - Challenges as early as 3 weeks have been studied but these do not have fidelity with actual practices clinicians and families have found helpful
- **Whiteley, P., D. Haracopos, et al. (2010). "The ScanBrit randomised, controlled, single-blind study of a gluten- and casein-free dietary intervention for children with autism spectrum disorders." Nutr Neurosci 13(2): 87-100.**
 - **Placebo group reassigned to treatment group at 12 months**
 - **Needs further study**

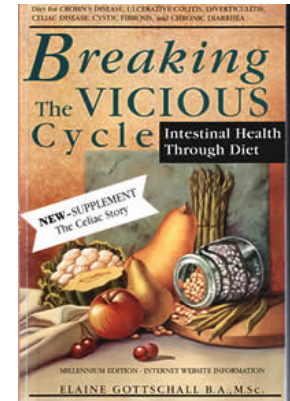
Diet Trials

- **Cade R et al: Autism and Schizophrenia: intestinal disorders. Nutr Neurosci, vol. 3: 57-72. 2000.**
- **Knivsberg: A randomized, controlled study of dietary intervention in autistic syndromes. Nutr Neurosci; 5(4):251-261; 2002.**
- **Knivsberg: Effect of a dietary intervention on autistic behavior. Focus on Autism and Other Developmental Disabilities, Vol. 18, No. 4, 248-257; 2003.**
- **Elder, J. H., Shankar, M., Shuster, J., Theriaque, D., Burns, S., & Sherrill, L: The gluten-free, casein-free diet in autism: Results of a preliminary double blind clinical trial. Journal of Autism and Developmental Disorders, 36, 413-420; 2006.**

GFCF: Weaknesses and Criticisms

- **Tendency for parents to substitute starchy and sugary GF/CF junk food products**
 - This has negative impact on microbiome and sabotages positive impacts diet may have
- **Other grains may also be causing allergy or sensitivity problems**
 - Corn in particular
 - Corn products in addition to corn as grain
 - Grains in general
- **Other foods in addition to wheat and dairy may be causing problems**
 - Soy, other common allergens, idiosyncratic food reactions

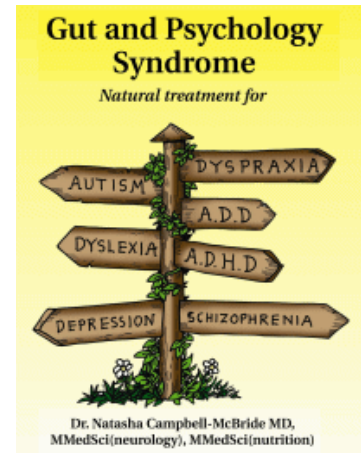
Specific Carbohydrate Diet



- Created by Dr. Sidney V. Haas
- Popularized by biochemist and author Elaine Gottschall
- Restricts the use of complex carbohydrates (disaccharides and polysaccharides)
 - Rationale: impaired breakdown promotes harmful microbiota
 - bacterial overgrowth
 - This leads to mucus, injury, malabsorption – and vicious cycle
- Eliminates refined sugar, all grains and starch from the diet
 - Utilizes nut flour in place of grain flour
- Study on SCD and ASD in progress in Johnson Center for child Development and Health, Austin TX

GAPS Diet

- SCD plus dairy avoidance
(except ghee – clarified butter)
until dairy is clearly well tolerated
- http://gapsdiet.com/GAPS_Outline.html
- http://gapsdiet.com/INTRODUCTION_DIET.html



Candidates for SCD or GAPS

- GFCFSF only moderately helpful
- Chronic GI inflammation or dysbiosis
- Chronic Bowel Issues:
 - Profuse diarrhea
 - Chronic Constipation
 - Altered stool quality: sandy, gritty, sticky, mucousy

Candidates for SCD or GAPS (cont)

- Behavior:
 - posturing, abdominal pressure, SIB, altered sleep, hyperactivity, marked changes in behavior before/after BM
- Lab data:
 - Celiac markers
 - Fecal Calprotectin,
 - Eosinophilic Protein X
 - Positive Lactoferrin
 - Elevated SED rate and CRP Behavior

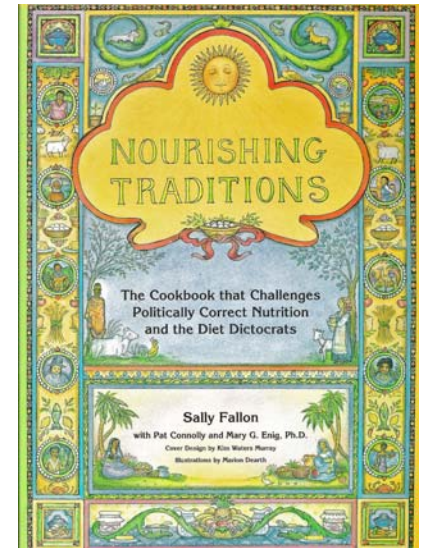
Body Ecology Diet

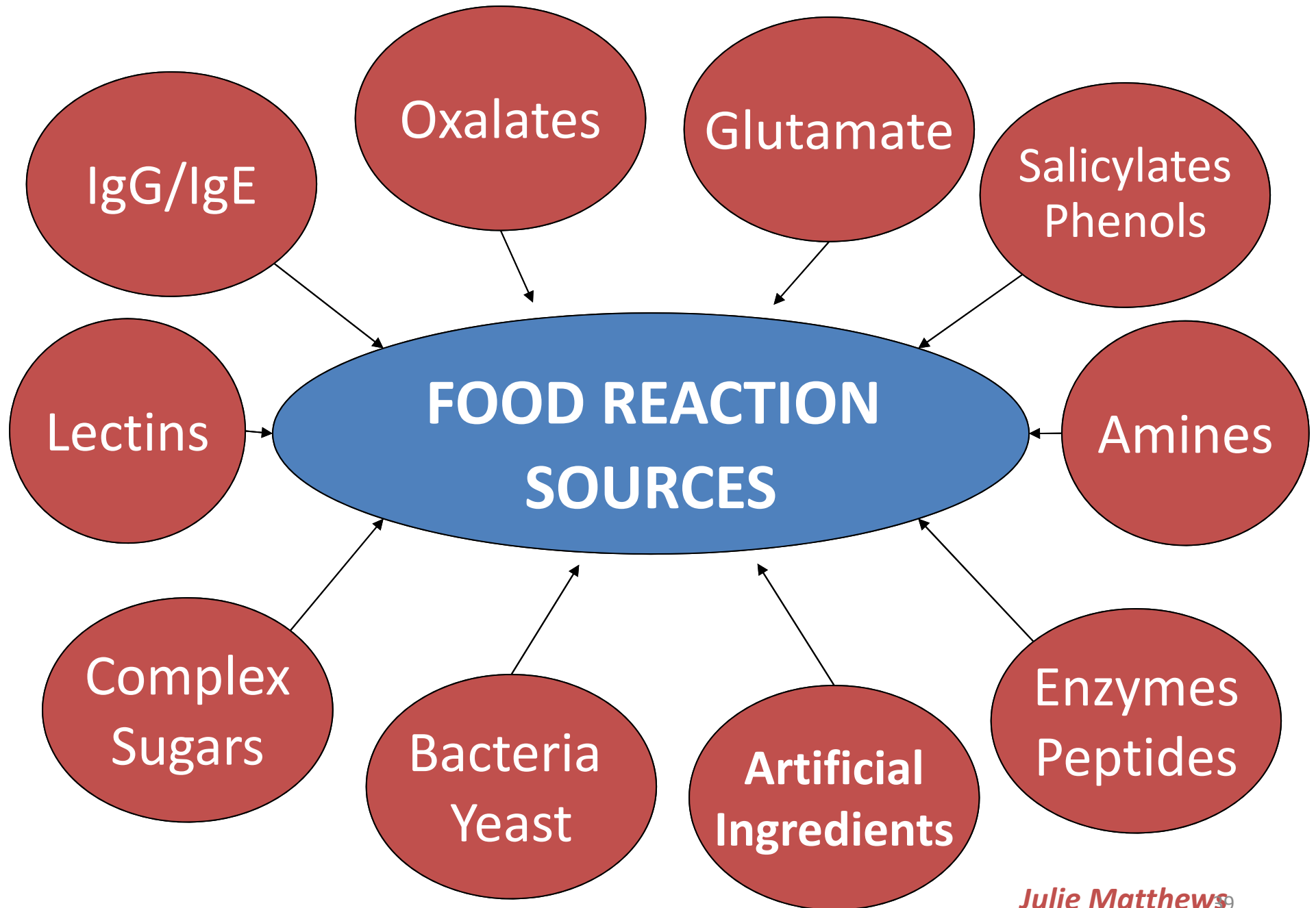
- Aims to protect interlocking relationships of immune, endocrine, circulatory and central nervous systems
- Dietary changes:
 - Addition of cultured foods
 - Home-culturing milk, vegetables, other foods
 - Change of quality of fats and oils
 - Drastic reduction of carbs and sugars
 - 80/20 Alkaline (vegetables) / acid (animal protein)
- <http://bodyecology.com/aboutbed.php>

**GMO- / Additive- / Pesticide-Free,
Organic, Biodynamic**

Weston Price / Nourishing Traditions

- **Nutrient dense unprocessed food**
 - Grass-fed, pasture-raised animal products
- **Lots of bone broths and saturated fats**
 - High fat can be hard for some, esp w gallbladder issues
- **Based upon observations of Weston Price, a dentist who observed relationships between dental health and diet in remote “primitive” cultures in the 1930s and 1940s**
- **Social movement for unprocessed food**
- **Paleo diet movement**





Diets that Avoid Specific Food Compounds

- **Examples:**
 - **Phenols/Salicylates**
 - **Oxalates**
 - **Amines**
 - **Glutamates**
 - **Lectins**
- **Specific symptom complexes may suggest utility of trial of each**

Elimination and Rotation Diets

- **Elimination**
 - Remove offending food for minimum 2 weeks
 - Identify foods to remove through testing or empirical removal of common offender foods
- **Rotation**
 - Avoid constant consumption of problem foods
 - Can rotate single foods, single food categories, multiple categories, or all items

Metabolic and Mitochondrial support

- **Empirical or test-based supplementation**
 - To support pathways associated with environmental vulnerability, e.g. methylation, Krebs cycle, oxidative phosphorylation
 - To restore imbalances, e.g. inverted zinc/copper ratio

Possible Brain Mechanisms 1:

What may be impacting brain

- **Metabolism**
- **Immune activation**
- **Microbiome**
- **Alteration of gut-blood or blood-brain barrier**
- **Neurochemical**
- **Neural (e.g. vagal afferents)**

Possible Brain Mechanisms 2:

How the brain may be impacted

- **Chemistry**
- **Metabolism**
- **Immune activation**
- **Mitochondrial function**
- **Glial Cells**
- **Neuronal function**
- **Electrophysiology: oscillations, coherence, signal amplitude**
- **Hypothesis: Connectivity – tract integrity: probably downstream of the above changes**

What happens in the brain when a child improves like this?

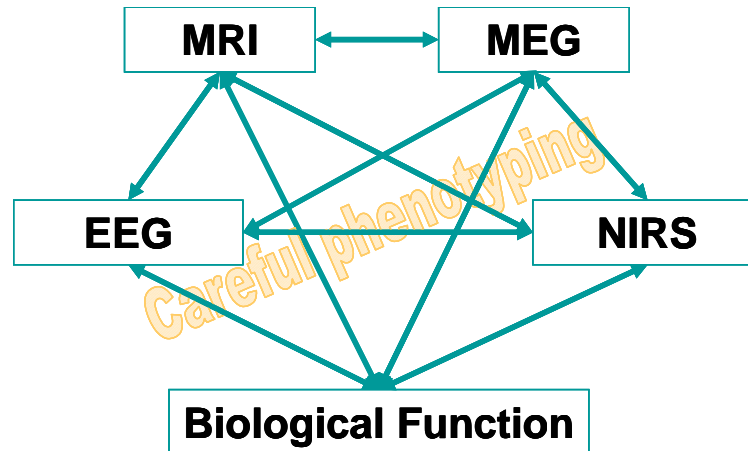


- **Treatment of this child including nutritional status and gut problems lead to a 50 point increase in IQ test performance and a dramatic increase in level of function**



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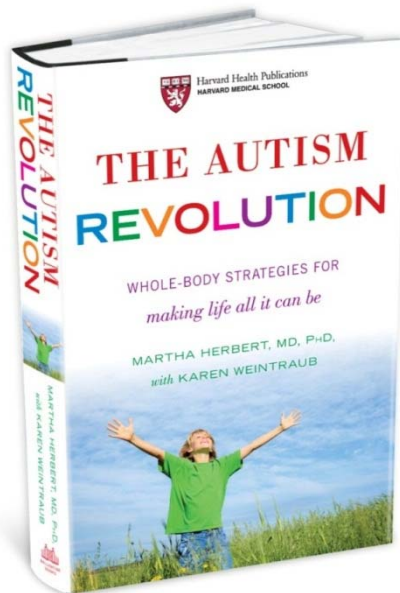
Treatment
Research
And
Neuro
Science
Evaluation of
Neurodevelopmental
Disorders



Integrative multimodal measurement platform
Optimization of measures that can detect change
In development, in regression, in improvement

Looking for collaborative projects!

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**Review of hidden
assumptions
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