

Scientific Foundations of a DAN! Protocol

Mini-DAN!
Auburn, Alabama
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Citations for this presentation

[http://www.autism.com/ari/dan/
scientificfoundations.html](http://www.autism.com/ari/dan/scientificfoundations.html)

Topics

- Controversies: MMR & thimerosal
- Consideration of “anecdotal”
- ARI’s Parent Ratings of treatments
- Several special topics

The Controversies - MMR – Thimerosal

- not to resolve the issues, but to convey both sides, eg recently,
 - Thimerosal safe (1-3)
 - MMR safe (4)
 - Thimerosal's adverse sequelae (5)
 - MMR not entirely safe (6-7)

Controversies

- Consider the diluting of data
 - eHg – CDC
 - CDC 1999
 - (8a-c)
 - CDC 1st data dilution
 - Verstraeten et al 2000 (8d)
 - Simpsonwood - CDC deliberates data dilutions
 - (9a-b,10b-c)
 - CDC 4th data dilution
 - Verstraeten et al 2003 in Pediatrics (11)
- MMR: Madsen et al 2002 - (4)

CDC findings 1999

Neurologic pathologies now common in children are strongly associated with thimerosal injections during infant vaccinations

(8b)

"A relationship will be considered plausible if statistically significant or a relative risk of 1.5 or higher is found."

CDC's original concern (8a)

CDC 1999 – Relative risk with 95% CI

- sleep disorders of non-organic origin = 4.98
- phase-disruption of 24-hour sleep-wake cycle = 53.64
- somnambulism or night terrors = 5.76
- attention deficit w/o mention of hyperactivity = 6.38
- attention deficit with mention of hyperactivity = 8.29
- developmental speech or language disorder = 2.09
- other developmental speech or language delay = 2.32
- unspecified delay in development = 2.08
- autism = 11.35

CDC findings in 2000

“... studies were conducted in 2000 by CDC to evaluate the dose-response effects of thimerosal on childhood neurodevelopmental disorders based upon evaluation of the VSD database... It was found that there were statistically significant relationships between increasing exposures to thimerosal and the following outcomes....:

1. for two months of age, an unspecified developmental delay, which has its own ICD-9 code.
2. Exposure at three months of age, Tics.
3. Exposure at six months of age, language and speech delays, which are two separate ICD-9 codes.
4. Exposure at one, three and six months of age, the entire category of neurodevelopmental delays, which includes all of these plus a number of other disorders (i.e., including autism)."

Rebuttals to diluted data “studies”

- rebuttals of studies based upon diluted data
 - Thimerosal (eg, 5, 8-10c)
 - Analysis of CDC’s data dilution (10c)
 - MMR (eg, 6-7)

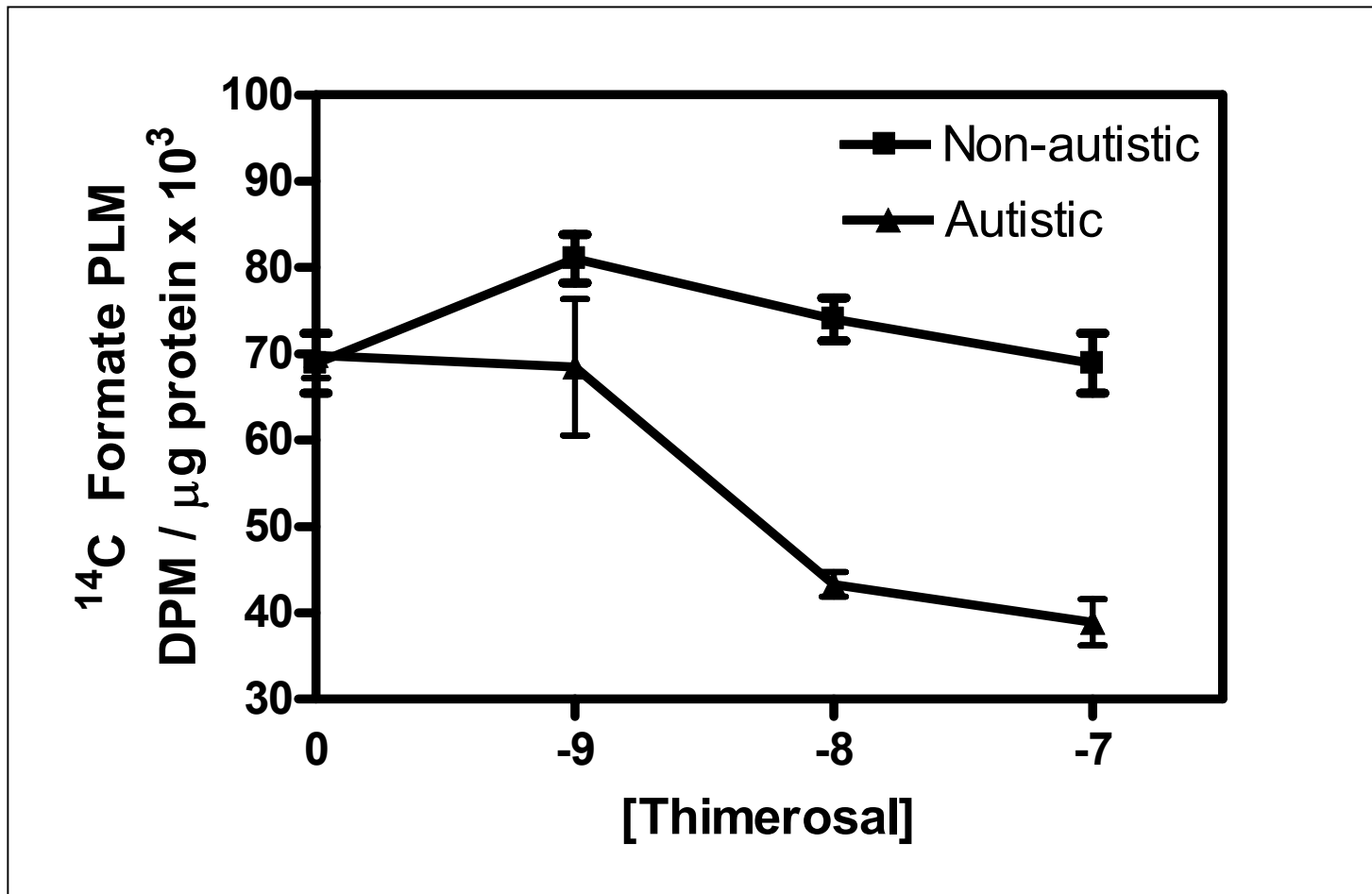
Controversies – Overview

- CDC's 1999 findings of association between thimerosal and add, adhd, tics, sleep & coordination problems, language disorders, and autism (8b)
- CDC's in-house paper (2000) of association between thimerosal and adhd, tics, language disorders, and autism (8d)
- CDC's pre-altered findings confirmed by Geier and Geier (12-16)
- Then the publishing of diluted data
 - (eg,11, critiqued in 10c)

More thimerosal cites

- Kills neurons (17-18)
- Impairs methionine synthase at post-vaccine physiological levels (19-21)
- Genetic predispositions (22-23)
- Impairs immunity (eg, 24-25)
- Induces autoimmunity (eg, 26-27)
- Baby Hair study Holmes et al
 - (implications for Rx)
 - (28-29)
 - Thimerosal miscellany (32-36a)

Lymphoblasts from autistic children show greater sensitivity to thimerosal than cells from non-autistic, same-sex siblings
- Richard Deth, PhD, et al



Implications of Holmes et al hair findings

- **Principle**

- An infant or toddler with impaired detoxification is likely to accumulate toxic metals and to develop adverse sequelae, especially if excessive exposures occur

- **Blood test's false negatives**

- Blood tests for toxic metals tend to reflect current exposures and not accumulation from prior exposures

Defense of anecdotal

- big studies virtually always statistical
 - w/o 100% applicability
- Actual medical practice relies upon anecdotal information from patients or parents of patients

Core of a DAN! approach

- **Case history**
- **Clinical exam**

- Heal the gut
- Optimize nutritional status
- Chelate if necessary
- Antivirals if necessary

- Overview in “Children with Starving Brains”
 - <http://www.autism-rxguidebook.com/>

ARI's Parent Ratings of treatments

- An important compilation!
- www.autism.com/ari/specialinterest/form34q.html
- www.autism.com/ari/specialinterest/form34q.pdf

Parent ratings

- Aderall

- 39% Got Worse
- 26% No Effect
- 35% Got Better
- 0.9 / 1 Better/Worse ratio

– No. of cases = 411

Parent ratings

- Antifungals: Nystatin
 - 5% Got Worse
 - 47% No Effect
 - 47% Got Better
 - 9.3 / 1 Better/Worse ratio
- No. of cases = 847

Parent ratings

- Removed Wheat

- 2% Got Worse
- 51% No Effect
- 47% Got Better
- 26 / 1 Better/Worse ratio

– No. of cases = 2983

Parent ratings

- Chelation - [new category]

- 2% Got Worse
- 25% No Effect
- 73% Got Better
- 34 / 1 Better/Worse ratio

– No. of cases = 187

Why use lab tests

- A doc asked about clinical impressions
 - Aren't they enough?
- Not necessarily, eg, one child
 - Didn't look sick, "seldom got sick"
 - elevated EBV titer
 - highly elevated NK
 - very low plasma and urinary AAs

Why use lab tests - 2

- acyclovir plus child-specific AAs
- from university dx of autism to accepted into kindergarten as NT

Citations supporting the four domains of a DAN! approach

- heal gut, fine-tune gi-system
- boost nutrition
 - (including methylation pathways)
- chelation
- antivirals
 - (other advanced testing)

heal gut, fine-tune gi-system

- Dietary interventions
- “...Gluten and/or casein free diet has been implemented to reduce autistic behaviour, in addition to special education, since early in the eighties... The reported results are... more or less identical; reduction of autistic behaviour, increased social and communicative skills, and reappearance of autistic traits after the diet has been broken.”

Intestinal pathology in autism

- Increased intestinal permeability - (37)
- Opioid peptides in circulation - (38-39)
- Food allergies - (40a-c)
- Non-classical nutritional impairments - (41-42)
- Dietary intervention in autism - (43-44)
 - Efficacy summaries: Parent Ratings data (45)

Intestinal pathology: MMR, vaccinal MV

- Initial MMR study, findings & hypothesis (46)
- Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children
 - Wakefield AJ et al
 - Lancet. 1998 28;351(9103):637-41

MMR, vMV, intestinal pathology

- Biopsy findings have been repeated, expanded
 - Royal “Free” gastroenterologists, etc (47-61)
 - Horvath & colleagues (62-63)
- Most findings focus upon gi pathology, not MV

MMR, vMV, intestinal pathology confirmed

- GI pathology: Supportive Editorial review in Am J Gastroenterology (64)
- Biopsy findings confirmed by:
 - Timothy Buie, MD, Harvard, Mass Gen (65)
 - Arthur Krigsman, MD, private practice
 - Elizabeth Mumper, MD, & colleagues (2004)

MMR, vMV, intestinal pathology

- Forced recantations
 - of MMR-autism hypothesis
 - of vMV-autism hypothesis
- Orthodox mantra
 - “no proof” of autism-MMR connection
- Intestinal pathology findings not recanted

MMR, vMV in autism: more evidence

- **vMV in PBMCs**
 - Published (66)
 - Additional support in clinical findings (67)

- **vMV in CSF (an autism subgroup)**
 - Institute of Medicine presentation by Jeff Bradstreet, M.D. (67)

vMV Clinical findings - summary

- confirmation of intestinal pathology
- vMV in intestinal tissues of many autistic children
- vMV in PBMCs of some autistic children
- vMV in CSF some autistic children
 - an iatrogenic variant of SSPE? (69-72)

MMR epidemiological finding

- “...there is biological plausibility and epidemiological evidence showing a direct relationship between increasing doses of mercury from thimerosal-containing vaccines and neurodevelopmental disorders, and measles-containing vaccines and serious neurological disorders.”
 - Geier & Geier 2004 (73)

MMR immunological findings

- ***VK Singh's Immunological findings (74-77)***
- The level of measles antibody...was significantly higher in autistic children as compared with normal children ($P = 0.003$) or siblings of autistic children ($P \leq 0.0001$).
- ...immunoblotting of measles vaccine virus revealed that the antibody was directed against a protein of approximately 74 kd molecular weight. The antibody to this antigen was found in 83% of autistic children but not in normal children or siblings of autistic children.
- Thus [many but not all] autistic children have a hyperimmune response to measles virus, which in the absence of a wild type of measles infection might be a sign of an abnormal immune reaction to the vaccine strain or virus reactivation.

MMR, MV, vMV side-effects

- Impairs immunity (78-83)
 - Much research from DE Griffin's group at Johns Hopkins
- Alters vitamin A profile (84-86)
- Low vitamin A affects immunity (eg, 87-88)

Immunoglobulins & vit-A

- Low Ig, Very common finding in autism, eg:
 - IgG – 368 (rr = 680-1445)
 - IgA – 41 (rr = 83-407)
- Vitamin A can increase IgA, IgG synthesis (88b-h)
- Malnutrition subserves low Immunoglobulins (eg, 88b)

Persisting vMV - Vitamin A therapy

Vitamin A helpful for wild type measles, especially in malnourished children

– (89-97)

Similarities between phenotypes of many autistic children and of malnourishment profiles in kwashiorkor and marasmus

• (98)

Susan Owens Iwo@iadfw.net

Nutritional significance of intestinal pathology

– vMV is not only cause of intestinal pathologies

- Adverse colonizations

– (99-106)

- Gastric, pancreatic and/or hepatic possibilities

– (53, 62a, 107-112)

MMR & Thimerosal: hypothetical corollary

- The MMR impairs immunity – (78-83)
- Thimerosal impairs immunity – (24)
- Corollary:
 - Concurrently injecting the MMR and a thimerosal-containing vaccine increases the risk of adverse sequelae, especially in sick, recently sick children, or genetically predisposed children.

IMO: Two guidelines

- Don't vaccinate sick infants or sick toddlers
 - They're likely to be low in GSH, thus
 - Impaired Detox
 - Impaired Immunity
- Avoid multiple multiples during the same vaccination incident

**Impaired Methylation Capacity and Increased
Oxidative
Stress in Children with Autism: Metabolic
Biomarkers
and Genetic Predisposition**

**Results of Intervention Trial with Folinic Acid,
Betaine, and Methyl-B12**

S. Jill James, Ph.D., Laurette Janak, M.O.M.,
Stepan Melnyk, Ph.D., Stefanie Jernigan, Paul Cutler, M.D.

**Accepted for Publication
in American Journal of Clinical Nutrition!!**

Methionine Cycle Metabolites

	Control Children n=33	Autistic Children n=20	p value
Methionine ($\mu\text{mol/L}$)	31.5 ± 5.7	19.3 ± 9.7	0.001
SAM (nmol/L)	96.9 ± 12	75.8 ± 16.2	0.01
SAH (nmol/L)	19.4 ± 3.4	28.9 ± 7.2	0.001
SAM/SAH ratio	5.2 ± 1.3	2.9 ± 0.8	0.001
Adenosine ($\mu\text{mol/L}$)	0.27 ± 0.1	0.39 ± 0.2	0.05
Homocysteine ($\mu\text{mol/L}$)	6.4 ± 1.3	5.8 ± 1.0	0.01

Proportion of Autistic Children within Normal Range
Before and After Supplementation

Metabolite	Normal Range ^a	Baseline	Folinic+Betaine	Folinic+Betaine +methylB12
Methionine (μmol/L)	> 24	1/8	5/8	7/8
SAM (nmol/L)	> 80	2/8	8/8	8/8
SAH (nmol/L)	< 23	2/8	7/8	7/8
SAM/SAH	> 4	1/8	7/8	7/8
Adenosine (μmol/L)	< 0.3	4/8	8/8	8/8
Homocysteine (μmol/L)	< 5.5	3/8	8/8	8/8
Cysteine (μmol/L)	<180	0/8	2/8	7/8
GSH (μmol/L)	> 5.4	0/8	2/8	7/8
GSSG (μmol/L)	< 0.33	0/8	2/8	8/8
GSH/GSSG	> 16	0/8	3/8	8/8

^a Range estimated to include 90% of control children

Dr. James' Important Caveat:

No single polymorphism alone can predict increased risk of autism because, by definition, polymorphisms are highly prevalent in normal people as well. It is possible, however, that specific combinations of these polymorphisms interact to shift specific metabolic pathways that are important in the pathogenesis of autism.

My comment:

Genetics are not the only way to impair metabolic processes. Whether acquired or genetic, gut and nutritional pathologies can impair metabolism, immunity, and detoxification and thereby increase risk for late-onset autism.

Nutritional pathologies – acquired and/or genetic

- eg, Glutathione (GSH)
 - Impaired CNS function (eg, 113-116)
 - Impaired detoxification (eg, 114, 117-119)
 - Impaired immunity (eg, 120-122)
 - Impaired mitochondrial function (eg, 123)
 - GSH & flu immunity (124-125)

Nutritional pathologies: GSH & Tylenol

- Tylenol depletes GSH
 - (126-134)
- Thus Tylenol impairs
 - Immunity
 - Detoxification

GI pathologies, nutrition, early case histories

- Clues to nutritional status
- Role of GSH
- Why my child?

Medical Histories: Why my child?

- *Placental, Fetal events?*
- *Colic? Otitis? Diarrhea? Other illness?*
- *Pro-inflammation gene-alleles?*
- Let's consider some examples...

Medical history

Chorioamnionitis - (may be silent)

Placental pathology

Fetal cytokines

Fetal brain effects

(135-142)

Pitocin use may have reflected chorioamnionitis

(see quotes in cites 138-139)

Medical history – low amino acids

Prolonged colic

Cow's milk allergy in breast-fed infants

(143-149)

Chronic diarrhea of infancy

(150-153)

Med history: excessively recurrent otitis

- Inflammation of the middle ear
 - bacterial
 - and/or
 - viral eg, **HSV, CMV**
 - or
 - neither
 - often gi component
 - Common mucosal immune system
- (154-158)

Med history: Excessively recurrent otitis

- Otitis subgroup low in GSH?
 - *Management of chronic otitis media with effusion: the role of glutathione*
– (159)
 - *Cow's milk allergy is associated with recurrent otitis media during childhood*
– (160)

GSH & thimerosal – Jill James et al 2004

- Thimerosal Neurotoxicity is Associated with Glutathione Depletion: Protection with Glutathione Precursors
 - In press in Neurotoxicology 2004

GSH & thimerosal – Jill James et al 2004

- “Although Thimerosal has been recently removed from most children's vaccines, it is still present in flu vaccines given to pregnant women, the elderly, and to children...”
- “The potential protective effect of GSH or NAC against mercury toxicity warrants further research as possible adjunct therapy to individuals still receiving Thimerosal-containing vaccinations.”

– (134b)

Caveat: sulfur hypersensitivity

- Some kids have adverse reactions to sulfur compounds
 - Sulfasalazine
 - DMSA
 - GSH
 - etc
- For more info:
- Susan Owens <lwo@iadfw.net>

Gluten encephalopathies

- Expanding spectrum of “celiac” disease (161-164)
- “Celiac” disease & bacteria (165-167)
- Wheat, gluten hypersensitivities (168-171)
- Gluten sensitivity & neurological illnesses (169,172-176)
- Immune aspects of gluten insensitivity (eg. 177-179)
- Enzymes & enzyme-antibodies (eg, 180-181)

Gluten encephalopathies

- Headache and CNS white matter abnormalities associated with gluten sensitivity
 - (174)
- Schizophrenic symptoms and SPECT abnormalities in a coeliac patient: regression after a gluten-free diet.
 - (175)
- Frontal cortical perfusion abnormalities related to gluten intake and associated autoimmune disease in adult coeliac disease
 - (176)
 - ***In all three studies, gluten-free diet was helpful***
- Remember ARI's Parent Ratings of dietary interventions

Chelation

- TTFD
- DMSA (166-174)

- DMPS?
- Other? (137)

Chelation principle

Generally, chelation is initiated only after healing the gut and optimizing nutritional status as much as possible and is carefully monitored by appropriate lab tests.

Chelation - TTFD

- Treatment of autism spectrum children with thiamine tetrahydrofurfuryl disulfide: a pilot study
- Conclusion: Thiamine tetrahydrofurfuryl disulfide appears to have a beneficial clinical effect on some autistic children, since 8 of the 10 children improved clinically.
 - [arsenic was chelated, also cadmium & lead]
 - (182; informative abstract)

Chelation efficacy - DMSA

- Chelation efficacy study
 - (163, informative abstract)
- Chelation PPT summary online
 - (184)
- Excellent DAN! PPT Presentations online
 - (185)
- Pediatric chelation miscellany
 - (eg, 186-194)

An Evaluation of the Relationship between Thimerosal, Childhood Developmental Disorders and Biological Markers for Mercury Susceptibility

J. J. Bradstreet, M.D.

David A. Geier, B.A.

Harold H. Harrison, M.D., Ph.D.

Jerrold J. Kartzinel, M.D.

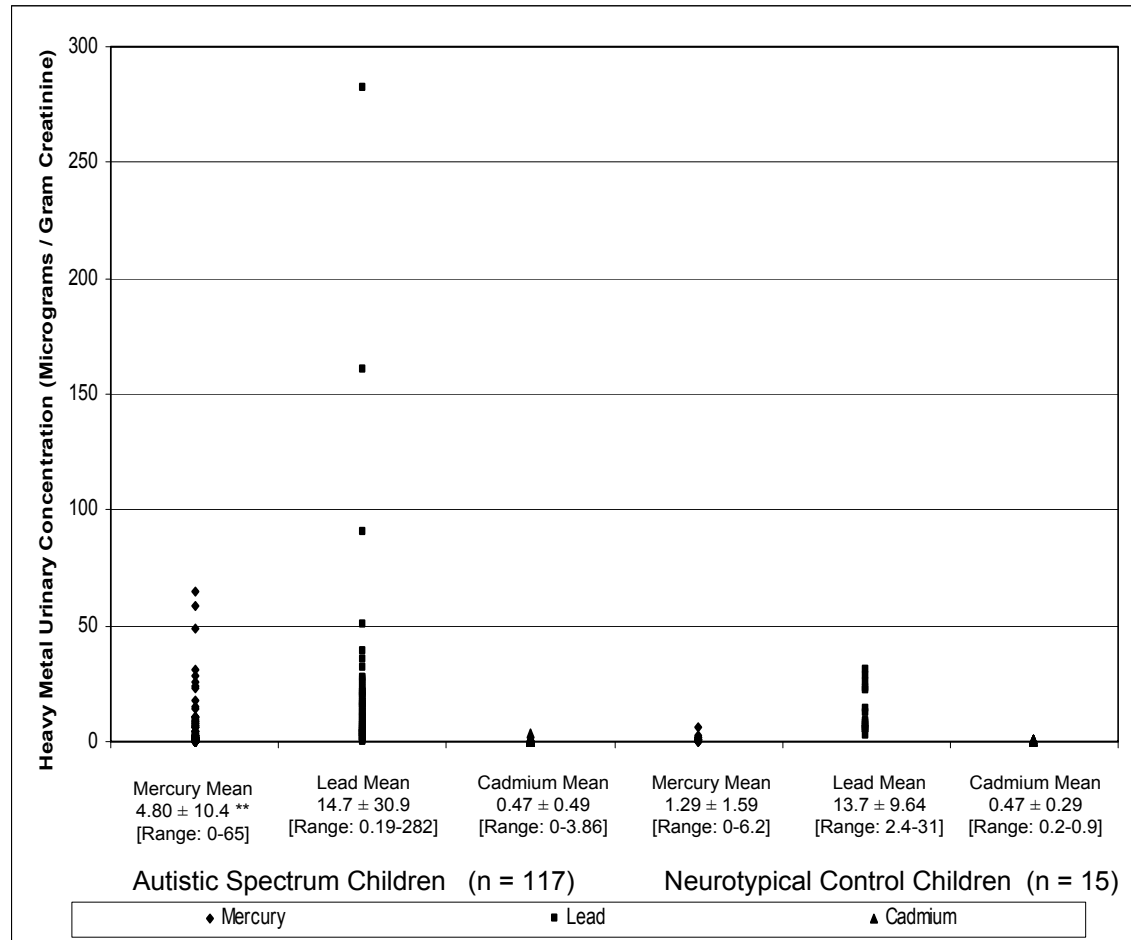
Alan D. Clark, M.D.

Mark R. Geier, M.D., Ph.D

[submitted for publication]

[data & summary presented DAN! 2004 LA]

Figure 2. A summary of the urinary heavy metal concentrations after DMSA provocation for cases and controls (control group I)



All p-values determined using the t-test statistic
 ** Relative Increase = 3.72 (P < 0.002)

Bradstreet et al – DMSA comparisons

- Autistic Spectrum Children (n = 117)
 - Mercury Mean
 - 4.80 ± 10.4 **
 - [Range: 0-65]

- Neurotypical Control Children (n = 15)
 - Mercury Mean
 - 1.29 ± 1.59
 - [Range: 0-6.2]

MTHFR weak-allele frequencies

- For the homozygous MTHFR 677TT genotype in our population with ASD, we found a 0.23 frequency, whereas it was 0.11 in our control population [~ 2 -fold statistically significant ($P < 0.002$) increase in frequency in ASD compared to controls (OR = 2.1, 95% OR CI = 1.4-3.1)]
 - ...the MTR 2756GG homozygous genotype frequency was 0.62 in our population with ASD, whereas the frequency was 0.10 in the control population [~ 6 -fold statistically significant ($P < 0.0001$) increase compared to controls (OR = 6.1, 95% OR CI = 3.0-12)]
- Bradstreet et al *ibid*

antivirals, other advanced testing

- Jaquelyn McCandless, MD & Sid Baker, MD, are among the DAN!-oriented physicians who have reported that appx 25-33% of their autistic patients respond positively to acyclovir or Valtrex. A few such responses have been dramatic.

antivirals

- HSV in autism literature (eg, 195-198)
- CMV... (eg, 199-200, see 201 re: Rasmussen's)
- EBV... (eg, 202-203)
- HHV6... (eg, 74-75, 77)

Miscellany

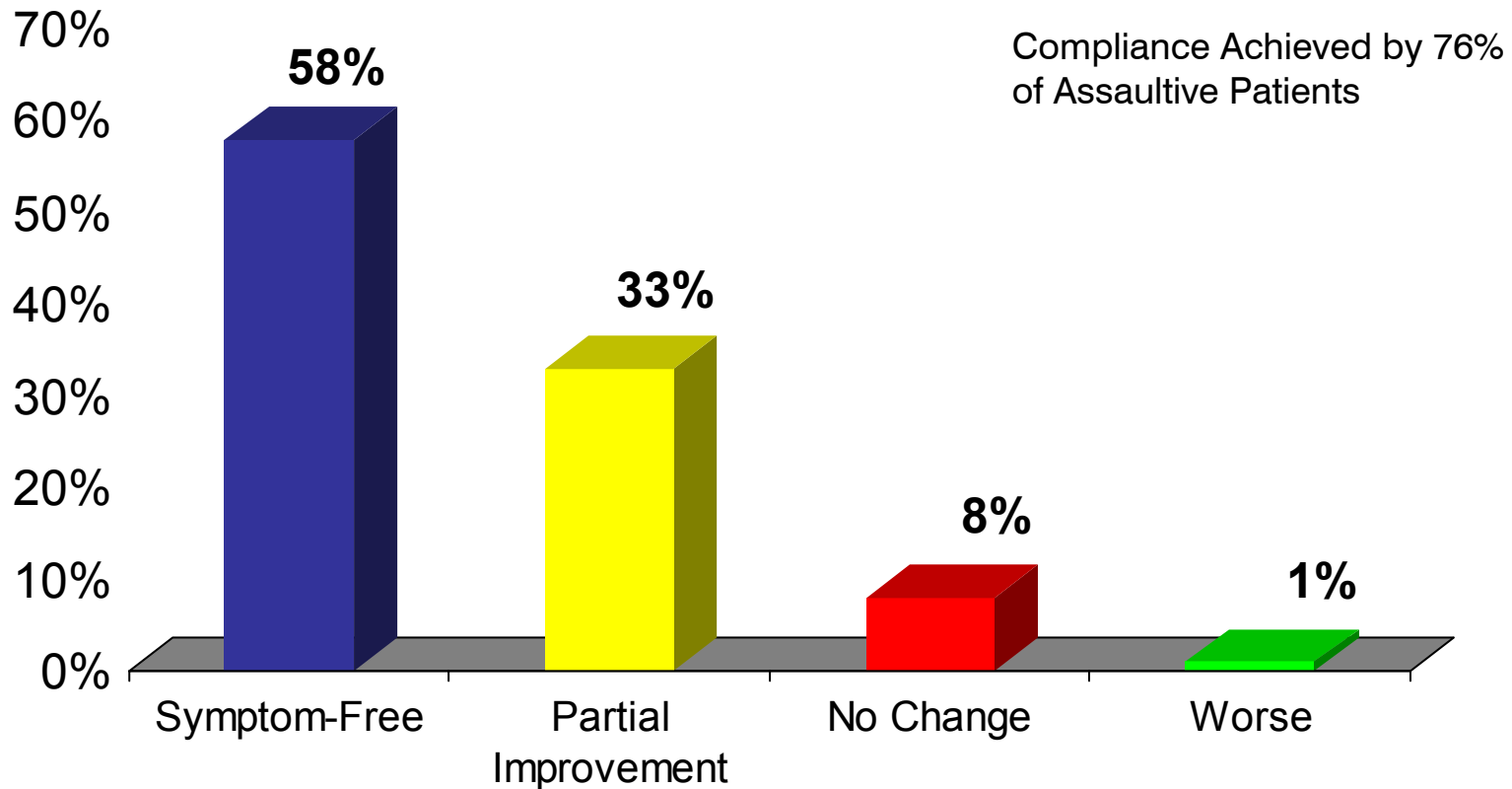
- Immune impairments in autism
 - (214-224)
- Methylcobalamin miscellany
 - (225-239)
 - A prior DAN! conference proceedings has excellent summary with cites, by Jim Neubrandner, M.D.
 - M.I.N.D. Institute is launching a mB12 study

Nutrition reduces violence

- Reduced violent behavior following biochemical therapy
 - Walsh WJ et al.
 - Pfeiffer Treatment Center
 - Physiol Behav. 2004 Oct 15;82(5):835-9
 - We conducted an outcome study to measure the effectiveness of biochemical therapy for 207 consecutive patients presenting with a diagnosed behavior disorder.
 - (240)

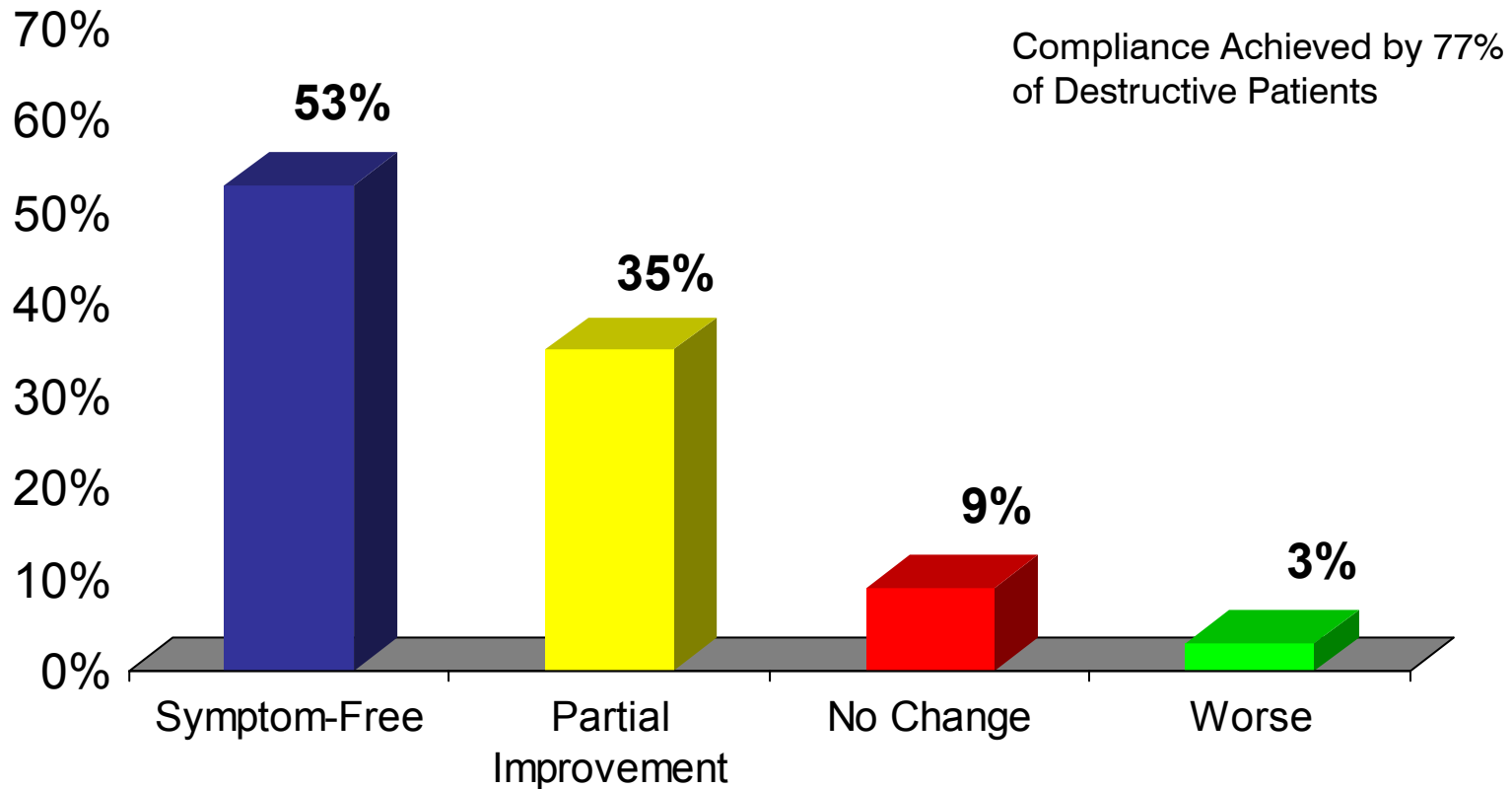
Assaultive Population

Nutrient Therapy Outcomes
For Compliant Patients (N = 105)



Destructive Population

Nutrient Therapy Outcomes
For Compliant Patients (N = 112)



Epileptiform patterns in autism

- A range of epileptiform and seizure activity, from irregular EEGs during sleep to severe seizures
 - (eg, 241-246)
- Frontiers include Vagal Nerve Stimulation and, perhaps in mild cases, improvements as nutritional status is optimized
 - (eg, 247-252)
- And always a caveat: be watchful
 - (eg, 253)

ATEC: Autism Treatment Evaluation Checklist

- by Autism Research Institute (ARI)

- ATEC assists parents, physicians and researchers to evaluate virtually any treatment for autism.
 - Convenient, no-cost Internet scoring procedure that calculates four subscale scores and a total score from the ATEC.
 - Scores are weighted according to the response and the corresponding subscale. The higher the subscale and total scores, the more impaired the subject.
 - Helpful for evaluating a child's treatment efficacy.
- <http://www.autismeval.com/ari-atec/index.html>