CADY

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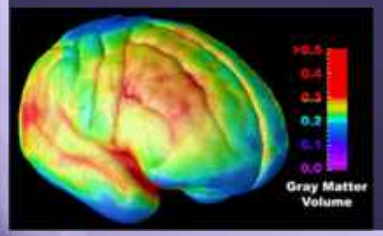
Integrating Mind and Body for Peak Performance



www.cadywellness.com

ADD, Autism, Depression, Schizophrenia and Neuroinflammation: The Moral Imperative of Integrative Medicine

Louis B. Cady, MD, FAPA

CEO, Founder – Cady Wellness Institute

Presented for A4M/MMI

September 11, 2020

I, Louis Cady MD, have the following current and historical conflicts to declare….

- Speaker honoraria previously received from:
  - Immunolaboratories, Great Plains Diagnostic Labs, LABRIX, National Procedures Institute

- Speaker's bureaus (active) for:
  - Takeda/Lundbeck

- **Historical data** – speaker's bureau for Allergan (Aventis), Arbor, Bristol-Myers Squibb, Celltech, Cephalon, Eli Lilly, Glaxo-Smith Kline, Janssen, McNeil, NEOS, Pfizer-Roerig, Sanofi~aventis, Searle, Sepracor, Shionogi, Shire, Sunovion, Takeda, Vaya Pharma, Wyeth-Ayerst

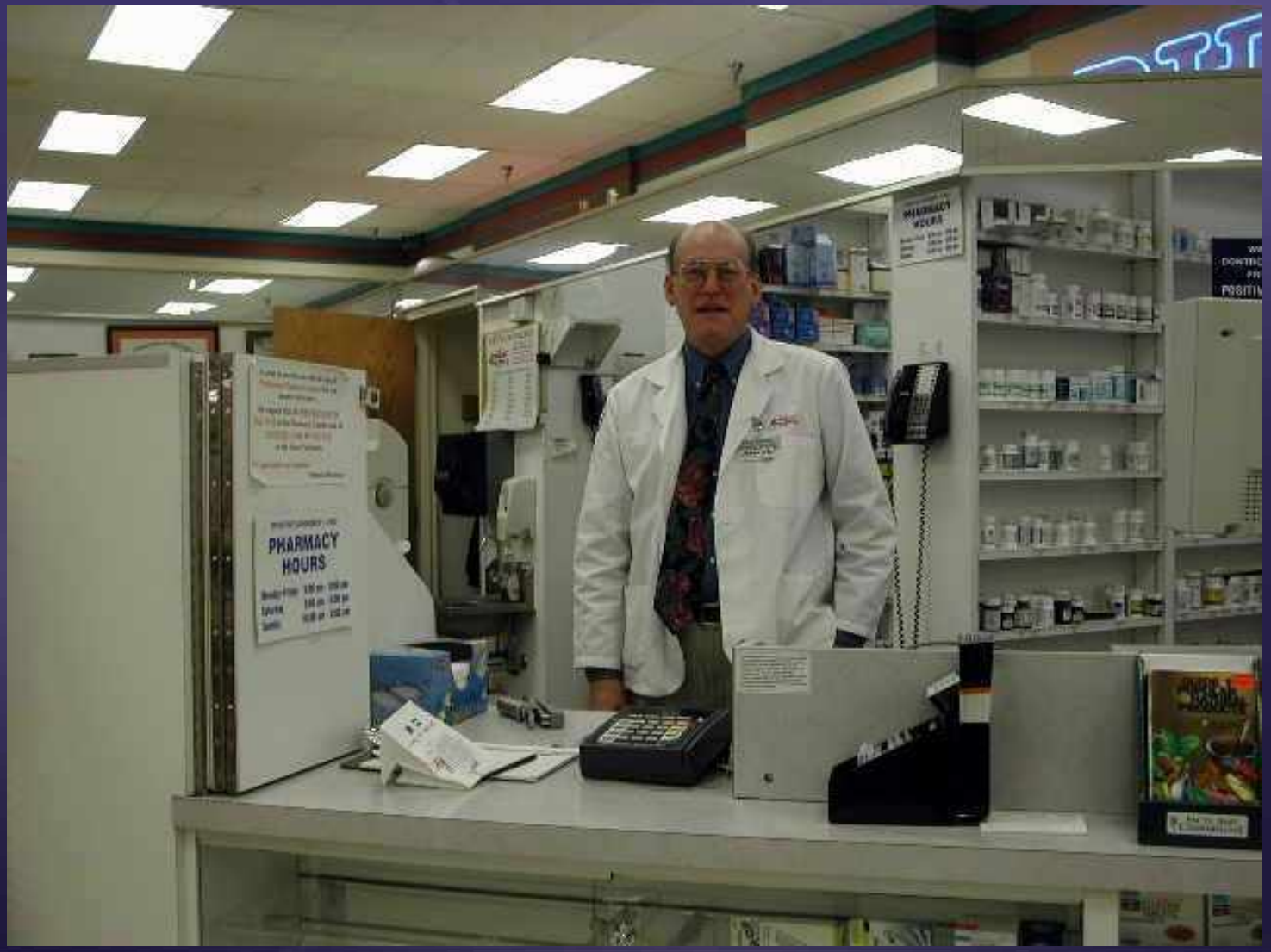
- Distributor – Pharmanex supplements & Biophotonic scanner

Nothing that touches on any of these companies will be presented

"The beginning of wisdom is the definition of terms." Socrates

- Moral [mores (L) = HABITS]:
  - "a person's standards of behavior or beliefs concerning what is and is not acceptable for them to do."
- Imperative:
  - "of vital importance; crucial." "An essential or urgent thing."
- Integrative:
  - "serving or intending to unify separate things."
- Medicine:
  - "the science or practice of the **diagnosis, treatment, and prevention** of disease."

Orientation: Slide 1
My Previous Notion of Therapeutic Options



Orientation: slide 2

- Can't possibly cover in-depth description of these mental disorders
- Limited time today to evaluate clinical cases and review the literature, (which is stupendously rich.)
- Foci:
  - What is technically & scientifically relevant
  - Of these, what is CLINICALLY relevant
- This presentation will alternate between a) clinical cases, b) topically relevant nutraceutical interventions, c) theory
- **Mechanisms of inflammation, and mitigating strategies, will be grouped together for ease of presentation.** These mechanisms of inflammation are documented or seen in all four of the psychiatric conditions in the title.

Orientation: slide 3

- This presentation will be rigorously clinical.
- I am a clinician, not a lab researcher.
- Not every intervention for every condition named (and its neuroinflammation will be covered under each disease entity.

Literature review – www.pubmed.gov August 8, 2020

	ADHD	Autism	Depression	Schizophrenia	Other brain diseases
Neuroinflammation	29	317	1,232	354	
Neuroinflammation, Omega 3 fatty acid	**4**	5	29	1	179 **(aggregate)**
MTHFR Neuroinflammation					1
Lithium neuroinflammation	0	1	12	1	80
Oxidative stress + neuroinflammation	11	63	197	47	
B-vitamin neuroinflammation	0	1	1	0	3
Probiotic + neuroinflammation	0	2	12	0	74!
Magnesium Neuroinflammation	0	1	2	1	26

Orientation: slide 4

"Tell me the facts and I'll learn.

Tell me the truth and I'll believe.

But tell me a story and it will live in my heart forever."

- Native American Proverb

My experience with a child with out of control "ADHD" - the story of Billy

- 8/1998 – 4 year old Eastern European adopted child – "ADD & behavioral problems, destructive."
  - First 3 years of life in orphanage
- Fam Psych Hx:
  - Dad – "substance induced paranoid psychosis"
  - Mother – "recurrent schizophrenic decompensations"

PATIENT NAME: _____ DATE: _____

Medication status: ( ) pre-treatment? ( ) on Rx? ( ) OFF of Rx?

PATIENT STATUS: CHILD

Check off the symptoms which are unusually troublesome for your child (or YOU, if you are an adult patient) which are clearly different from what other children or adults typically experience. PLEASE USE THE BACK SIDE OF THIS FORM TO AMPLIFY ON ANY OF THE "CHECKED" SYMPTOMS WHICH YOU FEEL I SHOULD KNOW MORE ABOUT.

ATTENTION PROBLEMS

- ☐ displays failure to give close attention to details; makes careless mistakes
- ☐ has difficulty with sustained attention
- ☐ doesn't listen even when spoken to directly
- ☐ has ***REAL trouble*** following through on instructions; fails to finish tasks
- ☐ difficulty organizing tasks/activities
- ☐ avoids, dislikes, or reluctant to engage in tasks requiring sustained mental effort (homework, work projects, etc.)
- ☐ loses things necessary for tasks/activities
- ☐ easily distracted by extraneous stimuli (sounds or sights in the environment)
- ☐ often forgetful in daily activities

HYPERACTIVITY, "WIGGLESOMENESS" PROBLEMS

- ☐ fidgets with hands or feet, squirms in seat
- ☐ leaves seat in classroom in which remaining in seat was expected, or can't stay put at work
- ☐ runs about; climbs excessively in inappropriate situations
- ☐ difficulty playing or engaging in leisure activities quietly
- ☐ often was "on the go" as if "driven by a motor"
- ☐ talks excessively - a "chatterbox"

PROBLEMS BEING IMPULSIVE

- ☐ blurts out answers before questions are completed
- ☐ difficulty waiting your turn
- ☐ interrupts or intrudes on others (butts into conversations)

For physician use only -
RECENT CLINICAL HISTORY:

PARENTS: Please feel in your child's CURRENT DRUG THERAPY... PLEASE LIST!

medication TAKEN	size of dose	WHEN

physician use...

ADHD Diagnostic Symptom Checklist, adapted from DSM-IV, by:
Louis B. Cady, M.D. - 611 Harriet Street - Suite 304 - Doctors Plaza
Evansville, IN 47710 ***www.drcady.com***

ADHD Diagnosis - DSM-IV or 5

- Symptoms present before age 7 years (12 years in DSM 5)
- Impairment from symptoms present in 2 or more settings
- Significant social, academic, or occupational impairment
- Exclude other mental disorders

Billy, cont.

- Some improvement
- 3/1999 – increasingly vile temper. Sad, dysphoric. "Back to square one."
  - Zoloft added.
  - Ritalin only lasting 1 ½ hours
- 5/1999 - 4 ½ yoa. Rehab Center testing:
  - Auditory comprehension = 2 y 11 mo's
  - Total language = 2 y 11 mo's
- 6/1999 – Flaxseed oil, L-tyrosine, Pediactive tabs added. In constant trouble ***Dad getting depressed.***

Billy, cont – 1999 - 2000

- methylphenidate and then amphetamine not working
- Temper to the point of clawing at his face. Sniffing. Now urinating in bed.
- 12/1999 – started on risperidone – 1mg in a.m. and ½ mg later in day
- 2/2000 – Psych testing – IQ 78
  - ADHD
  - Borderline intelligence
  - Processing problems
  - “r/o childhood psychosis”

Billy, late 2000

- Fall 2000:
  - Bit ***and*** stabbed his teacher with a pencil, kicked chair, wall, and desk, spat on floor and teacher. Obsessively lining up his cars in his room, tongue thrusting and smacking (? Tardive dyskinesia?)
- On risperidone, sodium valproate (VPA), and Oros-methylpheniate.
- 8/2001 – 2002 some better but still unpredictable. Meltdowns. Depakote increased. Olanzapine added.
- 8/2002 – throwing things against windows. VPA not working. Mood cycling.

Billy, 2003

- Ongoing unpredictability until Geodon started.
  - Less hyper
  - Dry in a.m.
  - Clearer speech and better eye contact.
- July 2003 – IgG food allergy testing ordered

Billy – IgG Food Sensitivities July 2003

- 21 + IgG reactions.. Of these…..
  - Cheese (3+)
  - Cow's milk (3+)
  - Goat's milk (2+)
  - Brewer's yeast (3+)
  - Millet (+1)
  - Lettuce (!) (+1)

Reviewed labs with internet savvy Mom (who did NOTHING).

June 7, 2004 – 6 years of tx; ONE YEAR AFTER IgG Testing!

- "Literally bouncing off the walls in the a.m."
- Almost knocked brother off second floor balcony
- Could not tolerate < 2 g VPA
- Threw stool over banister and tried to hit Mom on way up stairs. (Missed)
- Told Mom: "You're going to die, I'm going to make sure you're going to die."
- Things that make him angry: not putting peanut butter sandwich on plate "correctly."
- Waking up screaming. Making non-human, guttural sounds.
- Parents pursuing IP treatment

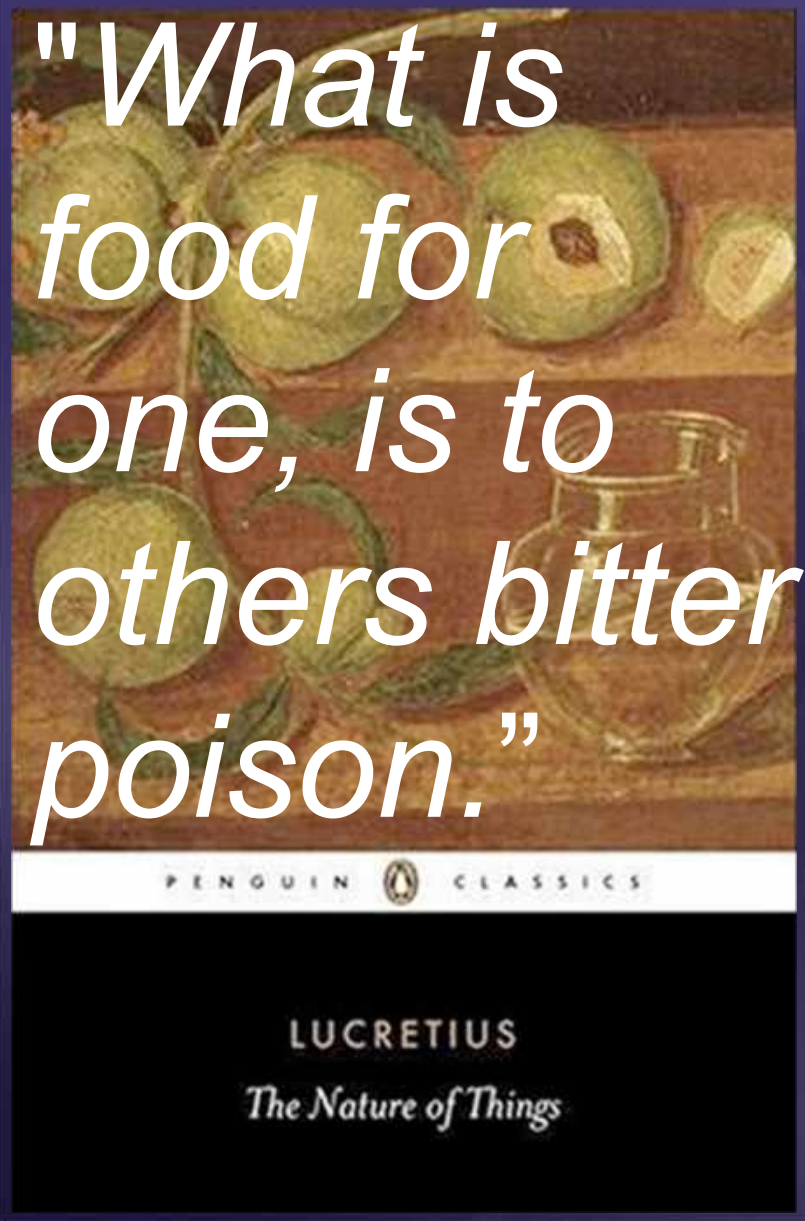
Radical interventions/ workup

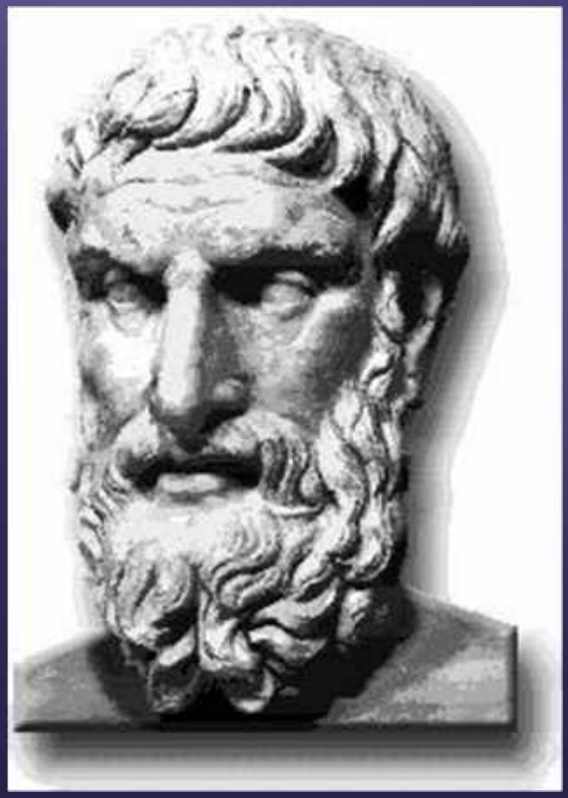
- June 2004 – Lithium added
  - Made him briefly toxic but symptoms improved.
  - Worked on getting him inpatient tx.
- Fatty acid panel ordered.
- **Told Mom to GET SERIOUS about food allergies/sensitivities**

IMMUNOLOGY

The forgotten component of "workups"

"*What is food for one, is to others bitter poison.*"





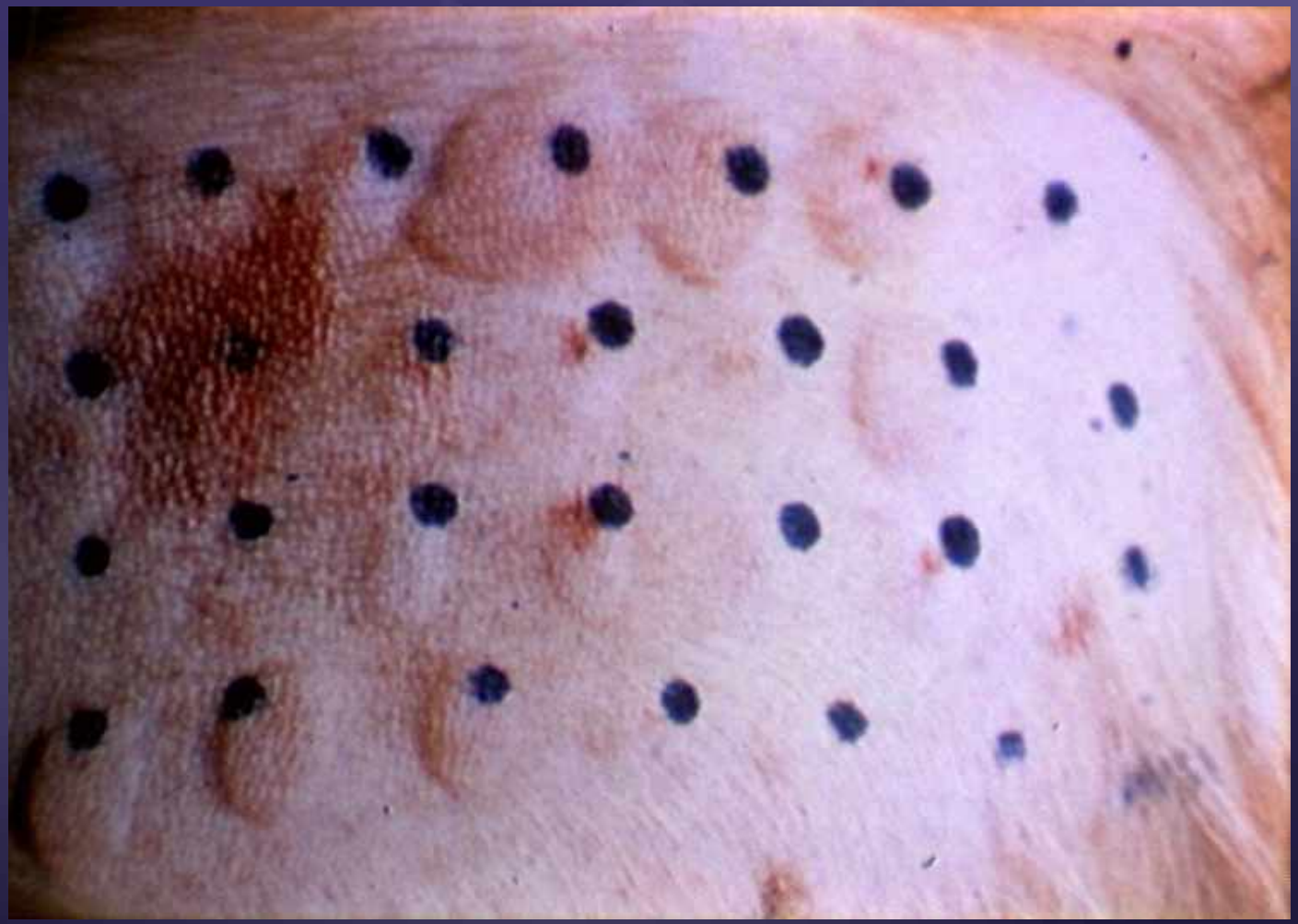
Lucretius – 099? B.C. – 055? A.D.

De rerum natura.

"The Three Little Ig's & Three Stories"

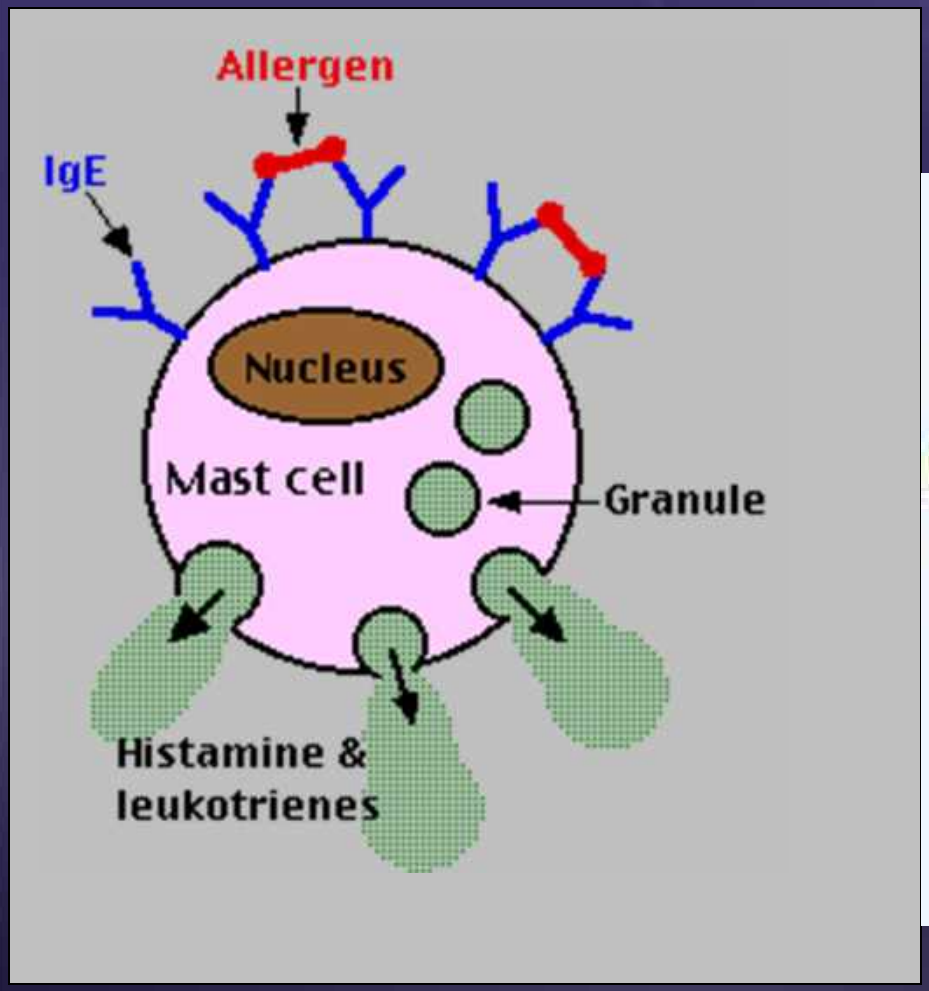
- Ig E xciting
- Ig G oing along
- Ig Norant

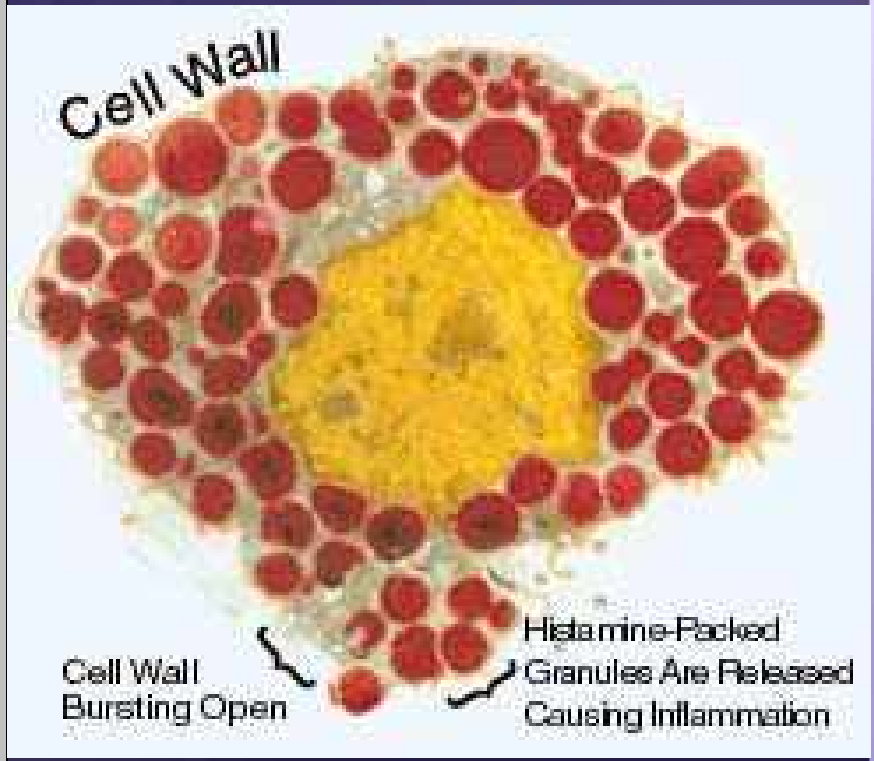
IgE Antibodies: catastrophic reactions vs. sneezes and itching (checked via skin tests or RAST)



http://pathmicro.med.sc.edu/ghaffar/skintest.jpg

CELLULAR immunity

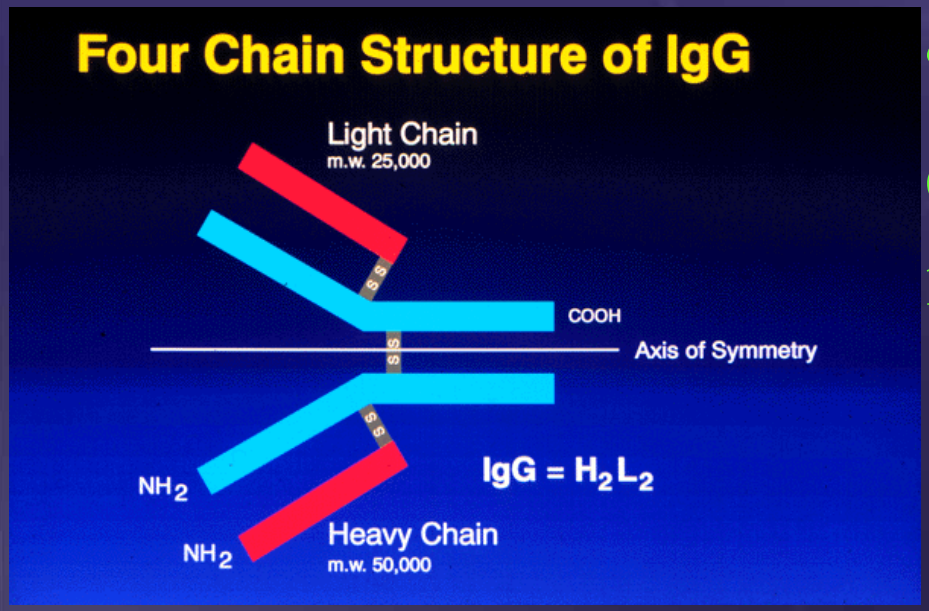




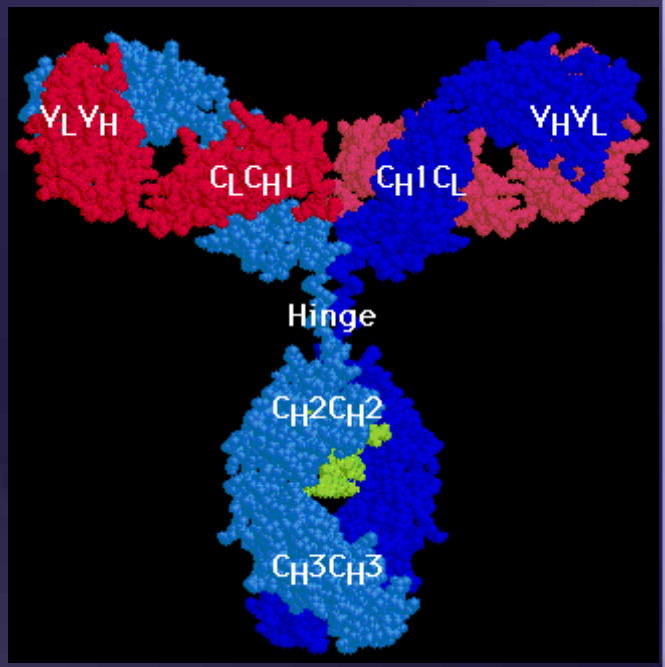
http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/M/MastCell.gif

www.souzaoenterprises.com/Allergiescomp.jpg

HUMORAL Immunity - IgG



"Globulin molecules capable of attacking the invading agent." [Guyton]



This model of human IgG1 was created by E. A. Padlan -- "Anatomy of the Antibody Molecule." *Molecular Immunology 31*:169 (1994)

Actions and downstream effects

- Direct action of antibodies:
  - **Agglutination**, **precipitation**, neutralization, lysis
- Downstream effects: **complement activation:**
  - Lysis, opsonization/phagocytosis, **chemotaxis**, **agglutination**, neutralization of viruses, **INFLAMMATORY EFFECTS**

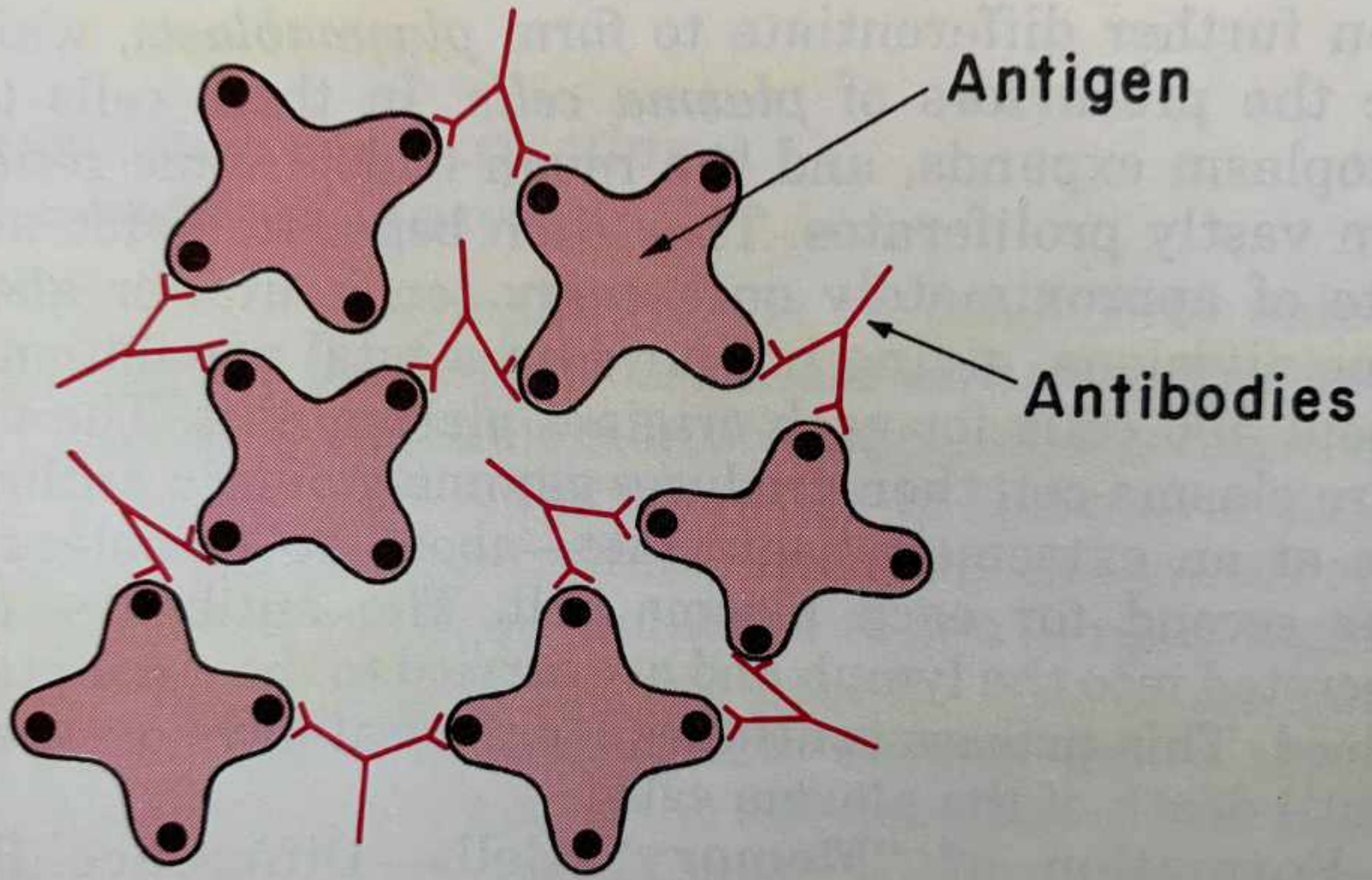
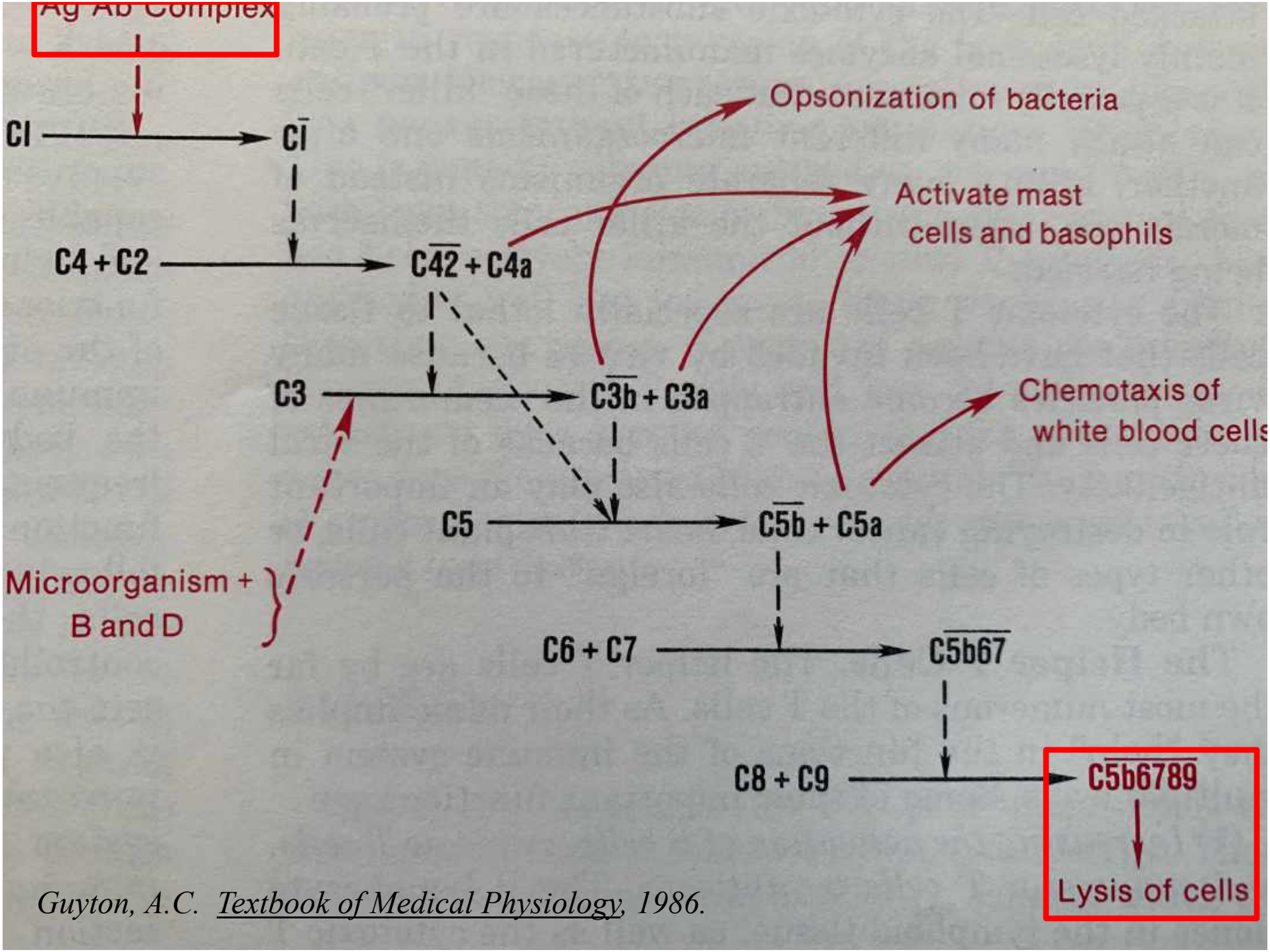


Figure 6–4. Binding of antigen molecules to each other by bivalent antibodies.

Guyton, A.C. Textbook of Medical Physiology, 1986.



Guyton, A.C. Textbook of Medical Physiology, 1986.

Downstream effects of complement

- Causes **secondary** brain injury and neuronal cell death by Membrane attack complex (MAC/C5b-9) in TBI.
  - Parry J et al. Eur J Trauma Emerg Surg. 2020 May 25.
- SC5b-9 found in 19/19 Guillain-Barré patients
  - 5/6 patients with chronic recurrent polyneuritis.
  - The more admissions, the higher the concentration at the 3rd – 5th day of admission.
    - Koski CL et al. J Clin Invest. 1987 Nov;80(5):1492-7.
- Inc. concentration of complement components C3a and C5a suggest involvement of the complement cascade om the pathogenesis of bipolar disorder.
  - Regina A et al. Assessment of complement cascade components in patients with bipolar disorder. Front Psychiatry. 2018 Nov 27;9:614.

Inflammation in ADHD

- The following were noted:
  - Above-chance comorbidity of ADHD with inflammatory and autoimmune disorders.
  - Association between ADHD and serum cytokines
  - Polymorphisms in genes assoc with inflammation seen in ADHD.
  - Early life exposure to environmental factors may raise risk for ADHD via an inflammatory mechanism
  - Animal studies using maternal immune activation documentation behavioral and neural outcomes c/w ADHD.

Dunn GA et al. Neuroinflammation as a risk factor for attention deficit hyperactivity disorder. Pharmacol Biochem Behav. 2019 Jul;182:22-34.

Role of systemic Inflammation on the brain: borrowing from Alzheimer's Disease literature

- "Human and animal studies suggest that inflammation occurring outside the central nervous system (systemic inflammation) may play a key role in promoting neurodegeneration, Alzheimer's disease pathology, and cognitive decline in older adults."
- Proinflammatory cytokines promote a proinflammatory environment in CND by **crossing the blood-brain barrier**, signaling through endothelial cells."

Walker KA et al. ACS Chem Neurosci. 2019 Aug 21;10(8):3340-3342,

Food Allergies and ADHD in the Literature

- Food allergies presumed to be related to ADHD
- Before 1976 – No known relationship between FA and ADD
- **1976** – IgE reactivity + food allergies = decreased IQ
- 1985 – d/c of antigenic foods = ADHD improvement
- 1993 – more confirmation
- 1994 – some kids that got better on diet did NOT have IgE reactivity
- 2003 – evidence mounting for non-IgE sensitivities related to food allergies]
- 2002 – 2011 Pelsser LM et al – **SIX** published papers (European and Dutch literature, cf: www.pubmed.gov).
- **66 papers – 8/19/2011**
- **82 papers – 8/30/2015**
- **107 papers 8/9/2020**

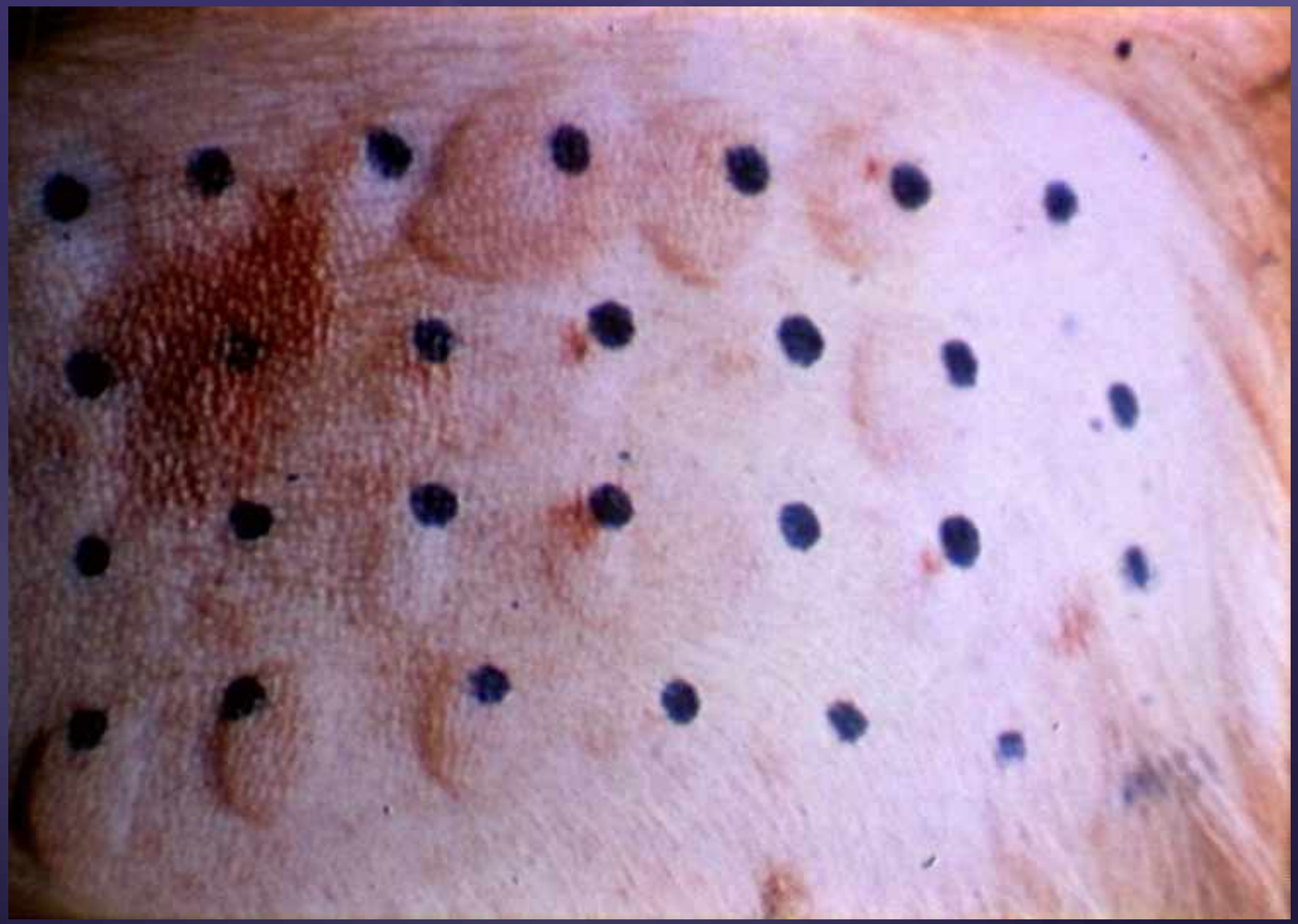
Millman, et al – the groundbreaking article

- "Allergy & Learning Disabilities in Children" – Annals of Allergy, 1976 [36:3, 149-160.]
- "The allergic tension-fatigue syndrome observed by Speer"
  - "***A symptom complex accepted by many allergists***."
- Food allergies established by scratch testing or intradermal injections
- Positive correlation between [IgE] food allergies and IQ scores.
  - ***The more the food allergies, the lower the IQ scores.***

The crossover study – no distinguishing between IgE and IgG

- "Effects of a few foods diet on ADD." Carter et al, Archives of Disease in Childhood, 1993;69:564-568.
- "Few foods" elimination diet
  - **59 of 78 children improved.**
- "This trial indicates that diet can contribute to behavior disorders in children and that this effect can be shown in a double blind, placebo controlled trial."
- "The ways in which [this] diet worked remain unclear. Toxic pharmacological, or allergic mechanisms could be involved, and the physiological effects of different foods may vary."

Review: this is IgE reaction… but it is NOT IgG



Oligoantigenic diet (w/o testing) – 2 studies

- "Controlled trial of oligoantigenic treatment in the Hyperkinetic Syndrome."
  - No testing performed
  - Children empirically placed on restrictive diet.
    - Two meats, two carb sources, two fruits, one vegetable, water, calcium, vitamins.
  - No food allergy symptoms were provoked; **ADHD improved.**
    - Egger et al. Lancet, March 9, 1985, 540-545.
- **"Does oligoantigenic diet influence hyperactive/conduct-disordered children – a controlled trial"**
  - ***Cross-over, placebo controlled, double blind*** **design to asses this in 49 children. No FA testing performed.**
    - **24% of children improved on diet change alone**
    - **44% of children improved on methylphenidate.**
- **"Dietary treatment cannot be neglected as a possible access to treating hyperactive/disruptive children and merits further investigation."**
  - **Schmidt MH et al. Eur Child Adolesc Psychiatry. 1097 June;6(2):88-95.**

Profound cautions

- "Effects of a few foods diet on ADD." Carter et al, Archives of Disease in Childhood, 1993;69:564-568 (cont.)
- "The treatment, as applied in this study, has disadvantages**. It is a difficult and exacting regimen, which puts a considerable strain on the whole family**. It is not yet clear whether modified diets can also be effective…. It may therefore be possible to devise a less restricted diet with similar levels of success."

- Cady impression: "Shooting in the dark is dangerous."

The appearance of IgG

- "Foods and additives are common causes of ADHD in children." Boris, et. al. Annals of Allergy, vol.. 72, 1994, 462-468.
- "DBPCF" - "double blind placebo controlled food challenge test"
- 4/19 children who showed improvement with removal of offending foods were non-atopic.

25% - NOT having IgE reactions

"IgE and Non IgE Food Allergy"

- Sabra, et al. Annals of Allergy, Asthma, and Immunology 2003;90 (Suppl 3)71-76.
- "The **gastrointestinal tract** serves not only a nutritive function but also is a major immunologic organ. Although previously thought to be triggered primarily by an IgE mediated mechanism of injury, **considerable evidence now suggests that non-IgE mechanisms may also be involved in the pathogenesis of FA ("food allergy").**

"Don't think either/or; think both/and."- Dan Burrus

- The most common food allergy in children is cow's milk protein allergy (IgE).
  - 49 children with symptoms suggesting cow's milk allergy were included (n=47).
  - All had
    - skin allergy (IgE) testing – only 2 children were +
    - Lymphocyte transformation test – 8 children +
- Conclusions:
  - IgE and LTT are not reliable tools for "establishing diagnosis"
  - "We conclude that a significant improvement in clinical symptoms can only be achieved with a strict elimination diet."
    - Lendvai-Emmert D et al. Orv. Hetil. 2019 Aug; 160(33):1311-1318.

> Front Cell Neurosci. 2019 Jul 16;13:320. doi: 10.3389/fncel.2019.00320. eCollection 2019.

Astrogliosis Associated With Behavioral Abnormality in a Non-anaphylactic Mouse Model of Cow's Milk Allergy

Nicholas A Smith [1], Danielle L Germundson [1], Colin K Combs [2], Lane P Vendsel [1], Kumi Nagamoto-Combs [1]

Affiliations + expand

PMID: 31379506 PMCID: PMC6646667 DOI: 10.3389/fncel.2019.00320

Free PMC article

Abstract

Etiology of neuropsychiatric disorders is complex, involving multiple factors that can affect the type and severity of symptoms. Although precise causes are far from being identified, allergy or other forms of hypersensitivity to dietary ingredients have been implicated in triggering or worsening of behavioral and emotional symptoms, especially in patients suffering from depression, anxiety, attention-deficit hyperactivity, and/or autism. Among such ingredients, cow's milk, along with wheat gluten, is commonly suspected. However, the contributory role of cow's milk in these disorders has not been elucidated due to insufficient pathophysiological evidence. In the present study, we therefore investigated neuroinflammatory changes that are associated with behavioral abnormality using a non-anaphylactic mouse model of cow's milk allergy (CMA). Male and female C57BL/6J mice were subjected to a 5-week oral sensitization procedure without or with a major milk allergen, beta-lactoglobulin (BLG). All mice were then later challenged with BLG, and their anxiety- and depression-associated behaviors were subsequently assessed during the 6th and 7th weeks. We found that BLG-sensitized male mice exhibited significantly increased anxiety- and depression-like behavior, although they did not display anaphylactic reactions when challenged with BLG. Female behavior was not noticeably affected by BLG sensitization. Upon examination of the small intestines, reduced immunoreactivity to occludin was detected in the ileal mucosa of BLG-sensitized mice although the transcriptional expression of this tight-junction protein was not significantly altered when measured by quantitative RT-PCR. On the other hand, the expression of tumor necrosis factor alpha (TNFα) in the ileal mucosa was significantly elevated in BLG-sensitized mice, suggesting the sensitization had resulted in intestinal inflammation. Inflammatory responses were also detected in the brain of BLG-sensitized mice, determined by the hypertrophic morphology of GFAP-immunoreactive astrocytes. These reactive astrocytes were particularly evident near the blood vessels in the midbrain region, resembling the perivascular barrier previously reported by others in experimental autoimmune encephalitis (EAE) mouse models. Interestingly, increased levels of COX-2 and TNFα were also found in this region. Taken together, our results demonstrated that BLG sensitization elicits inflammatory responses in the intestine and brain without overt anaphylactic signs of milk allergy, signifying food allergy as a potential pathogenic factor of neuropsychiatric disorders.

Keywords: anxiety; astrocyte; depression; food allergy; intestine; neuroinflammation; occludin; tumor necrosis factor.

Smith, NA et al. Front Cell Neurosci. 2019 Jul 16;13-320.

Astrogliosis Associated With Behavioral Abnormality in a Non-anaphylactic Mouse Model of Cow's Milk Allergy

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- "Allergy or other forms of hypersensitivity to dietary ingredients have been implicated in triggering or worsening of behavioral & emotional symptoms, especially in patients suffering from depression, anxiety, *attention-deficit hyperactivity*, and/or autism."
- Neuroinflammatory changes assoc with behavioral abnormalities using a non-anaphylactic mouse model of cow's milk allergy.
- BLG (beta lactoglobulin) exposed male mice exhibited significantly increased anxiety and depression-like behavior. (No anaphylactic reactions seen.)
- TNF-alpha elevated in the ileal mucosa.

Inflammatory responses also detected in brain of BLG-sensitize mice, with hypertrophic morphology of GFAP-immunoreactive astrocytes.

Detour: Clinical manifestations of EFAD

- Dermatitis
- Increased appetite and caloric intake in infants (adults?!)
- Failure of wound healing
- **Irritability**
- Alopecia, dry hair, dandruff
- Brittle nails
- **Increased susceptibility of infections**
- Thirst, polydipsia, polyuria
- Liver fatty infiltration
- Increased capillary fragility
- RBC fragility
- Increased Cholesterol/HDL ratio

Essential Fatty Acid findings: Billy

	Value	Reference range
EPA	3 (L)	20 - 80
DHA	32 (L)	70 - 150

Scientific basis for focus on PUFA's

- Brain = most lipid rich organ (50% of dry brain weight)
- Composition:
  - 60% phospholipids
  - DHA (22:6n-3_ is the most abundant (> 40% of all brain PUFA's) in brain membrane phospholipids.

Hsu, M et al. Beneficial effects of omega-3 fatty acid supplementation in schizophrenia" possible mechanisms. Lipids Health Dis. 2020 Jul 3;19(1):159.

The Omega 3 Fatty Acid (+) ADHD (+) Neuroinflammation

- Prevention of cerebral palsy, autism spectrum disorder, and attention deficit-hyperactivity disorder.
  - Strickland AD . Med Hypotheses. 2014 May;82 (5):522-8.
- Can omega-3 fatty acids and tocotrienol-rich vitamin E reduce symptoms of neurodevelopmental disorders?
  - Dumpricht E, Rockway S. Nutrition. 2014 Jul-Aug;30(7-8):733-8.
- Omega 3 polyunsaturated fatty acids through the lifespan: implication of psychopathology
  - Pusceddu MM et al. Int J Neuropsychopharmacol. 2016 Dec 30;19(12):pyv078.
- Neuroinflammation in autism: plausible role of maternal inflammation, dietary Omega 3, and Microbiota
  - Madore C et al. Neural Plasti. 2016:2016:3597209.

PUFA's critical across the life cycle.

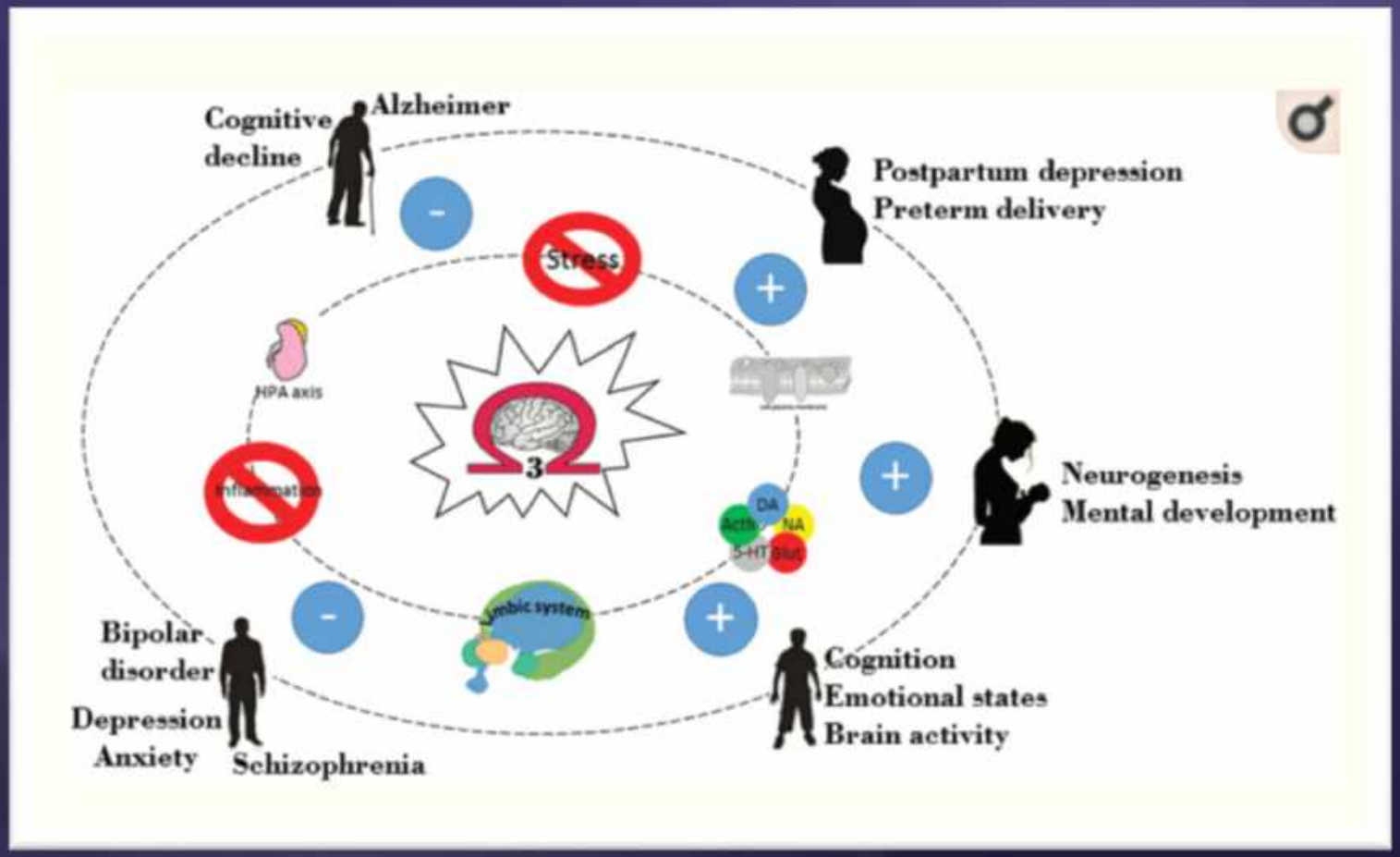

Illustration from: Pusceddu MM et al. N-3 polyunsaturated fatty acoids through the lifespan: implication for psychopathology. Int J Neurospcyhopharmacol. 2016 Dec; 19(112):pyw078

The American Journal of
CLINICAL NUTRITION

Essential fatty acid metabolism in boys with attention-deficit hyperactivity disorder.

L J Stevens, S S Zentall, J L Deck, M L Abate, B A Watkins, S R Lipp, and

This Article
Am J Clin Nutr October 1995 vol. 62 no. 4 761-768

» Abstract *Free*
Full Text (PDF) *Free*

- The present study found that 53 subjects with ADHD had significantly lower concentrations of key fatty acids in the plasma polar lipids (20:4n-6, 20:5n-3, and 22:6n-3) and in red blood cell total lipids (20:4n-6 and 22:4n-6) than did the 43 control subjects
- "…but the precise reason for lower fatty acid concentrations in some children with ADHD is not clear."

of 20:4n-6 and 22:6n-3 than did 32 subjects with ADHD with few EFA-deficiency symptoms. The data are discussed with respect to cause, but the precise reason for lower fatty acid concentrations in some children with ADHD is not clear.

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Neuroscience & Biobehavioral Reviews

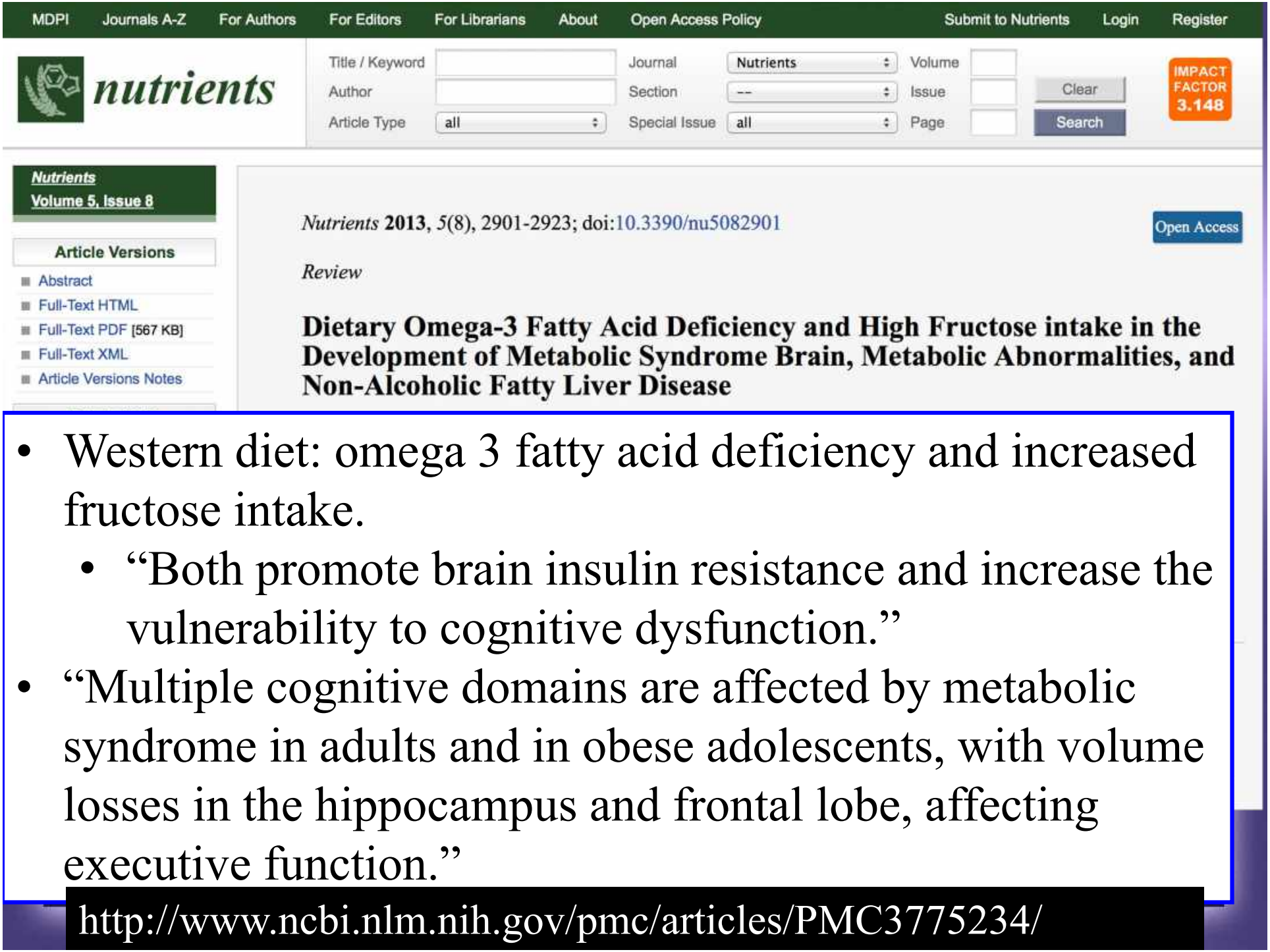
Volume 45, September 2014, Pages 369–378

Review

Food for thought: Dietary changes in essential fatty acid ratios and the increase in autism spectrum disorders

Kim van Elst[a], Hilgo Bruining[a, b], Barbara Birtoli[c], Christian Terreaux[c], Jan K. Buitelaar[d], Martien J. Kas[a],

- "We argue that a change in the ratio of n-6/n-3, especially during early life, may induce developmental changes in brain connectivity, synaptogenesis, cognition and behavior that are directly related to ASD."



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  - "Both promote brain insulin resistance and increase the vulnerability to cognitive dysfunction."
- "Multiple cognitive domains are affected by metabolic syndrome in adults and in obese adolescents, with volume losses in the hippocampus and frontal lobe, affecting executive function."

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3775234/

Another problem: omega 6: omega 3 ratio

- Data merged from:
  - two cross-sectional studies – 219 children ages 7 – 12
  - One study of 133 adults 65 – 79 yoa.
    - Lower ratio of omega 6: omega 3 seen in adults with a college degree.
- Conclusion: very few American children met even the lower recommendations for EPA and DHA intake.

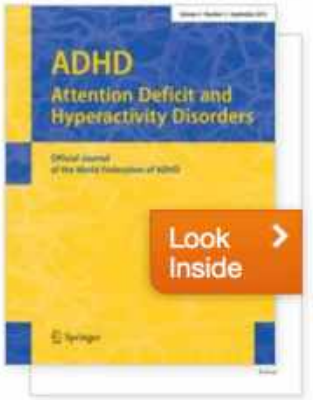
Sheppard KW, Cheatham CL . Omega-6/Omega3 fatty acid intake of children and older adults in the US: dietary intake in comparison to current dietary recommendations and the Health Eating Index. Lipids Health Dis. 2018 Mar 9;17(1):43.

ADHD Attention Deficit and Hyperactivity Disorders
September 2013, Volume 5, Issue 3, pp 303-311

Date: 06 Apr 2013

Altered serum mono- and polyunsaturated fatty acid levels in adults with ADHD

G. Irmisch, J. Richter, J. Thome, A. J. Sheldrick, R. Wandschneider



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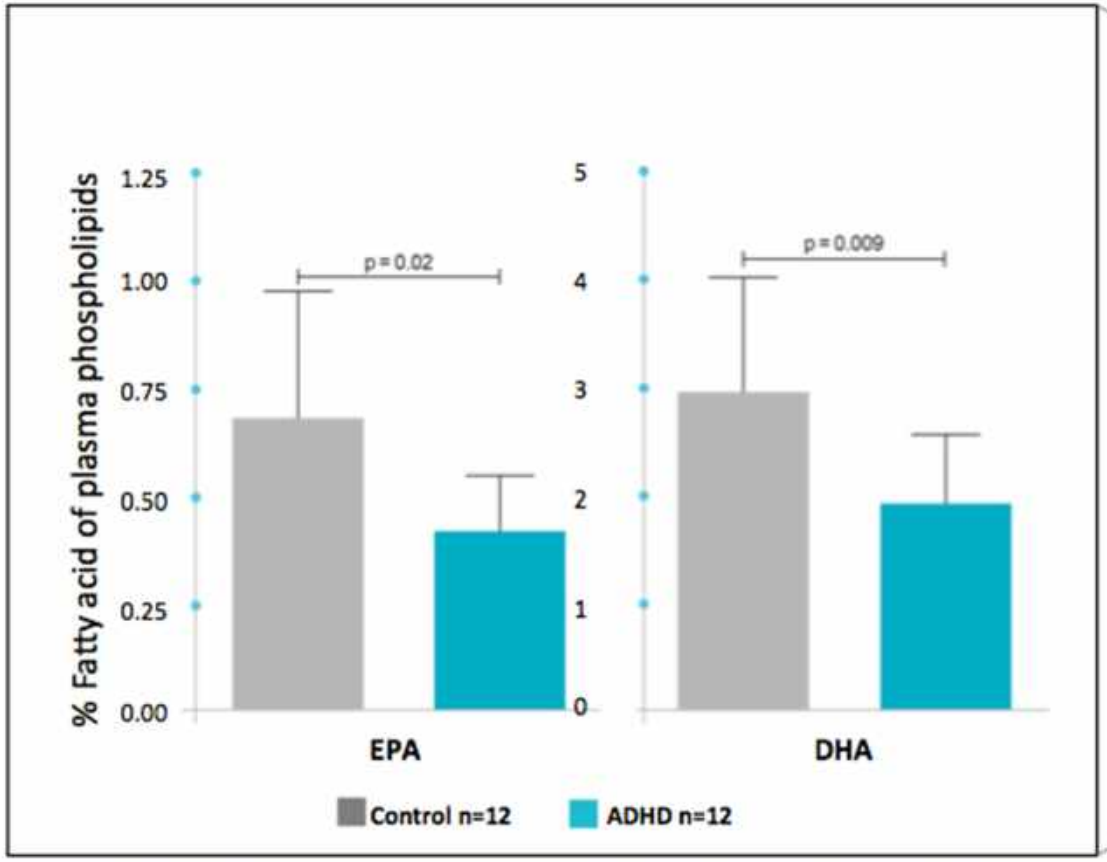
2 Shares

- In Adults with ADHD:
  - DECREASED DHA, AA, and DHGLA
- "We could demonstrate that a lack of polyunsaturated FAs in blood serum of subjects with ADHD persists into adulthood. Furthermore, we could show that adult ADHD symptomatology positively correlates with elevated levels of saturated stearic and monounsaturated FAs HGLA were lower than controls."

symptomatology positively correlates with elevated levels of saturated stearic and monounsaturated FAs.

Reduced Levels of Omega-3 Fatty Acids are Associated with ADHD



Study	Average Age
Mitchell et.al 1987	9
Stevens et.al 1995	9.1
Young et.al 2004	30
Chen et.al 2004	8.5
Antalis et.al 2006	23
Spahis et.al 2008	9
Colter et.al 2008	14
Gow et.al_a 2013	14
Gow et.al_b 2013	14

Antalis et al., Prostaglandins Leukot Essent Fatty Acids, 2006. 75(4-5): p. 299-308.

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Med Hypotheses. 2012 Oct;79(4):456-61. doi: 10.1016/j.mehy.2012.06.021. Epub 2012 Jul 15.

Polyunsaturated fatty acids as putative cognitive enhancers.

Yehuda S.

Author information

Abstract

This summary demonstrates that a deficiency in brain PUFAs will lead to cognitive deficits, while supplementation of PUFAs can rehabilitate cognitive deficits, as manifested in attention deficit hyperactivity disorder, stress/anxiety, and aging.

PUFA's as cognitive enhancers

- Low dose PUFA supplementation study
- French community dwellers aged 70 or over reporting subjective memory complaints; NOT DEMENTED.
- PUFA – 800 mg DHA / 225 mg EPA
- Less cognitive decline over 36 months.

Hooper C et al. Cognitive changes with omega-3 polyunsaturated fatty acids in non-demented older adults with low omega-3 index. J Nutr Health Aging. 2017; 21(9):968-993

PUFA + Methylphenidate (Ritalin)

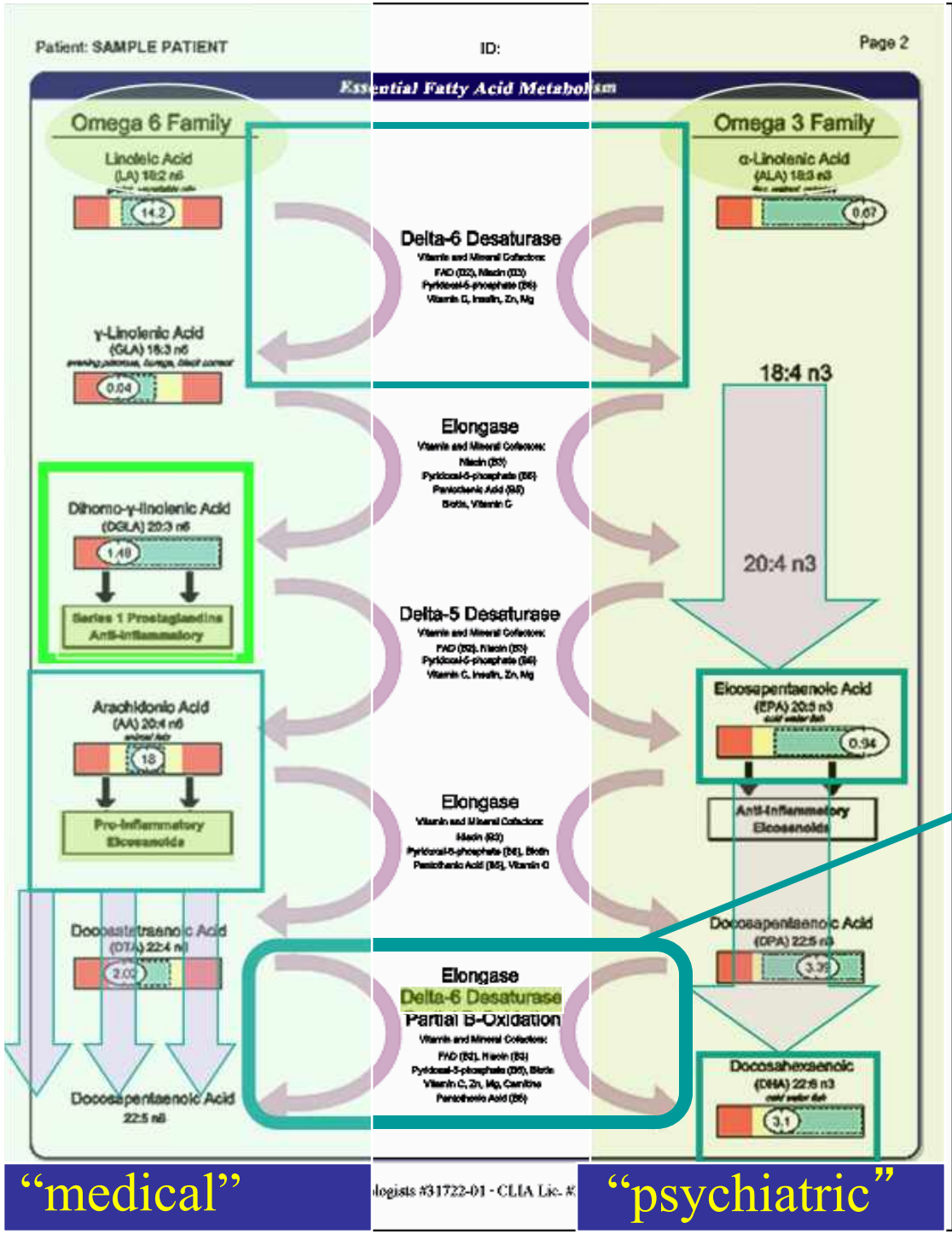
- 40 children with ADHD in study, 2014.
  - 82.5% boys, 17.5% girls
- Two groups:
  - MPH + PUFA
  - MPH + placebo
- Response to treatment (reduction of at least 25% of signs)
  - MPH + Placebo 60%
  - MPH + PUFA ***90%***

Moghaddam MF et al. Effectiveness of methylphenidate and PUFA for the treatment of patients with ADHD" a double-blinded randomized clinical trial. Electron Physician. 2017 May25;9(5):4412-4418

ADHD Medications are not without risk

- Rat study – 5 different doses of MPH for 21 days.
  - Highest doses were 10mg/kg and 20 mg/kg
  - However, MPH in all doses markedly increased lipid peroxidation, mitochondrial oxidized glutathione (GSSG) level, Interleukin 1β (IL-1β) and Tumor Necrosis Factor α (TNF-α) in isolated hippocampus.
- Chronic treatment with high doses of MPH can cause oxidative stress, neuroinflammation and neurodegeneration in hippocampus of adult rats.
  - Motaghinejad M et al. Neurosci Lett. 2016 Apr 21;619:106-13.

Should we use this??



Further elongation problems: lack of nutrients

- REQUIRED for delta-6 desaturase:
  - Magnesium
  - Zinc
  - B vitamins
    - FAD (B2)
    - Niacin (B3)
    - P-5-P (B6)
  - C
  - insulin

Supplement Facts

Serving Size 1 Softgel
Servings Per Container 60

Amount Per Serving		% Daily Value
Calories	15	
Total Fat	1.5 g	2%*
Polyunsaturated Fat	1 g	**
Marine Lipid Concentrate	1.3 g	**
DHA (Docosahexaenoic acid triglyceride)	750 mg	**
EPA (Eicosapentaenoic acid triglyceride)	250 mg	**

* Percent Daily Values are based on a 2,000 calorie diet.
** Daily Value not established.

Ingredients: Marine lipid concentrate (one or more of: anchovy, calamari, sardine, and mackerel oil), softgel shell (gelatin, glycerin, water), contains 2 percent or less of natural lemon flavors, rosemary extract, and mixed tocopherols and ascorbyl palmitate (antioxidants). **Contains: Fish (anchovy, sardine, and mackerel).**

[redacted]

Supplement Facts

Serving Size 1 Soft Gel Capsule
Servings Per Container 120

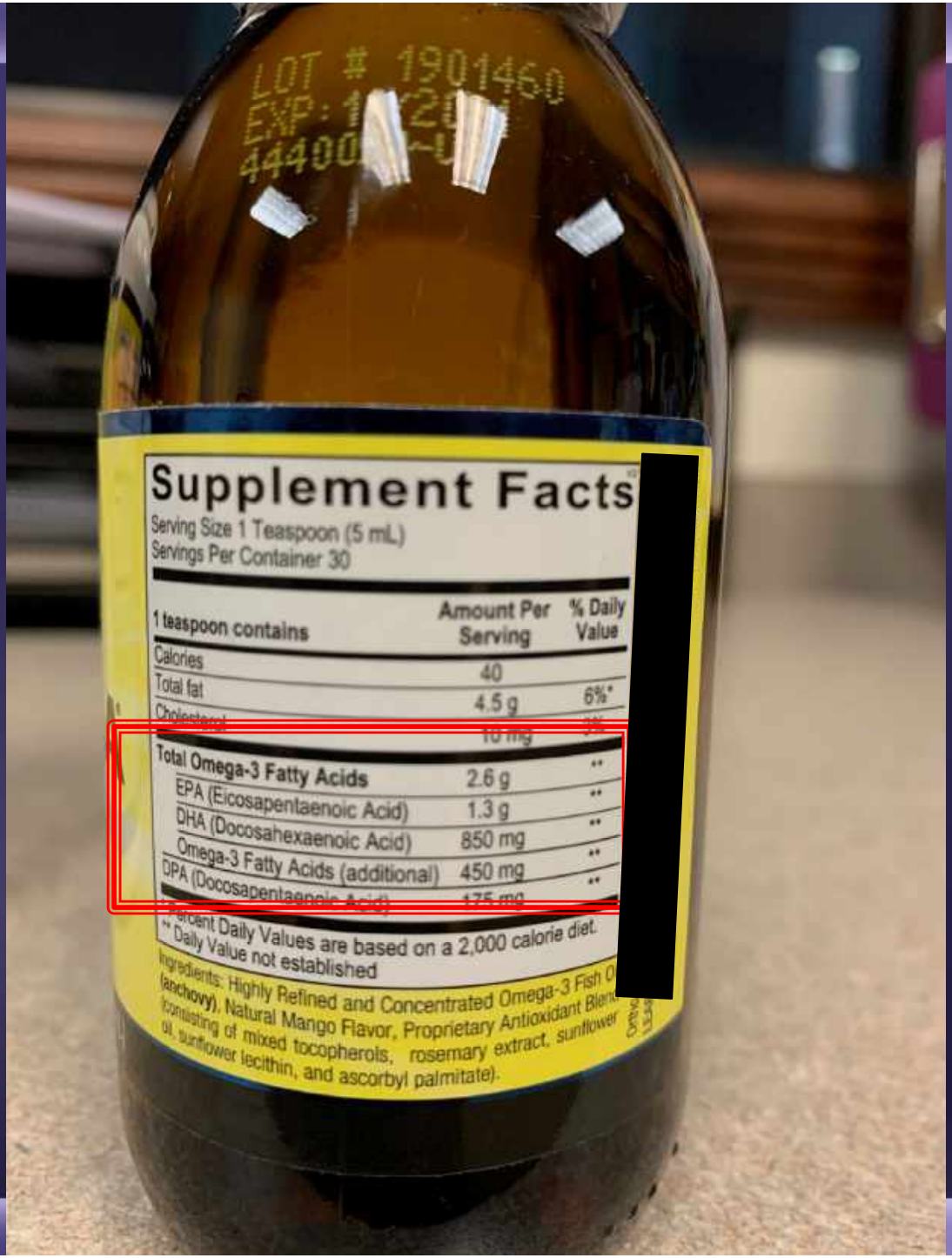
1 soft gel capsule contains	Amount Per Serving	% Daily Value
Calories	15	
Total fat	1.5 g	2%*
Cholesterol	<5 mg	<2%
Total Omega-3s (as Triglycerides)	950 mg	**
EPA (Eicosapentaenoic Acid)	430 mg	**
DHA (Docosahexaenoic Acid)	390 mg	**
Omega-3s (additional)	130 mg	**
DPA (Docosapentaenoic Acid)	50 mg	**

** Daily Value not established
* Percent Daily Values are based on a 2,000 calorie diet.

Ingredients: Highly Refined and Concentrated Omega-3 Fish Oil **(anchovy)**, Capsule Shell (gelatin, glycerin, purified water), Natural Lemon/Lime Flavor, and a Proprietary Antioxidant Blend (consisting of natural tocopherols, rosemary extract, and ascorbyl palmitate).

[redacted]

Professional Strength: Not for sale through


LOT # 1901460
Supplement Facts
Serving Size 1 Teaspoon (5 mL)
Servings Per Container 30
1 teaspoon contains
Amount Per Serving
% Daily Value
Calories 40
Total fat 4.5 g 6%*
Total Omega-3 Fatty Acids 2.6 g **
EPA (Eicosapentaenoic Acid) 1.3 g **
DHA (Docosahexaenoic Acid) 850 mg **
Omega-3 Fatty Acids (additional) 450 mg **
* Percent Daily Values are based on a 2,000 calorie diet.
** Daily Value not established
(anchovy), Natural Mango Flavor, Proprietary Antioxidant Blend
(consisting of mixed tocopherols, rosemary extract, sunflower
oil, sunflower lecithin, and ascorbyl palmitate).

Key principles of essential fatty acid supplementation are:

- Do not use large doses of a generic omega 6 or omega 3 fish oil and presume that you are going to get adequate amounts of EPA and DHA out the bottom of the pathways.
- The only two sources of fish oil high in PUFA's that we get are from eating fish or taking fish oil. Period. If we don't eat fish, we should probably be on fish oil.
- We DO have the ability to synthesize the critical PUFA's, including EPA and DHA, from precursors, but in order to do so, we must have adequate amounts of the critical trace minerals.

Rationale to consider Omega-3's in ADHD & psychiatry

- Lipids are important for brain health
- Abnormal lipid balances are associated with ADHD.
- Lipid levels (in blood and brain) might be affected by different parameters (e.g., diet, metabolism)
- Therefore, why not put more of the good lipids into the brain?

- ☐ has ***REAL trouble*** following through on instructions; fails to finish tasks
- ☐ difficulty organizing tasks/activities
- ☐ avoids, dislikes, or reluctant to engage in tasks requiring sustained mental effort (homework, work projects, etc.)
- ☐ loses things necessary for tasks/activities
- ☐ easily distracted by extraneous stimuli (sounds or sights in the environment)
- ☐ often forgetful in daily activities

seat was expected, or can't stay put at work

- ☐ runs about; climbs excessively in inappropriate situations
- ☐ difficulty playing or engaging in leisure activities quietly
- ☐ often was "on the go" as if "driven by a motor"
- ☐ talks excessively - a "chatterbox"

PROBLEMS BEING IMPULSIVE

- ☐ blurts out answers before questions are completed
- ☐ difficulty waiting your turn
- ☐ interrupts or intrudes on others (butts into conversations)

For physician use only -
RECENT CLINICAL HISTORY:
Dramatically better
↓ food allergy testing & elim. diet.

(M) ↓ VPA to only 1 in p.m. b.c. he was oversedated when got his original VPA.

"7. d. we realize a mistake [re allergic foods] it disrupts our family."

Handwriting improving. Making A's in school. Teacher says, "He's a totally different child."

PARENTS: Please fill in your child's
CURRENT DRUG THERAPY... PLEASE LIST!

medication &/or supplements	size of dose	WHEN TAKEN
1/2 Lithium		6:30a.m
2 36mg Concerta		6:30a.m
2 1000 Fish Oil		6:30a.m
1 Depakote		5 p.m.
1 Depakote		7 p.m
1/2 Clonidine		6:30p.m
2 1000mg Fish Oil		6:30p.m

ADHD Diagnostic Symptom Checklist, adapted from DSM-IV, by:
Louis B. Cady, M.D. · 611 Harriet Street - Suite 304 - Doctors Plaza
Evansville, IN 47710 www.drcady.com

FEB 2005

The only time that [redacted] is out of control is in the a.m. before he gets his Concerta, or at the evening before the clonidine kicked in.

Mom put him on a really strict diet and his symptoms were amazingly improved. Mom has tried three different types of locks on the pantry.

Mom jokes that she and her husband now will ask "OK, what did you get into?" when he comes home from school and he is clearly not under control. On once occasion, he had a substitute, allowed him to sit wherever, and sat next to a little girl who had a blueberry muffin.

It has gotten down to a brand distinction – he can have the new Frito Lay fresh potatoe chips. But on Lay's potatoe chips – shouldn't be having reaction, but was. Mom called the manufacturer and found out that the oil in which the chips were fried was cross-contaminated.

"His appetite is huge now – every since I moved them over to this diet, all my kids eat all the time."

Both girls and [redacted] as well as [redacted] are on this diet. Mom notes that other children can have soy milk flavored with carob, but any kind of chocolate, of any nature, gets him off balance. He is also more sucsceptible to types of margarine. No soy ice cream or rice milk ice cream has been found.

She also notes that his cycling is retrospectively possibly related to food issues.

School performance – Chronologically – 4rth grade, but now on testing between KG and third grade level. Previously, was only testing at age 5 or 6.

On the diet, he no longer has the big temper issues. Mood is still up and down, but not to the depressive end – just more or less "frantic."

- Dr. [redacted] has found a metabolic disorder in [redacted]. Started him on 1 tsp Levocarn 10%, oral (generic equiv for carnitor 10% 118ml) – per Dr.

The American Journal of
CLINICAL NUTRITION

Essential fatty acid metabolism in boys with attention-deficit hyperactivity disorder.

L J Stevens, S S Zentall, J L Deck, M L Abate, B A Watkins, S R Lipp, and

This Article
Am J Clin Nutr October 1995 vol. 62 no. 4 761-768

» Abstract *Free*
Full Text (PDF) *Free*

- The present study found that 53 subjects with ADHD had significantly lower concentrations of key fatty acids in the plasma polar lipids (20:4n-6, 20:5n-3, and 22:6n-3) and in red blood cell total lipids (20:4n-6 and 22:4n-6) than did the 43 control subjects
- "…but the precise reason for lower fatty acid concentrations in some children with ADHD is not clear."

of 20:4n-6 and 22:6n-3 than did 32 subjects with ADHD with few EFA-deficiency symptoms. The data are discussed with respect to cause, but the precise reason for lower fatty acid concentrations in some children with ADHD is not clear.

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Neuroscience & Biobehavioral Reviews

Volume 45, September 2014, Pages 369–378

Review

Food for thought: Dietary changes in essential fatty acid ratios and the increase in autism spectrum disorders

Kim van Elst[a], Hilgo Bruining[a, b], Barbara Birtoli[c], Christian Terreaux[c], Jan K. Buitelaar[d], Martien J. Kas[a],

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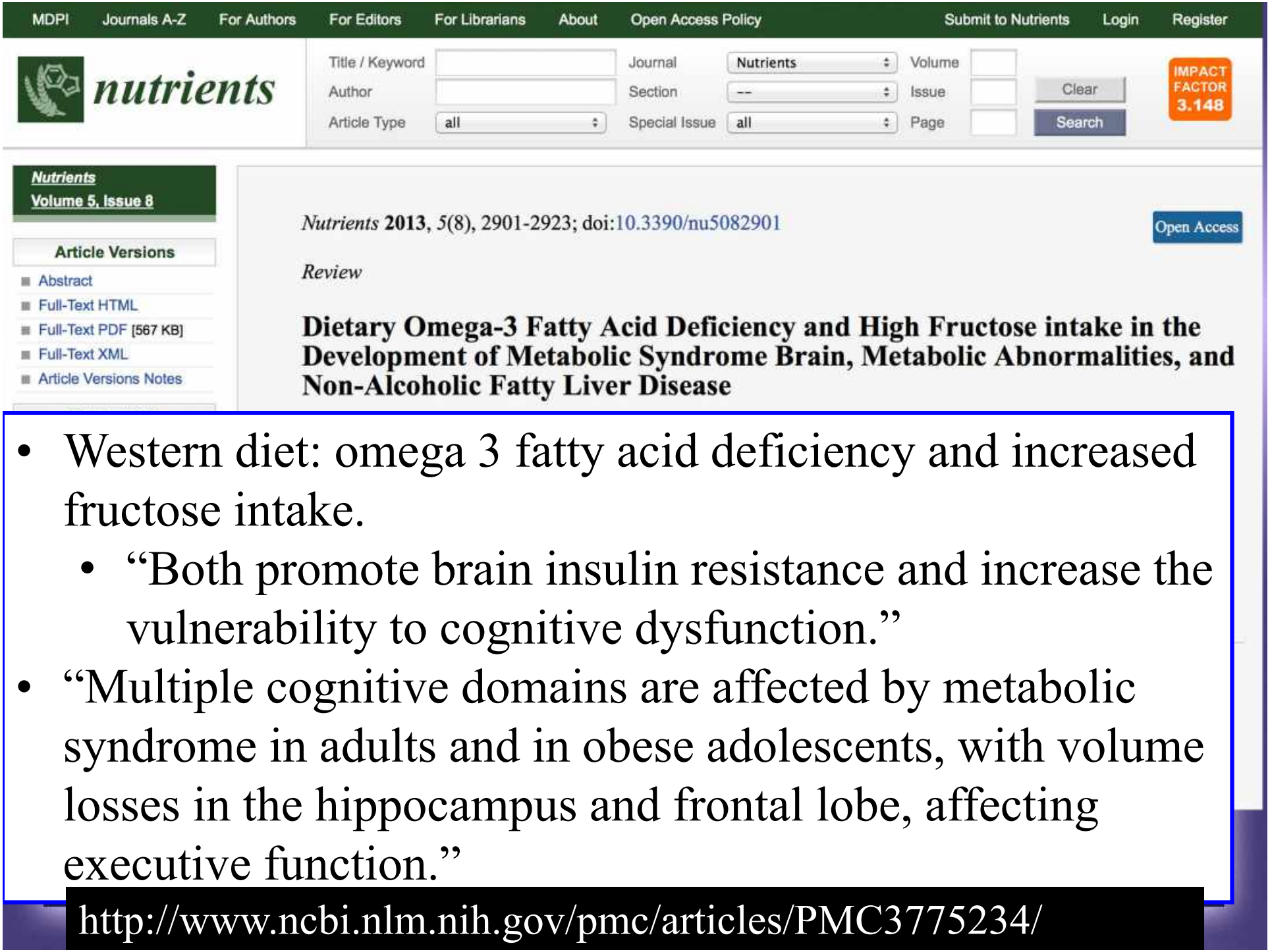

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http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3775234/

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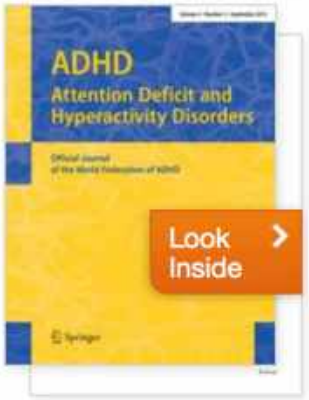

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- "We could demonstrate that a lack of polyunsaturated FAs in blood serum of subjects with ADHD persists into adulthood. Furthermore, we could show that adult ADHD symptomatology positively correlates with elevated levels of saturated stearic and monounsaturated FAs.HGLA were lower than controls."

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Yehuda S.

Author information

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A literature review

- PUFA ADHD – 76 citations
- PUFA neuroinflammation – 75 citations
- Omega 3 fatty acid ADHD neuroinflammation – 4

www.pubmed.gov August 9, 2020

PUFA's

- Imbalanced levels of PUFA's in ASD and ADHD
  - PUFA's exert potent immunomodulatory activities.
- Sources:
  - Poor nutritional diversity
  - Nutrient deficiency
    - Madore C et al. Neuroinflammation in autism: plausible role of maternal inflammation, dietary omega 3, and microbiota. Neural Plast. 2016;2016:3597209.

The Omega 3 Fatty Acid (+) ADHD (+) Neuroinflammation: the literature of four papers

- Prevention of cerebral palsy, autism spectrum disorder, and attention deficit-hyperactivity disorder.
  - Strickland AD . Med Hypotheses. 2014 May;82 (5):522-8.
- Can omega-3 fatty acids and tocotrienol-rich vitamin E reduce symptoms of neurodevelopmental disorders?
  - Dumpricht E, Rockway S. Nutrition. 2014 Jul-Aug;30(7-8):733-8.
- Omega 3 polyunsaturated fatty acids through the lifespan: implication of psychopathology
  - Pusceddu MM et al. Int J Neuropsychopharmacol. 2016 Dec 30’19(12):pyv078.
- Neuroinflammation in autism: plausible role of maternal inflammation, dietary Omega 3, and Microbiota
  - Madore C et al. Neural Plasti. 2016:2016:3597209.

Prevention of cerebral palsy, autism spectrum disorder, and attention deficit-hyperactivity disorder [with DHA and antioxidant]

- Hypothesis is stated that CP, ASD, and ADHD are “all caused by an exaggerated central nervous system inflammatory response to prenatal insult.”
- This pre-natal insult may be:
  - One or more episodes of ischemia-reperfusion
  - Infectious disease of the mother or the fetus
  - Other causes of maternal inflammation such as allergy or autoimmune disease

Strickland AD . Med Hypotheses. 2014 May;82 (5):522-8.

Prevention of cerebral palsy, autism spectrum disorder, and attention deficit-hyperactivity disorder [with DHA and antioxidant]

- "The resultant fetal inflammatory hyper-response injures susceptible neurons in the developing white matter of the brain in specific areas at specific gestational ages.
  - 19-34 weeks post conception for CP
  - 32-40 weeks for ADHD
  - 36-48 weeks for ASD.
- Effects occur because "present diets limit intake of effective antioxidants and omega-3-polyunsaturated fatty acids," with an excess of Omega-6.

Strickland AD . Med Hypotheses. 2014 May;82 (5):522-8.

Childhood depression

- 12 year old 7th grader. Intake Nov 15, 2019.
- “Worried about food being contaminated and that he is going to have a heart attack.”
- “Worried about the lead in his pencils hurting him.”
- Things “getting stuck in his head – “like tunes, sports, good stuff.”
- Holding saliva in his mouth constantly.
- Admits to “getting bored some times.”
- Math teacher comments about “careless errors.”
- Already started on Escitalopram 10 mg by pediatrician Oct 26. Increased to 20 mg Nov. 4.

On exam:

- From intake: “Alert, pleasant, remarkably poised, self-confident, mature and communicative. He is a straight talking, ‘put it all out on the table’ kind of kid. He is extremely refreshing. He clearly wants to get better.”
- Childhood depression inventory relevant positives:
  - “I worry that bad things will happen to me.”
  - “Many bad things are my fault.”
  - “I cannot make up my mind about things.”
  - “There are some bad things about my looks.”
  - “I have to push myself all the time to do my schoolwork.”
  - “I worry about aches and pains many times.”
  - “I can never be as good as other kids.”

DSM5 review

Anxiety

- Constant worry
- Repetitive, senseless thoughts
- Fearful feelings
- Keyed up/on edge
- Trouble concentrating

Miscellaneous

- Feeling life is not worth living
- Fear of dying
- Frequent crying or weeping

Depression:

- Sad/depressed/down in the dumps
- Lack of/loss of interest in things
- Decrease in appetite and weight (due to obsessionality)
- Trouble concentrating
- Frequent thoughts of death. Of suicide he says, “oh, no. I don’t want to do that.”

“If you just know the names of the terms you absolutely know nothing and nothing about it.”

- Richard P. Feynman, Ph.D.

Questions

- Diagnoses:
  - Psychotic disorder?
  - AD(H)D?
  - Mixed depression/anxiety?
  - Other?
- What to do?
  - (already on max ***adult*** dose of escitalopram)
    - Add antipsychotic?
    - Add concomitant antidepressant?
    - Add ADD medication?
    - Refer for even more intense psychotherapy?
- How long do you think it will take to get him better?

The differential dx and treatment plan:

- Differential/case management ideas:
  - OCD
  - Mixed depression/anxiety
  - Features of mild ADHD
  - Doubt psychotic disorder
  - Potential MTHFR polymorphism as a fundamental weakness
  - Possible cytochrome p450 2D6 hypermetabolic genotype ("SSRI pathway")
- Tx:
  - Leave escitalopram alone
  - L-methylfolate 800 ug – ½ q am x 3-5 d, then 1 q am
  - 5-HTP 50 mg + P5P supplement before bedtime.
  - Haloperidol 0.1 mg – ½ or 1 before bedtime, or ½ - 1 twice daily ONLY AS NEEDED FOR SEVERE OCD SYMPTOMS. ***DO NOT FILL FOR ONE WEEK UNLESS NEEDED.***
- LABS – cheek swab for pharmacogenomic testing
- FOLLOW UP – one month.

The follow up – Dec 13, 2019

Anxiety

- ~~Constant worry~~
- ~~Repetitive, senseless thoughts~~
- ~~Fearful feelings~~
- ~~Keyed up/on edge~~
- ~~Trouble concentrating~~

Miscellaneous

- ~~Feeling life is not worth living~~
- ~~Fear of dying~~
- ~~Frequent crying or weeping~~

Depression:

- ~~Sad/depressed/down in the dumps~~
- ~~Lack of/loss of interest in things~~
- ~~Decrease in appetite and weight (due to obsessionality)~~
- ~~Trouble concentrating~~
- ~~Frequent thoughts of death or suicide.~~

Only 2 symptoms remained:
- "a tiny bit" of constant worry
- Increase in appetite (which was HEALTHY)

Current Rx :

- Escitalopram 20 mg
- L-methylfolate – 800 ug daily
- 5HTP with P5P before bedtime.
- NO HALOPERIDOL WAS USED.

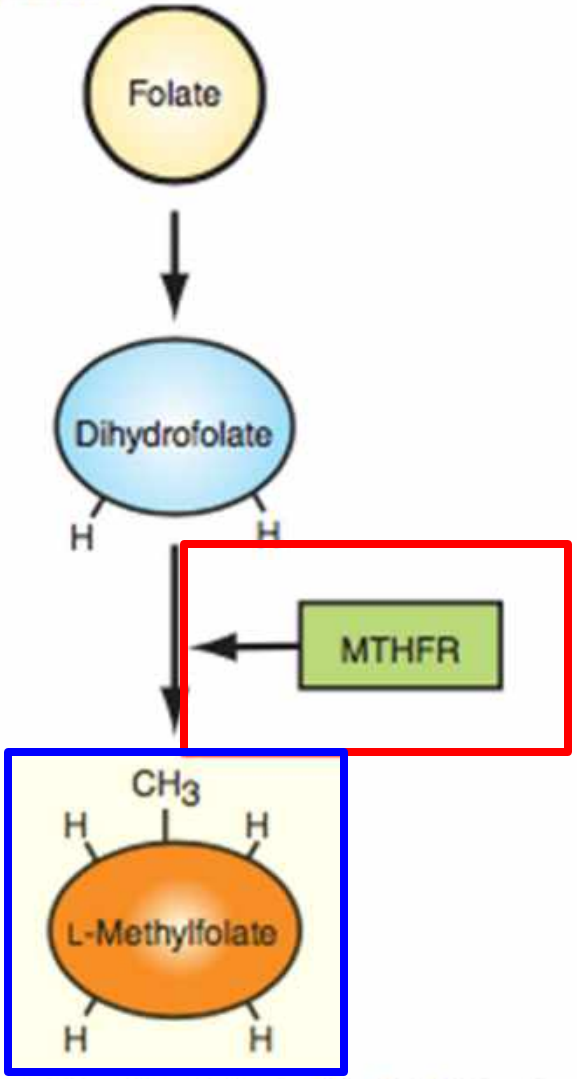
RELEVANT LABS & status

GENE		
SLC6A4 (SERT)	S/S	SSRI's don't work well
MTHFR - C677T - A1298C	 C/C C/C	 Perfect. This is the major gene. Worst POSSIBLE genotype at minor gene – needs L-MF
COMT	Val/met	The best genotype "right down the middle."
Cyp 2D6	2/4	NORMAL SSRI metabolizer (escitalopram)
Cyp 2B6	1/1	Bupropion *would* work if ever needed.
OPRM1 – a "lagniappe"	G/G	Worst POSSIBLE genotype – opioids will not work for pain (if ever needed)

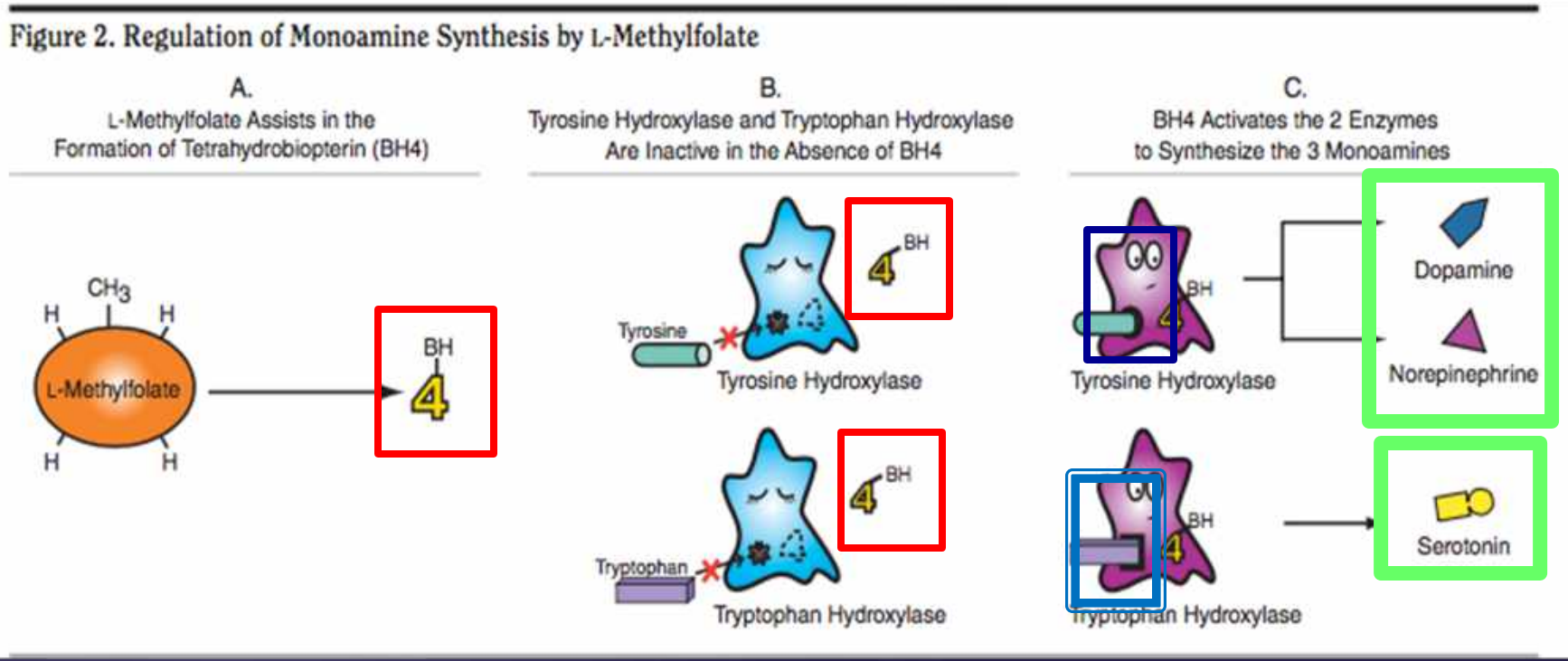
STATUS – 12/13/2019

- Fully resolved OCD + mixed depression/anxiety
- MTHFR polymorphism – “homozygous at the A1298C gene”
- Poor SLC6A4 – might not even need escitalopram in the future.
- Plan is taper the escitalopram as able and see back in four months.

Figure 1. Synthesis of L-Methylfolate From Folate



Abbreviations: C = carbon, H = hydrogen, MTHFR = methylene tetrahydrofolate reductase.



Strategy: test for "MTHFR genotype."

References:

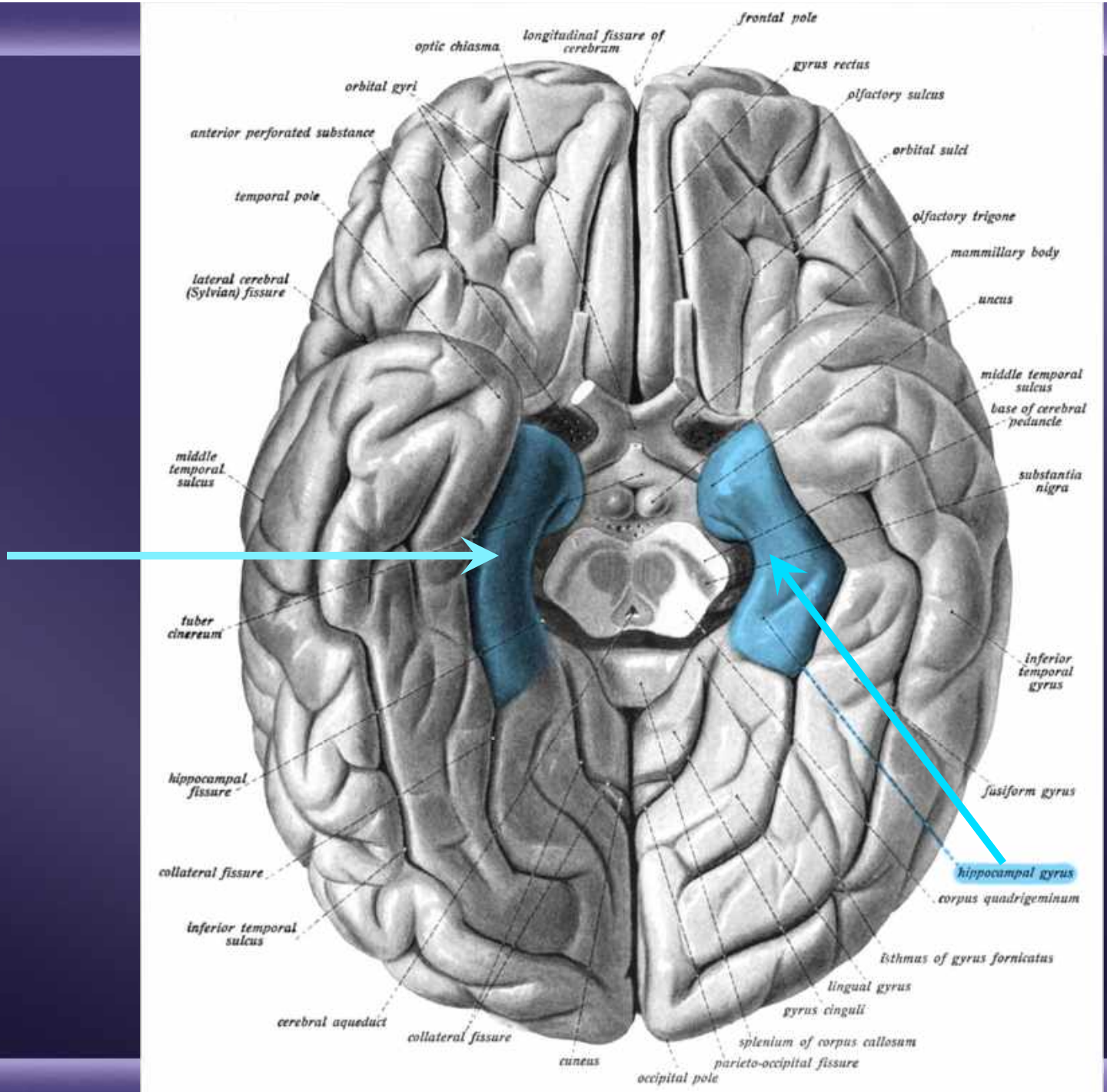
www.genomind.com www.genesight.com

Stahl SM. L-methylfolate: a vitamin for your monoamines. J Clin Psychiatry. 20089 Sep;69(9):1352-3

L-methylfolate does make more than make happy brain chemicals…

- It may moderate against regional brain shrinkage over two years.
- 167 Adults 19 – 79 yoa; 90 left at two-year follow-up.
- Changes mapped in 10 anatomically defined and manually raced regions of interest.
- Carriers of **T allele in MTHFR (C677T** gene) showed **increased parahippocampal gyrus shrinkage**.
- Our findings warrant further investigation of the effects of neuroinflammation on structural brain change throughout the lifespan

Persson N et al. Regional brain shrinkage over two years: individual differences and effects of pro-inflammatory genetic polymorphisms. Neuroimage. 2014 Dec;103:334-348.


frontal pole
longitudinal fissure of cerebrum
optic chiasma
gyrus rectus
orbital gyri
olfactory sulcus
anterior perforated substance
orbital sulci
temporal pole
olfactory trigone
mammillary body
lateral cerebral (Sylvian) fissure
uncus
middle temporal sulcus
base of cerebral pedancle
middle temporal sulcus
substantia nigra
tuber cinereum
inferior temporal gyrus
hippocampal fissure
fusiform gyrus
collateral fissure
hippocampal gyrus
corpus quadrigeminum
inferior temporal sulcus
isthmus of gyrus fornicatus
lingual gyrus
gyrus cinguli
cerebral aqueduct
collateral fissure
splenium of corpus callosum
cuneus
parieto-occipital fissure
occipital pole

Parahippocampal gyrus

- Grey matter cortical region of the brain that surrounds the hippocampus and is part of the limbic system.
- Plays role in memory encoding and retrieval.
- Asymmetry has been observed in schizophrenia.
  - McDonald B et al Am J Psychiatry. 2000 Jan;157(1):40 – 7.
- May play a role in social context as well including "paralinguistic elements of verbal communication" (e.g., SARCASM).
  - Hurly D "The Science of Sarcasm (Not That You Care). NYTimes.com June 3, 2008. Cites work of Katherine P. Rankin. https://nyti.ms/3ftsLQi . Accessed 08/03/2020/

Mild MTHFR Deficiency Alters Inflammatory and Lipid Pathways

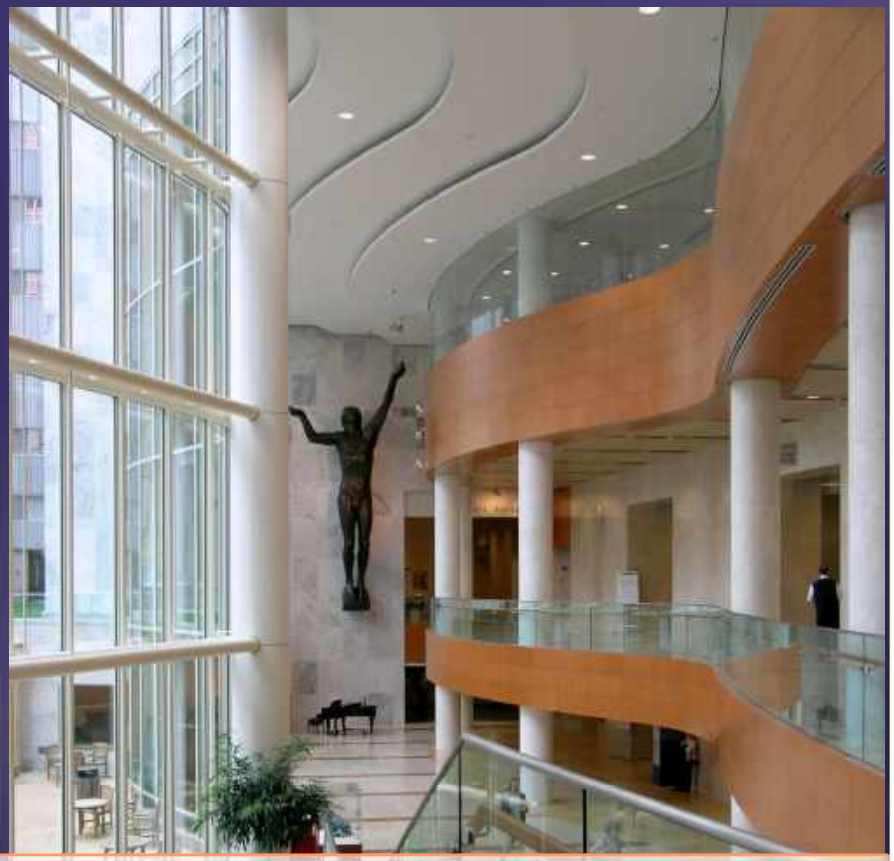
- Known:
  - dietary and genetic folate disturbances can lead to nonalcoholic fatty liver disease (NAFLD)
  - MTHFR 677 C / T causes mild MTHFR deficiency with lower 5-MTHFR.
- Rat study: wild type and MTFHR +/- mice fed control diet or high fat diet for 8 weeks.
  - On control diet with MTHFR deficiency - microvesicular steatosis with expression changes in lipid regulators (Xbp1s and Cyp7a1.)
  - On HF diet, MTHFR def. exacerbated changes in inflammatory mediators and introduces additional effects on inflammation (Saa2) and lipid metabolism (Nr1h4, Srebf1c, Ppara, and Crot).

Leclerc D et al. (title above). Mol Nutr Food Res. 2019 Feb;63(3):e1801001

Foundational matters:

- "The neo-Kraepeliain revolution in psychiatric diagnosis." Eur Arch Psychiatry Clin Neurosci. 1995;245 (4-6) 196-201.
  - Take home point: don't just consider the SYMPTOMS

- "We know from extensive research that early-life stress, adversity, and especially trauma present prominent risks for the later development of psychopathology."
  - Kalin, NH. Am J Psychiatry 177:1; January 2020.
  - Cf also: Walker, P. Complex PTSD: From Surviving to Thriving. © 2013
    - Take home point: remember the possibility of trauma and brain changes from early childhood ages on.



"If you can only read one article in your entire career at Mayo on psychotherapy, read this one."

- John Graf, MD

Clinician's View

Greben, S.
Can Psychiatr. Assoc Journ. Vol 22 (1977): 371-380

ON BEING THERAPEUTIC*

STANLEY E. GREBEN, M.D.[1]

"On Being Therapeutic"

The purpose of this paper is to examine attitude to bear upon the attempt to

large number of American Professors of Psychiatry at that time. He had been a biochemist. While doing research with schizophrenic patients at the McLean Hospital near Boston he listened to the patients from whom he was drawing samples of blood. He listened for two reasons: first, he was a trained scientific observer and second, he wanted to understand his subjects as people. His feeling that what they said and did made sense turned his interest toward clinical psychiatry and psychotherapy, an interest which developed into his conviction that psychotherapy was important in the treatment of all psychiatric patients, and which persisted over a long subsequent career. Whitehorn's work was a natural step forward from the holistic psychobiological approach of his predecessor, Adolph Meyer; and he tried to bring a scientific

or re-establishment of hope (3). He has come to this conclusion both through formal studies of psychotherapy (5) and through observations of healers in various cultures (2).

At Johns Hopkins, then, in the formative years of my thinking as a psychotherapist, I was influenced by teachers who carried the conviction that psychotherapy works, and that it is of almost universal applicability for psychoneurotic and psychotic patients. It must be pointed out, however, that this occurred within a milieu of medical tradition: of careful physical examination, detailed history taking, continued ongoing search for constitutional (that is genetic) and biochemical contributions which might help to explain the patient's plight, and of somatic (physical and biochemical) therapies which would help to improve his state of health and mind.

When, as a senior resident, I spent a year in England at the Maudsley Hospital, I found that Aubrey Lewis, the Professor, was highly sceptical of psychotherapy as he was of all areas in psychiatry. I was always amused

*Presented at the annual meeting of the Ontario Psychiatric Association, January 1977. Manuscript received May 1977.
[1]Psychiatrist-in-Chief, Mount Sinai Hospital, Toronto; Professor of Psychiatry, University of Toronto, Toronto, Ont.

Psychodynamics and holistic medicine

- Some therapists [doctors] stand out as uniquely effective.
- Academics are no better.
- “Every potential therapist [doctor] must have a floor and a ceiling to his therapeutic capacity.”
- Some gifted therapists [doctors] are able to say why they succeed; others can’t explain it. “A great deal of what they do ‘right’ is intuitive.”

Greben's "Seven Habits"

- Empathy & concern
- Warmth
- Interaction
- Ability to ***arouse hope*** *
- Expectation of improvement
- "Not to despair"
- Reliability & Friendliness

****Requires clinical depth and breadth of knowledge***

Example: Integrative Treatment of Schizophrenia

- (Psychodynamic:
  - do not neglect psychotherapy!)

- Biological ≡ Holistic
  - Biological – "of or relating to biology or to life and living processes."
    - [Merriam-Webster]
  - This is the very essence of INTEGRATIVE medicine.

Commence Treatment!!

BEHAVIORS/PHENOTYPE
depressed?
anxious?
meltdowns
OCD?
Bipolar/schizophrenia
"Autism"

NT's – 5HT, NE, DA. Membrane stabilization. Antipsychotics.

- THYROID PROBLEMS? Trace elements?
- Adrenal and sex hormones?
- GI issues?
- Excess screen time (video games, "dopamine resistance"?)

Workup:

- Conventional labs incl. ALL thyroid testing and adrenal/sex hormone testing.
- FUNCTIONAL (integrative) labs
  - IgG panel
  - OAT
  - Heavy metals
  - Mold panels

Pharmacogenomics

WHAT ARE THE GENES?
MTHFR - enough NT's made?
COMT - breakdown
CypP450 - adequacy of treatment?

RX:

- Conventional meds – antidep, ADHD Rx, mood stabilizers.
- GI meds/supplements
- Supplements, foundational nutritionals (eg. L-MF).
- Diet modification

adequate proteins to make them?
Digestion?
Omega 3 fatty acids?
Vitamin D
Inflammatory cytokines (IgG reactions?)
shift of NE to DA with HPPA from clostridia?
OSA? Sleep disorder?

Childhood trauma – abuse, neglect

Case presentation

- Alan – presents on Feb 16, 2007, diagnosed with depression vs. psychosis.
  - Previous treatment at Pfeiffer Treatment Center
- He appeared notably fatigued and grossly over-sedated.
- Morose and depressed. Lucid. Intelligent.

Past history

- “Ever since I can remember, I’ve always had the same feelings about things – how people treat each other and stuff like that.” “My feelings just kept getting worse and worse the more I was picked on. That was the only thing that was wrong, people just calling you names and stuff.”
- Alan became suicidal in middle school – 8th grade year. “I just thought everyone was making fun of me, so why should I go on?”

- Treated with fluoxetine in the past for depression
- Stopped being able to do homework as a sophomore in high school
- “I was just really resentful of my parents a lot during the past few months [at that time] – I just started yelling at them in front of the therapist guy.”
- Partially stabilized by previous MD on aripiprazole (20 mg), olanzapine (20 mg) and sertraline (50mg).
- Per Mom – “It was hard for him to be out and be around a lot of people.”

2007 - 2009

- **More explosive outbursts.** Lamotrigine (200 mg) added topiramate continued
- "I know that I'm acting ridiculous – like a schizophrenic, but I feel good, and I'm talking more to everybody, and I'm trying to get my point across, and I don't feel as evil as I used to."

June 30, 2009

- He comments that he feels his "mouth is going faster than his thoughts."
- Mom reports that "traveling out here (to appointment) wears on him." "He does better when he's quiet and in the house."

- RX:
  - **Olanzapine 30 mg 9 pm**
  - **Aripiprazole 20 mg a.m.**
  - **Topiramate 100 mg HS**
  - **Lamotrigine 200 mg in a.m.**
  - **Duloxetine – 120 day**
  - **Modafinil – 100 mg daily**
  - 5HTP 100 mg in the a.m.

INTEGRATIVE MEDICINE TESTING finally ordered!

Integrative ("functional") medical testing done TESTING

- Micronutrient analysis (functional intracellular analysis) – deficiencies in:
  - Vitamins A & D, zinc, Oleic acid, antioxidant capacity
- **IgG food allergy testing 7/22/2009**
  - **12 total sensitivities**
    - 2+ to eggs, ***cow's milk, wheat***, brewer's yeast
    - 1+ to cheese, mung bean, oat, pork, pumpkin, sesame, tuna & baker's yeast.

Patient "Alan"

Patient Age:	26	*Time of Collection:*	Not Given
Sex:	M	*Print Date:*	11/29/2012

Comprehensive IgG Food Allergy Test + C. albicans, S. cerevisiae (94) - Serum

Dairy	
Casein	2.66
Cheese	2.36
Goat Cheese	2.07
Milk	2.24
Mozzarella Cheese	1.46
Whey	2.14
Yogurt	3.16
Legumes - Beans and Peas	
Garbanzo Bean	1.83
Green Bean	1.56
Kidney Bean	1.43
Lentil	1.14
Lima Bean	1.06
Pea	1.35
Pinto Bean	1.28
Soybean	1.83
Fruit	
Apple	2.45
Apricot	2.87
Banana	3.85
Blueberry	4.00
Coconut	1.90
Cranberry	4.64
Grape	3.17
Grapefruit	2.75
Lemon	5.37
Orange	3.15
Papaya	4.29
Gliadin	7.03
Millet	1.91
Oat	1.35
Rice	1.71
Rye	2.12
Sorghum	4.08
Wheat Gluten	10.88
Wheat	4.09
Fish / Seafood	
Cod Fish	1.46
Crab	1.88
Halibut	1.92
Lobster	1.06
Salmon	3.37
Sardine	1.37
Shrimp	1.24
Tuna	0.86
Meat/Fowl	
Beef	2.65
Chicken	1.74
Egg White	1.24
Egg Yolk	1.80
Lamb	1.55
Pork	1.21
Turkey	1.62
Nuts and Seeds	
Almond	1.62
Cashews	1.32
Flax	1.53

SCHIZOPHRENIA AND GLUTEN

1 Nonmedical Interventions for **Schizophrenia**: A Review of Diet, Exercise, and Social Roles.

Helman DS.

Holist Nurs Pract. 2020 Mar/Apr;34(2):73-82. doi: 10.1097/HNP.0000000000000369.

PMID: 32049694

Schizophrenia is a major mental illness with a disease course that is influenced by lifestyle. The risk-benefit ratio for alternative interventions is more favorable than for antipsychotics in long-term treatment. Dietary interventions may target autoimmune features, vitam ...

“ Cite < Share

2 Going Against the Grains: **Gluten**-Free Diets in Patients Without Celiac Disease-Worthwhile or Not?

Lerner BA, Green PHR, Lebwohl B.

Dig Dis Sci. 2019 Jul;64(7):1740-1747. doi: 10.1007/s10620-019-05663-x.

PMID: 31102129 Review.

This review examines the evidence for use of the GFD in patients without celiac disease who self-report intestinal and/or extraintestinal symptoms (non-celiac **gluten sensitivity**), as well as for enhancement of athletic performance and treatment of autism, rheumatoid ...

“ Cite < Share

3 Gut permeability and mimicry of the Glutamate Ionotropic Receptor NMDA type Subunit Associated with protein 1 (GRINA) as potential mechanisms related to a subgroup of people with **schizophrenia** with elevated antigliadin antibodies (AGA IgG).

Čiháková D, Eaton WW, Talor MV, Harkus UH, Demyanovich H, Rodriguez K, Feldman S, Kelly DL.

Schizophr Res. 2019 Jun;208:414-419. doi: 10.1016/j.schres.2019.01.007. Epub 2019 Jan 24.

PMID: 30685393

Schizophrenia patients compared to controls had a higher prevalence of positivity to ASCA IgA ($p = 0.004$) and IgG ($p < 0.001$). ...GRINA IgG was higher in **schizophrenia** patients than in healthy controls (0.43 ± 0.30 vs. 0.22 ± 0.24, $p < 0.001$). Logistic regress ...

“ Cite < Share

4 A study of anti-gliadin antibodies in first-episode patients with **schizophrenia** among a Chinese population.

Yang H, Jiang Y, Chen Z, Wu J, Qiu C, Meng Q.

Psychiatry Res. 2019 Feb;272:454-457. doi: 10.1016/j.psychres.2018.12.161. Epub 2018 Dec 29.

PMID: 30611964

1 Mood disorders and non-celiac **gluten sensitivity**.

Casella G, Pozzi R, Cigognetti M, Bachetti F, Torti G, Cadei M, Villanacci V, Baldini V, Bassotti G.

Minerva Gastroenterol Dietol. 2017 Mar;63(1):32-37. doi: 10.23736/S1121-421X.16.02325-4. Epub 2016 Sep 20.

PMID: 27647538 Review.

The association between **gluten** related disorders and psychiatric diseases has been firmly demonstrated. Non-celiac **gluten sensitivity** (NCGS) is a syndrome diagnosed in patients responsive to **gluten**-free diet after ruling out celiac disease and wheat al ...

Cite Share

2 Non-Celiac **Gluten sensitivity**: the new frontier of **gluten** related disorders.

Catassi C, Bai JC, Bonaz B, Bouma G, Calabrò A, Carroccio A, Castillejo G, Ciacci C, Cristofori F, Dolinsek J, Francavilla R, Elli L, Green P, Holtmeier W, Koehler P, Koletzko S, Meinhold C, Sanders D, Schumann M, Schuppan D, Ullrich R, Vécsei A, Volta U, Zevallos V, Sapone A, Fasano A.

Nutrients. 2013 Sep 26;5(10):3839-53. doi: 10.3390/nu5103839.

PMID: 24077239 **Free PMC article.** Review.

Non Celiac **Gluten sensitivity** (NCGS) was originally described in the 1980s and recently a "re-discovered" disorder characterized by intestinal and extra-intestinal symptoms related to the ingestion of **gluten**-containing food, in subjects that are not affected ...

Cite Share

3 **Gluten Sensitivity**.

Catassi C.

Ann Nutr Metab. 2015;67 Suppl 2:16-26. doi: 10.1159/000440990. Epub 2015 Nov 26.

PMID: 26605537 **Free article.**

Non-celiac **gluten sensitivity** (NCGS) is a syndrome characterized by intestinal and extraintestinal symptoms related to the ingestion of **gluten**-containing food in subjects who are not affected by either celiac disease (CD) or wheat allergy (WA). ...In recent y ...

Cite Share

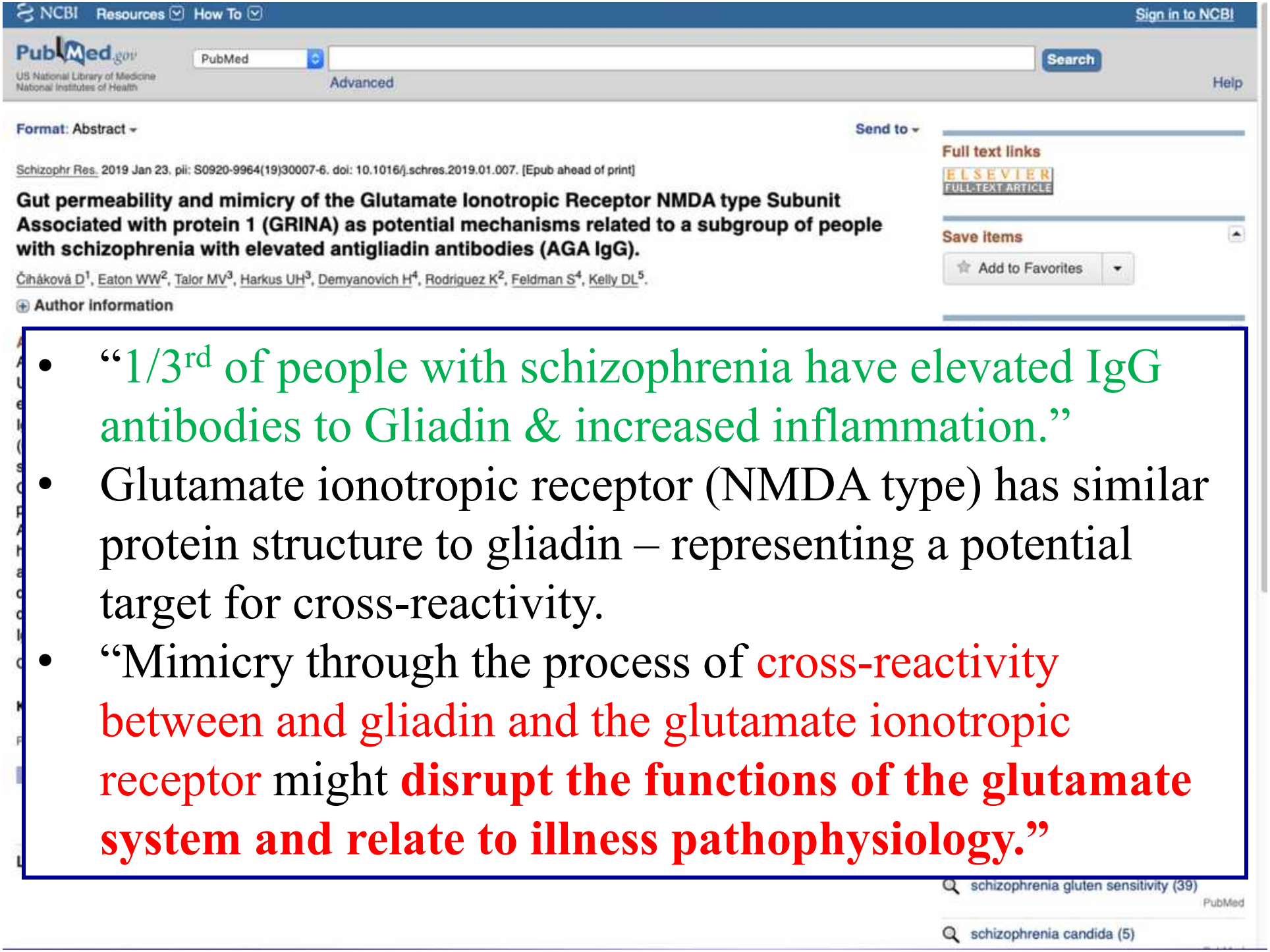
4 Use of a **Gluten**-Free Diet in **Schizophrenia**: A Systematic Review.

Levinta A, Mukovozov I, Tsoutsoulas C.

Adv Nutr. 2018 Nov 1;9(6):824-832. doi: 10.1093/advances/nmy056.

PMID: 30325398 **Free PMC article.**

We performed a systematic review of the literature to determine whether adherence to a **gluten**-free diet (GFD) leads to improved outcomes for patients with **schizophrenia**. ...Further research is required to examine the biomarkers of **gluten sensitivity** an ...



- "1/3rd of people with schizophrenia have elevated IgG antibodies to Gliadin & increased inflammation."
- Glutamate ionotropic receptor (NMDA type) has similar protein structure to gliadin – representing a potential target for cross-reactivity.
- "Mimicry through the process of cross-reactivity between and gliadin and the glutamate ionotropic receptor might **disrupt the functions of the glutamate system and relate to illness pathophysiology."**

Differential antibody responses to gliadin-derived indigestible peptides in patients with schizophrenia

- Evaluation: IgG and IgA antibodies against indigestible gliadin-derived peptide antigens by ELISA
- 169 patients with schizophrenia; 236 controls.
- RESULTS:
  - **Patients with schizophrenia had increased levels of plasma IgG against the gamma-gliadin-derived fragment (AAQ6C) compared to control subjects.**
  - No difference against NATIVE gliadins between patient and control groups.

McLean RT et al. Translational Psychiatry. 2017 May 9;7(5):e1121.

Gliadin – a definition

"GLIADIN is the alcohol soluble fraction of gluten and is the primary antigen leading to an inflammatory reaction in the small intestine, characterized by chronic inflammatory infiltrate and villous atrophy."

From Chapter 17 – Molecular Basis of Diseases of Immunity. Beenhouwer, DO. Molecular Pathology, © 2009, pages 291-304. (https://www.sciencedirect.com/science/article/pii/B9780123744197000172)

Another recent schizophrenic patient for comparison

William Shaw, Ph.D Director 11813 W. 77th Street, Lenexa, KS 66214 (913) 341-8949 Fax (913) 341-6207

Requisition #:	453307	Physician Name:	LOUIS CADY MD
Patient Name:	[redacted]	Date of Collection:	10/5/2016
Patient Age:	20	Time of Collection:	09:00 AM
Sex:	M	Print Date:	10/18/2016

Comprehensive IgG Food Allergy Test + C. albicans, S. cerevisiae (94) - Serum

Dairy	
Casein	12.51
Cheese	11.42
Goat's Milk	8.33
Cow's Milk	11.76
Mozzarella Cheese	8.13
Whey	9.30
Yogurt	10.57
Legumes - Beans and Peas	
Garbanzo Bean	1.19
Green Bean	1.77
Kidney Bean	1.70
Lentil	0.94
Lima Bean	1.17
Pea	3.62
Pinto Bean	1.32
Soybean	1.38
Fruit	
Apple	1.10
Apricot	1.71
Banana	1.57
Blueberry	1.58
Coconut	1.15
Cranberry	1.02
Grape	1.00
Grapefruit	1.05
Lemon	1.21
Orange	1.03
Papaya	1.22
Peach	0.99
Pear	1.08
Pineapple	1.50
Plum (Prune)	1.70
Strawberry	1.11
Watermelon	1.10
Grains	
Barley	1.19
Buckwheat	1.31
Corn	1.09
Gliadin	4.70
Millet	0.92
Oat	1.38
Rice	1.33
Rye	1.10
Sorghum	1.37
Wheat Gluten	4.24
Wheat	5.23
Fish / Seafood	
Cod Fish	1.50
Crab	2.09
Halibut	0.93
Lobster	1.22
Salmon	1.06
Sardine	0.94
Shrimp	1.22
Tuna	1.17
Meat/Fowl	
Beef	1.43
Chicken	1.43
Egg White	2.60
Egg Yolk	1.90
Lamb	1.34
Pork	1.12
Turkey	1.63
Nuts and Seeds	
Almond	1.35
Cashews	2.19
Flax	1.10
Hazelnut	1.26
Peanut	2.11
Pecan	1.20
Pistachio	2.69
Sesame	1.23
Sunflower	1.14
Walnut	1.18

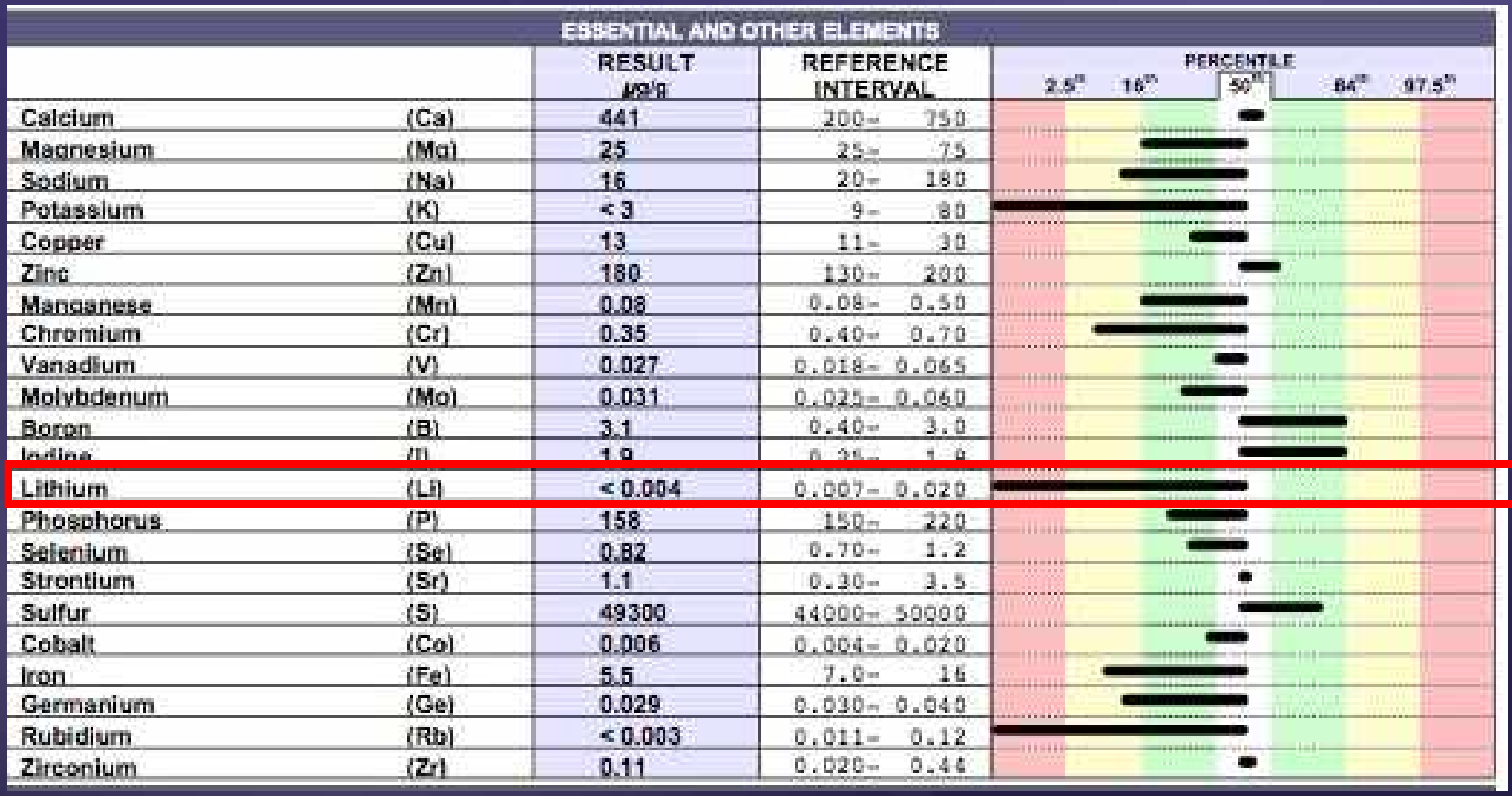
Testing performed by The Great Plains Laboratory, Inc., Lenexa, Kansas. The Great Plains Laboratory has developed and determined the performance characteristics of this test. This test has not been evaluated by the U.S. Food and Drug Administration.

8/12/2009 Follow-up

- Very irritable and sarcastic at appointment.
- Continue baseline Rx as is.
- NEW: start diet – dairy free, gluten free
- NEW: start vitamins:
  - 4000 IU Vitamin D daily
  - Flavored cod liver oil
  - "ACES" – A, C, E, and Selenium

Last four months January 21, 2010

- On IgG diet. "He has been doing well on it."
- At Christmas, however, he "went off of it." Had cookies everywhere – couldn't keep him out of the wheat. Following that gluten feast he exploded on New Year's eve.
- Prior to that, his last explosive episode was in May – and has been good pretty well up until New Year's eve. When the two brothers got in the car it set Alan off. "It was bad."
- After the outburst, Alan specifically wanted to go back on the diet program. "He seems really good [now]."
- More functional medicine testing ordered.



ESSENTIAL AND OTHER ELEMENTS		RESULT µg/g	REFERENCE INTERVAL	PERCENTILE 2.5th 16th 50th 84th 97.5th
Calcium	(Ca)	441	200- 750	
Magnesium	(Mg)	25	25- 75	
Sodium	(Na)	16	20- 180	
Potassium	(K)	< 3	9- 80	
Copper	(Cu)	13	11- 30	
Zinc	(Zn)	180	130- 200	
Manganese	(Mn)	0.08	0.08- 0.50	
Chromium	(Cr)	0.35	0.40- 0.70	
Vanadium	(V)	0.027	0.018- 0.065	
Molybdenum	(Mo)	0.031	0.025- 0.060	
Boron	(B)	3.1	0.40- 3.0	
Iodine	(I)	1.9	0.25- 1.9	
Lithium	(Li)	< 0.004	0.007- 0.020	
Phosphorus	(P)	158	150- 220	
Selenium	(Se)	0.82	0.70- 1.2	
Strontium	(Sr)	1.1	0.30- 3.5	
Sulfur	(S)	49300	44000- 50000	
Cobalt	(Co)	0.006	0.004- 0.020	
Iron	(Fe)	5.5	7.0- 16	
Germanium	(Ge)	0.029	0.030- 0.040	
Rubidium	(Rb)	< 0.003	0.011- 0.12	
Zirconium	(Zr)	0.11	0.020- 0.44	

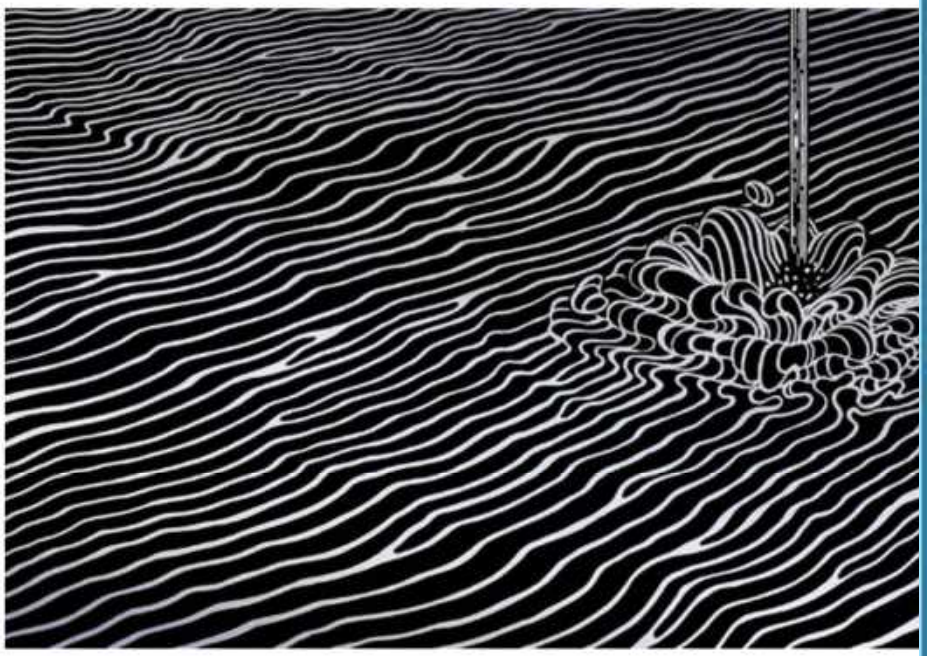
April 15, 2013
Low dose Lithium orotate started

The New York Times

SundayReview | OPINION

Should We All Take a Bit of Lithium?

By ANNA FELS SEPT. 13, 2014



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THE idea of putting a mind-altering drug in the drinkin
stuff of sci-fi, terrorist plots and totalitarian governmen
the outcry that occurred when putting fluoride in the wa
proposed, one can only imagine the furor that would en
thing were ever suggested.

Nutritional Lithium: A Cinderella Story

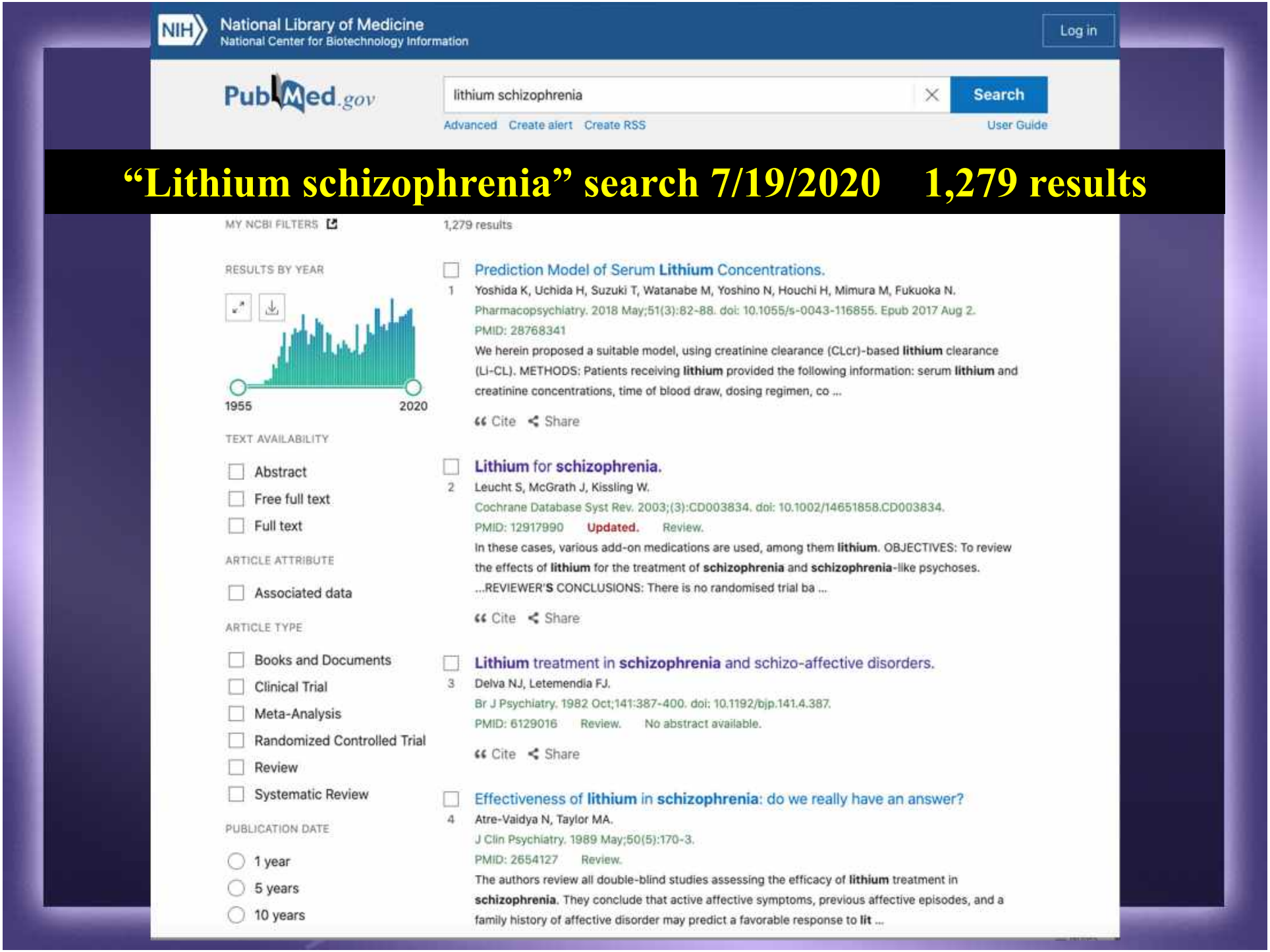
THE UNTOLD TALE OF THE MINERAL THAT TRANSFORMS LIVES AND HEALS THE BRAIN

By James M. Greenblatt, MD & Kayla Grossmann, RN

ESSENTIAL AND OTHER ELEMENTS

		RESULT µg/g	REFERENCE INTERVAL	PERCENTILE 2.5th 16th 50th 84th 97.5th
Calcium	(Ca)	361	200– 750	
Magnesium	(Mg)	29	25– 75	
Sodium	(Na)	21	20– 180	
Potassium	(K)	4	9– 80	
Copper	(Cu)	12	11– 30	
Zinc	(Zn)	200	130– 200	
Manganese	(Mn)	0.07	0.08– 0.50	
Chromium	(Cr)	0.30	0.40– 0.70	
Vanadium	(V)	0.022	0.018– 0.065	
Molybdenum	(Mo)	0.030	0.025– 0.060	
Boron	(B)	12	0.40– 3.0	
Iodine	(I)	2.3	0.25– 1.8	
Lithium	(Li)	0.017	0.007– 0.020	
Phosphorus	(P)	198	150– 220	
Selenium	(Se)	0.85	0.70– 1.2	
Strontium	(Sr)	0.95	0.30– 3.5	
Sulfur	(S)	49100	44000– 50000	
Cobalt	(Co)	0.004	0.004– 0.020	
Iron	(Fe)	5.2	7.0– 16	
Germanium	(Ge)	0.034	0.030– 0.040	
Rubidium	(Rb)	0.005	0.011– 0.12	
Zirconium	(Zr)	0.019	0.020– 0.44	

Repeat testing 13 months later – May 21, 2014
(after lithium orotate)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Clinical Trial
Meta-Analysis
Randomized Controlled Trial
Review
Systematic Review
PUBLICATION DATE
1 year
5 years
10 years
1 Prediction Model of Serum Lithium Concentrations.
Yoshida K, Uchida H, Suzuki T, Watanabe M, Yoshino N, Houchi H, Mimura M, Fukuoka N.
Pharmacopsychiatry. 2018 May;51(3):82-88. doi: 10.1055/s-0043-116855. Epub 2017 Aug 2.
PMID: 28768341
We herein proposed a suitable model, using creatinine clearance (CLcr)-based lithium clearance (Li-CL). METHODS: Patients receiving lithium provided the following information: serum lithium and creatinine concentrations, time of blood draw, dosing regimen, co ...
Cite Share
2 Lithium for schizophrenia.
Leucht S, McGrath J, Kissling W.
Cochrane Database Syst Rev. 2003;(3):CD003834. doi: 10.1002/14651858.CD003834.
PMID: 12917990 Updated. Review.
In these cases, various add-on medications are used, among them lithium. OBJECTIVES: To review the effects of lithium for the treatment of schizophrenia and schizophrenia-like psychoses. ...REVIEWER'S CONCLUSIONS: There is no randomised trial ba ...
Cite Share
3 Lithium treatment in schizophrenia and schizo-affective disorders.
Delva NJ, Letemendia FJ.
Br J Psychiatry. 1982 Oct;141:387-400. doi: 10.1192/bjp.141.4.387.
PMID: 6129016 Review. No abstract available.
Cite Share
4 Effectiveness of lithium in schizophrenia: do we really have an answer?
Atre-Vaidya N, Taylor MA.
J Clin Psychiatry. 1989 May;50(5):170-3.
PMID: 2654127 Review.
The authors review all double-blind studies assessing the efficacy of lithium treatment in schizophrenia. They conclude that active affective symptoms, previous affective episodes, and a family history of affective disorder may predict a favorable response to lit ...

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PLoS One. 2019 Jan 29;14(1):e0209223. doi: 10.1371/journal.pone.0209223. eCollection 2019.

Lithium is able to minimize olanzapine oxidative-inflammatory induction on macrophage cells.

Fernandes MS[1,2], Barbisan F[3], Azzolin VF[3], do Prado-Lima PAS[4], Teixeira CF[1], da Cruz Jung IE[1], Assmann CE[5], Riffel RT[2,6], Duarte MMMF[1,7], Aguiar-Ribeiro EM[8], da Cruz IBM[1,3].

Author information

Abstract

Conclusion:
"Lithium may attenuate olanzapine-induced oxidative & inflammatory responses that result from metabolic side effects associated with olanzapine."

PMID: 30695037 PMCID: PMC6350970 DOI: 10.1371/journal.pone.0209223

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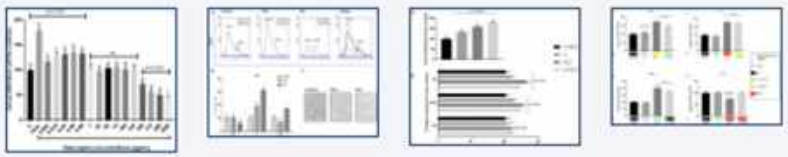

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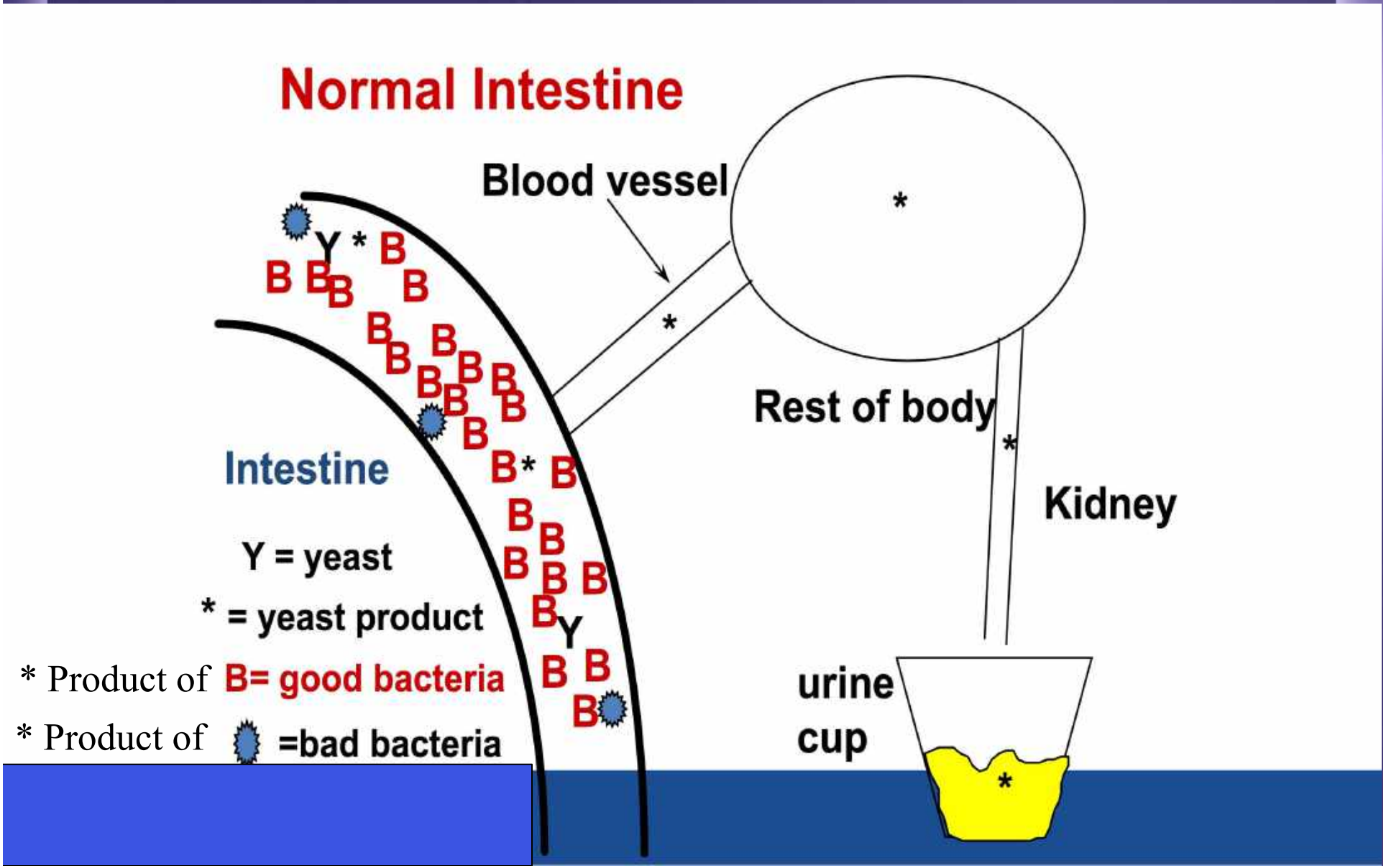
Putative role of trace element deficiencies in mental disorders

Diagnosis	Relevant elements
Depression:	Zn,Cr, Se, Fe, Co, I
PMDD, binge eating	Cr
Schizophrenia	Zn, Se, (and, per other articles, Li.)
Cognitive deterioration/ dementia	B, Zn, Fe, Mn, Co V
Autism	Zn, Mn, Cu, Co
Attention deficit disorder	Fe (check FERRITIN ***and*** Fe)

Excess quantity (overexposure, genetic error) can also lead to mental disturbances.

Janka Z. Ideggyogy Sz. 2019 Nov 30;72(11-12):367-379.

OAT Test: also useful for nutrient analysis



Intestinal Microbial Overgrowth

Yeast and Fungal Markers

1	Citramalic	0.11	-	2.0		0.34
2	5-Hydroxymethyl-2-furoic		≤	18	H	33
3	3-Oxoglutaric		≤	0.11		0.03
4	Furan-2,5-dicarboxylic		≤	13	H	20
5	Furancarbonylglycine		≤	2.3		0.09
6	Tartaric		≤	5.3		0.12
7	Arabinose		≤	20	H	31
8	Carboxycitric		≤	20		0.67
9	Tricarballylic		≤	0.58		0.05

November 18, 2012
Mild elevation – probiotic started

Probiotic in the gut… for neuroinflammation in the brain

The gut to brain neuroinflammatory connection (in obesity)

- Gut microbiota are relevant in mood disorders, eating behaviors, and body detoxification of persistent organic pollutants (POP)
- Modulation of gut-derived signals to the brain in a context of obesity = involved in the development of **neuroinflammation (which can alter behaviors)**

Choi B s-Y et al. Int J Obes. 2020 June 10. doi10/1038/s41366-020-0618-3. (Online ahead of print)

Role of Interleukin-6 in Depressive Disorder

- Evidence from animals & clinical studies show increased peripheral or central cytokine interleukin -6 levels playing an important role in stress reaction, depressive disorder, and physical disorder comorbid with depression
- Increased release of IL6 – associated with MDD prognosis and tx response.
- "The important role of neuroinflammation in MDD pathogenesis has created a new perspective that the combining of blood IL-6 and other depression-related cytokine levels may help to classify MDD biological subtypes."
- Agents cites as helpful: current antidepressants, "herb medication," pre-/probiotics.

Ting, E Y-C. In J Mol. Sci. 2020 Mar 22;21(6):2194.

January 2010 to 2014

- November 2012 – *high* IgG allergies to dairy and wheat. Diet again emphasized.
- Elemental lithium deficiency noted (functional testing)
- August 2014 – elevated Arabinose on OAT test – treated with Nystatin
- Probiotics added to deal with acid reflux
- Macro and Micronutrient deficiencies identified in hair testing and organic acid testing.
- Generally stable. Subtle improvement. No more meltdowns. No more concerns about going out in public.

Gastrointestinal (GI) candidiasis

4 of 5 papers in the literature "schizophrenia candida"

- 1. **Clozapine found to inhibit yeast budding to hyphal transition**. *This and other antifungals* might have therapeutic activity in the future.
  - Midkif J et al. **Small molecule inhibitors of the Candida albicans budded-to-hyphal transition act through multiple signaling pathways.** PLoS One. 2011;6(9):e25395.
- 2. Cyclic dipeptides from food and intestinal yeast cyclic dipeptides may play a role in causing psychiatric disorders such as schizophrenia. From cancer research, cyclic dipeptides such as cyclo (proline-phenylalanine) have been found to activate the pathways of apoptosis and to cause programmed cell death.
  - Semon BA. Dietary cyclic dipeptides, apoptosis and psychiatric disorders: a hypothesis. Med Hypotheses. 2014 Jun;82(6):740-3.

3. Odds ratio of schizophrenia with candida albicans seropositivity

- Case control differences investigated regarding candida albicans.
- 947 individuals studied
  - 261 with schizophrenia (139 of which had 1st episode schizophrenia
  - 270 with bipolar disorder
  - 277 non-psychiatric controls
- **C. albicans seropositivity conferred increased odds for a schizophrenia diagnosis (OR 2.04-9.53, P⩽0.0001).**
  - Severance EG et al. Candida albicans exposures, sex specificity and cognitive deficits in schizophrenia and bipolar disorder. NPJ Schizophr. 2016; 2: 16018.
    - Published online 2016 May 4.
      - Full article: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4898895/

4. Probiotic normalization of Candida albicans in schizophrenia: A randomized, placebo-controlled, longitudinal pilot study.

- Longitudinal, double-blind, placebo-controlled pilot investigation of 56 outpatients with schizophrenia. Studied impact of probiotic treatments on yeast antibody levels, and between levels of antibodies and abdominal discomfort/ psychiatric symptoms.
- "Results from this pilot study hint at **an association of C. albicans seropositivity with worse positive psychiatric symptoms**, which was confirmed in a larger cohort of 384 males with schizophrenia."

Severance EG et al. Brain Behav Immun. 2017 May;62:41-45.

How to order the labs (Lab Corp, Quest):

- Candida antibodies – IgG, IgA, Ig M with QUANTITATIVE TITERS
- Gluten:
  - Anti-gliadin antibodies - IgG, IgA, IgM with quantitative titers
  - Tissue trans-glutaminase

Organic Acids Test - Nutritional and Metabolic Profile

Metabolic Markers in Urine	Reference Range (mmol/mol creatinine)		Patient	Reference Population - Males Age 13 and Over
Intestinal Microbial Overgrowth				
Yeast and Fungal Markers				
1 Citramalic	0.11 - 2.0		0.72	
2 5-Hydroxymethyl-2-furoic	≤ 18	H	59	
3 3-Oxoglutaric	≤ 0.11		0	
4 Furan-2,5-dicarboxylic	≤ 13	H	45	
5 Furancarbonylglycine	≤ 2.3		0.61	
6 Tartaric	≤ 5.3		0.46	
7 Arabinose	≤ 20	H	48	
8 Carboxycitric	≤ 20		1.0	
9 Tricarballylic	≤ 0.58		0.02	

Fungal markers went up; ***Nystatin started.***

August 31, 2014

Gliadin IgG/IgA Ab Prof, EIA *Reported On: 4/26/2018 10:12*

Deamidated Gliadin Abs, IgA	2	units	0-19	CB	F

Negative	0 - 19
Weak Positive	20 - 30
Moderate to Strong Positive	>30

Deamidated Gliadin Abs, IgG	3	units	0-19	CB	F

Negative	0 - 19
Weak Positive	20 - 30

Candida Antibodies IgG, IgA, IgM *Reported On: 4/26/2018 10:12*

Candida Antibodies IgG	<30	U/mL	0-29	BN	F

Results for this test are for research purposes only by the assay's manufacturer. The performance characteristics of this product have not been established. Results should not be used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure.

Candida Antibodies IgM	<10	U/mL	0-9	BN	F

Results for this test are for research purposes only by the assay's manufacturer. The performance characteristics of this product have not been established. Results should not be used as a diagnostic procedure without confirmation of the diagnosis by another medically

Originally Reported On: 4/17/2018 10:34 AM Accession: 588844 Patient ID: 4

Off-target effects of psychoactive drugs revealed by genome-wide assays in yeast

Drug	effect
81 compounds	“inhibited wild-type yeast growth”
Fluoxetine	“interfered with establishment of cell polarity
Cyproheptadine	Targeted essential genes with chromatine-remodeling roles
Paroxetine	Interfered with RNA metabolism genes
Clozapine Haloperidol Pimozide	**All had “off target” effects in yeast**

Ericson E et al. PLoS Genet. 2008 Aug 8;4(8):e1000151. doi: 10.1371/journal.pgen.1000151.on

Another off-target effect of clozapine

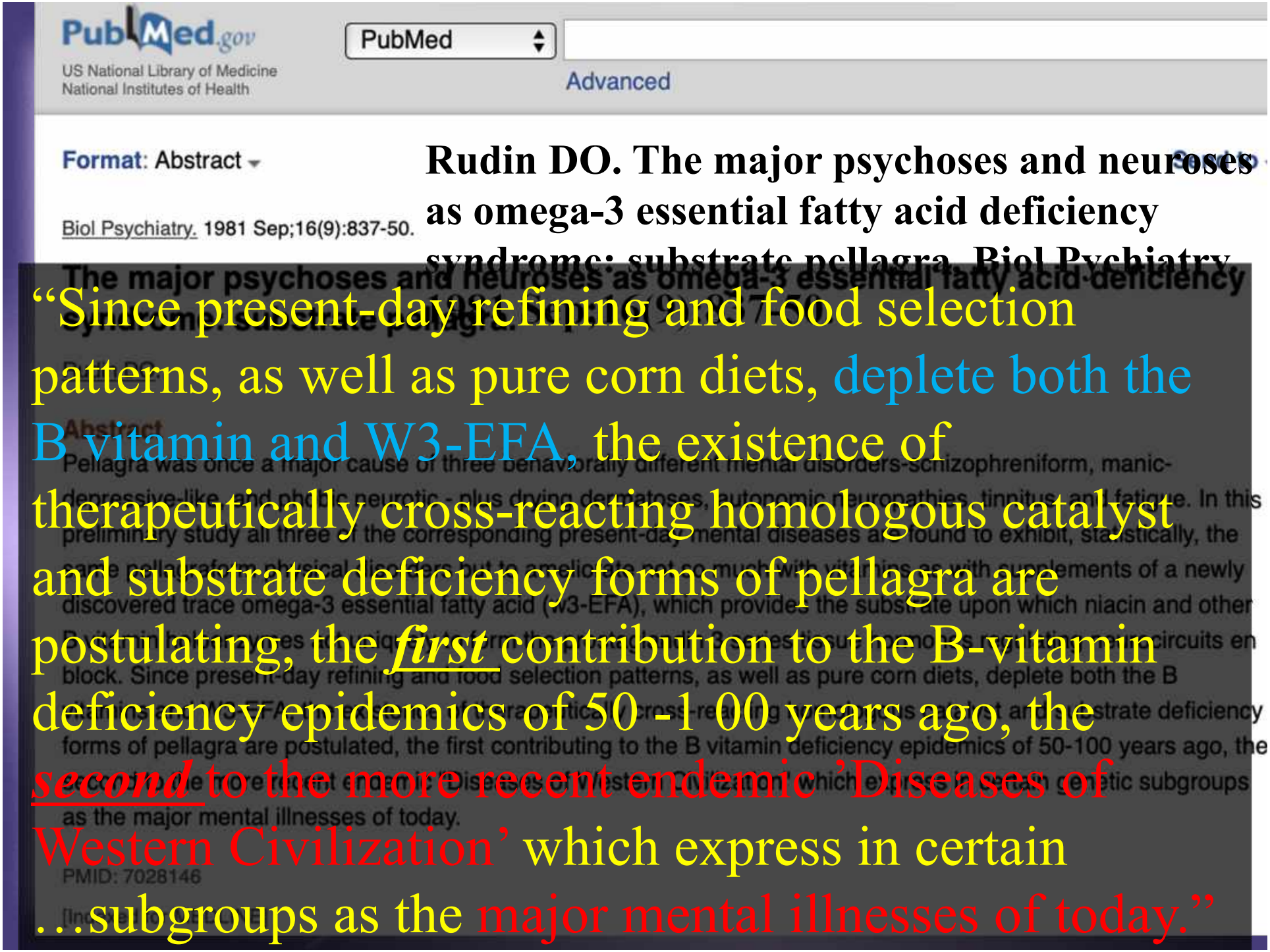
- AA makers upregulated in bipolar disorder & schizophrenia, associated with neuroinflammation.
- "The increase iPLA2 expression following clozapine suggests increased production of anti-inflammatory DHA metabolites, and, with increased BDNF and drebrin, clear neuroprotective action."

Kim, H-W, et al. Effects of chronic clozapine administration on markers of arachidonic acid cascade and synaptic integrity in rat brain. Psychopharmacology (Berl). 2012 Aug;222(4):663-74.

A mashup from the literature…

- “MTHFR deficiency schizophrenia” – 8 citations
- “Vitamin D deficiency schizophrenia” – 133
- “B12 deficiency schizophrenia” – 37
- “B-vitamin deficiency schizophrenia – 2
- “PUFA deficiency schizophrenia” – 9
- “Omega 3 schizophrenia”

PubMed Search – updated August 9, 2020


PubMed.gov
US National Library of Medicine
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Format: Abstract
Biol Psychiatry. 1981 Sep;16(9):837-50.
Rudin DO. The major psychoses and neuroses as omega-3 essential fatty acid deficiency
“Since present-day refining and food selection patterns, as well as pure corn diets, deplete both the B vitamin and W3-EFA, the existence of therapeutically cross-reacting homologous catalyst and substrate deficiency forms of pellagra are postulating, the first contribution to the B-vitamin deficiency epidemics of 50 -1 00 years ago, the second to the more recent endemic ’Diseases of Western Civilization’ which express in certain …subgroups as the major mental illnesses of today.”

- PUFA decreases noted in schizophrenia patients
- DHA in peripheral blood (plasma and erythrocyte membranes) as well as brain of schizophrenia patients at different developmental phases of the disorder.
- **Omega 3 supplementation most effective in patients with low PUFA baseline.**
  - Hsu, M et al. Beneficial effects of omega-3 fatty acid supplementation in schizophrenia" possible mechanisms. Lipids Health Dis. 2020 Jul 3;19(1):159.
- Beneficial effects found more in mood disorders (MDD & bipolar): **"omega 3 PUFA supplementation reduces symptoms of depression."**
  - Ross BM et al. Omega-3 fatty acids as treatments for mental illness: which disorder and which fatty acid? Lipids Health Dis. 2007 Sep 18;6:21.
- EPA may be more efficacious in schizophrenia than DHA
  - (ibid.)

Alan – updates

- March 26, 2019:
  - "We go out every day. We're going to restaurants now, and we are going anywhere without hesitation."
  - "Each day I have more energy and less anxiety. When I'm out and about in the cars – it doesn't bother me any more….. It's like a whole new experience."
  - RX:
    - Clozapine (300 mg bedtime), vortioxetine, Vitamin D3. L-methylfolate in a.m. , Coenzyme Q10,
    - Medical Rx per his primary care MD
    - Still on IgG diet.
- October 21, 2019
  - "Every day we're getting out and doing things."
  - Back on e-bay selling guitar stuff.
  - Went to the Fall Festival twice, including watching the parade.
  - No affective symptoms. Not paranoid. Good energy.

Integrative Interventions & how to consider them

- Diagnose accurately. But don't misdiagnose.
- Consider IgG food sensitivities
- Omega 3
- MTHFR
- Magnesium
- GI health/candida

Focal brain inflammation, autism & strategies

AUTISM

- ASD children – social/learning disabilities that affect up to 1/80 children in US (2013).
- No pathogenesis or reliable biomarkers.
- Many children with ASD regress around age 3
  - Often after a specific event such as reaction to vaccination, infection, stress, or trauma implying some epigenetic triggers.
- ASD children respond disproportionally to stress
- They are affected by food and skin allergies

Theoharides TC et al. Focal brain inflammation and autism . J Neuroinflammation. 2013 Apr 9;10:46.

Autism: a master class in one article

- Autism = biologically based neurodevelopmental disorder affecting two domains: (1) impairment in social skills, (2) restricted/repetitive behavioral pattern of interest.
- Symptoms can be observed before 3 yoa.
- Strong genetic and environmental factors raise the occurrence]
- ACh, 5-HT, DA, GABA, Glu, andHA neurotransmitters implicated in the onset and progression of ASD
- All prescription Rx used have significant side effects

Eisaa N et al. Front Neurosci. 2018;12:304. Free downloadble .pdf here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5964170/

Joey: Seen for intake in my office – 9/5/2012

(all photos of this child used with express permission of his mother)

- Alert. Serious. Intent on toys. Played with them loudly. Not speaking in complete sentences. Phonated repetitively.
- Huddled down and pulled his lunch box in front of him when I asked him a question.
- Obsessive play with toys. "Push push push."
- Known to be demonstrably hypothyroid

Extensive laboratory testing ordered. Thyroid Rx restarted (at low dose).

December 5, 2012 follow-up

- RX:
  - Porcine thyroid 1 ½ grains for KNOWN hypothyroidism (with PERFECT labs); Nystatin; high dose MVI with B-complex; GSH precursors, Cod liver oil, B6, Vit C, probiotics, 1 mg ionic Lithium.
  - On food antigen diet.
- Family now able to go to church and sit in pew. Went to MGM's 95th birthday party.
- Mental Status Examination:
  - Alert, pleasant, happy, engaging. Talking more. Gait improved. Speech much more intelligible. Played happily and cooperatively with Dad.

Relevance of these supplements in ASD

Intervention	documentation
Nystatin	Kantarcioglu AS et al. Mycopathologia. 2016. (1 paper)
B-complex	Wang T et al , Bjorklund et al – 2 papers on "B-complex autism neuroinflammation") . 30 papers exist on "B-complex autism."
Glutathione	19 results – "glutathione autism neuroinflammation"
Cod liver Oil (PUFA)	5 results – "omega 3 neuroinflammation autism"
B6	4 results – "B6 neuroinflammation autism"
Vitamin C	60 results of "Vitamin C autism"
Probiotics	2 results for "probiotics neuroinflammation autism" 159 results for "probiotics autism"

Search on www.pubmed.gov August 10, 2020

Microbiota-Gut-Brain Axis: Yeast Species Isolated from Stool Samples of Children with Suspected or Diagnosed Autism Spectrum Disorders and In Vitro Susceptibility Against Nystatin and Fluconazole

- Candia in intestines causes lower absorption of carbs and minerals, and higher toxin levels.
- 3 year deposited yeasts isolated from stool samples of children with dx'ed or suspect ASD
- This was coupled with a 17 year retrospective analysis.
- 57.4% of stool specimens + for candida albicans.

Kantarcioglu, AS et al. Mycopathologia. 2016 Feb;181(1-2):1-7.

Mouse study of gestational B-vitamin supplementation which alleviate the PM2.4-induce autism –like behavior and hippocampal neurodevelopment in mice offspring.

- PM 2.5 (fine particulate matter) = worldwide environmental issue – induces hippocampus injury and leads to autism-like behavior (communication deficits and stereotyped repetitive behavior in children through neuroinflammation and neurodegeneration)
- Folic acid, B6 and B12 used in treatment group
- "B-vitamin significantly alleviated neurobehavioral impairment reflected in social communication disorders."
  - Also corrected synaptic loss and it educed mitochondrial damage in hippocampus

Wang, T et al. Ecotoxicol Envrion Saf. 2019 Dec 15:185:109686.

Microbiota-Gut-Brain Axis: Yeast Species Isolated from Stool Samples of Children with Suspected or Diagnosed Autism Spectrum Disorders and In Vitro Susceptibility Against Nystatin and Fluconazole

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The REST of the Story - Joey

9/5/2012

9/15/2013

Discussion of holistic options

- If ADHD, Autism, Depression, or schizophrenia is diagnosed, assume neuroinflammation.
- Strategies:
  - Fish oil
  - Magnesium
  - L-methylfolate.
  - Eliminate identified food antigens.
  - Probiotics.
  - Anti-candida Rx.

Palace of Fine Arts – 1893. Daniel Burnham, architect
(Now part of the Museum of Science and Industry, Chicago, IL)

"Make no little plans

*…they have **no** magic to stir men's blood* and *probably themselves will not be realized.* ***Make big plans****;* ***aim high in hope and work****, remembering that a noble, logical diagram once recorded will never die, but long after we are gone be a living thing, asserting itself with ever-growing insistency."*

Daniel Burnham (1846-1912)
World famous Chicago architect and the single reason that Chicago was named the site of the ***Columbian Exposition*** (World's Fair) in 1893.

Commence Treatment!!

BEHAVIORS/PHENOTYPE
depressed?
anxious?
meltdowns
OCD?
Bipolar/schizophrenia
"Autism"

NT's – 5HT, NE, DA. Membrane stabilization. Antipsychotics.

- THYROID PROBLEMS? Trace elements?
- Adrenal and sex hormones?
- GI issues?
- Excess screen time (video games, "dopamine resistance"?)

Workup:

- Conventional labs incl. ALL thyroid testing and adrenal/sex hormone testing.
- FUNCTIONAL (integrative) labs
  - IgG panel
  - OAT
  - Heavy metals
  - Mold panels

Pharmacogenomics

WHAT ARE THE GENES?
MTHFR - enough NT's made?
COMT - breakdown
CypP450 - adequacy of treatment?

RX:

- Conventional meds – antidep, ADHD Rx, mood stabilizers.
- GI meds/supplements
- Supplements, foundational nutritionals (eg. L-MF).
- Diet modification

adequate proteins to make them?
Digestion?
Omega 3 fatty acids?
Vitamin D
Inflammatory cytokines (IgG reactions?)
shift of NE to DA with HPPA from clostridia?
OSA? Sleep disorder?

Childhood trauma – abuse, neglect

Perhaps the ability not only to acquire the confidence of the patient, but to deserve it, to see what the patient desires and needs, comes through the sixth sense we call intuition, which in turn comes from wide experience and deep sympathy for and devotion to the patient, giving to the possessor remarkable ability to achieve results.

...William J. Mayo, MD - 1935