

MTHFR and more

Genetic and Environmental

Treatments to improve

your life

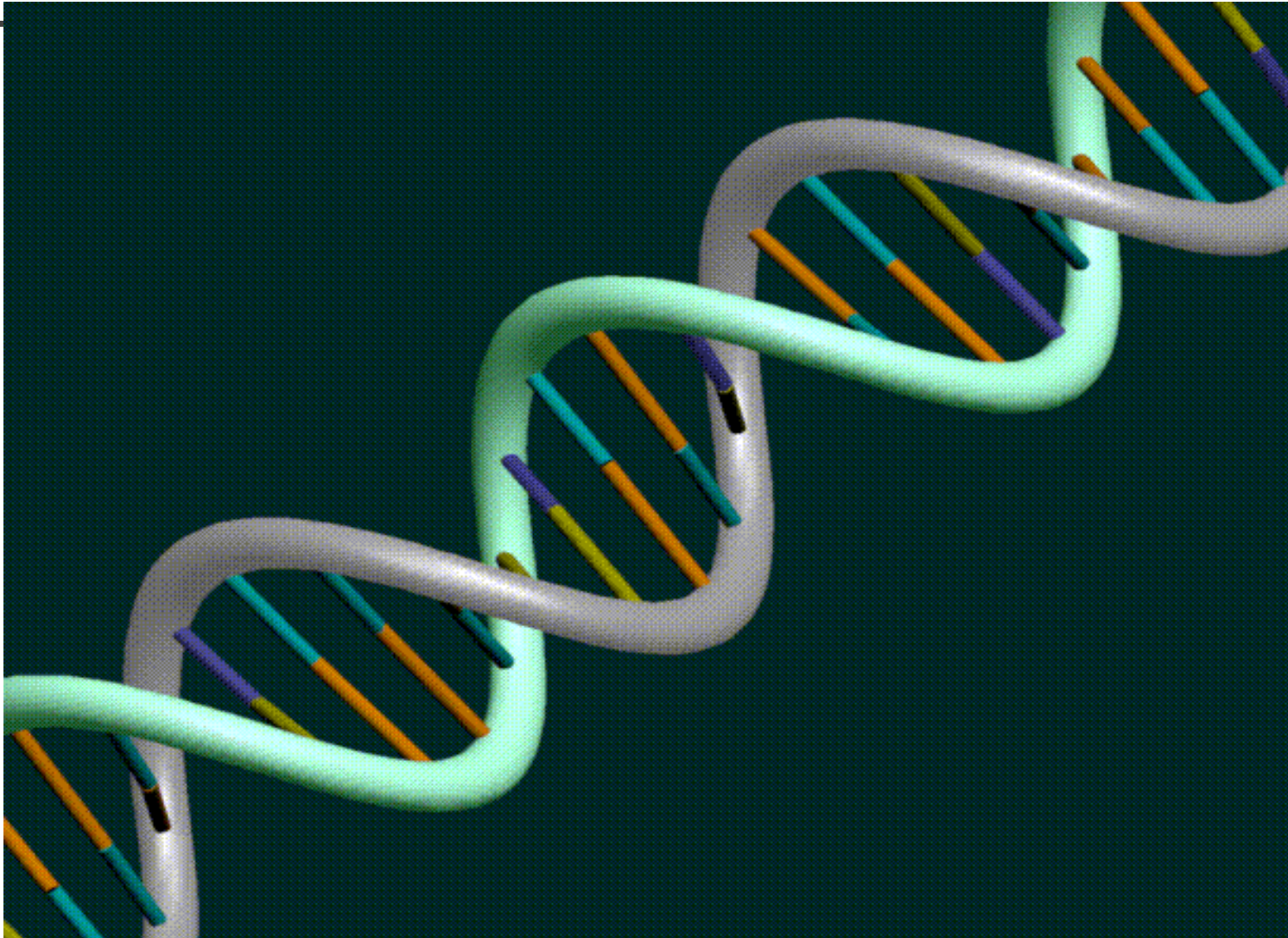
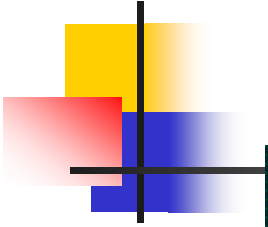
Neil Rawlins, MD



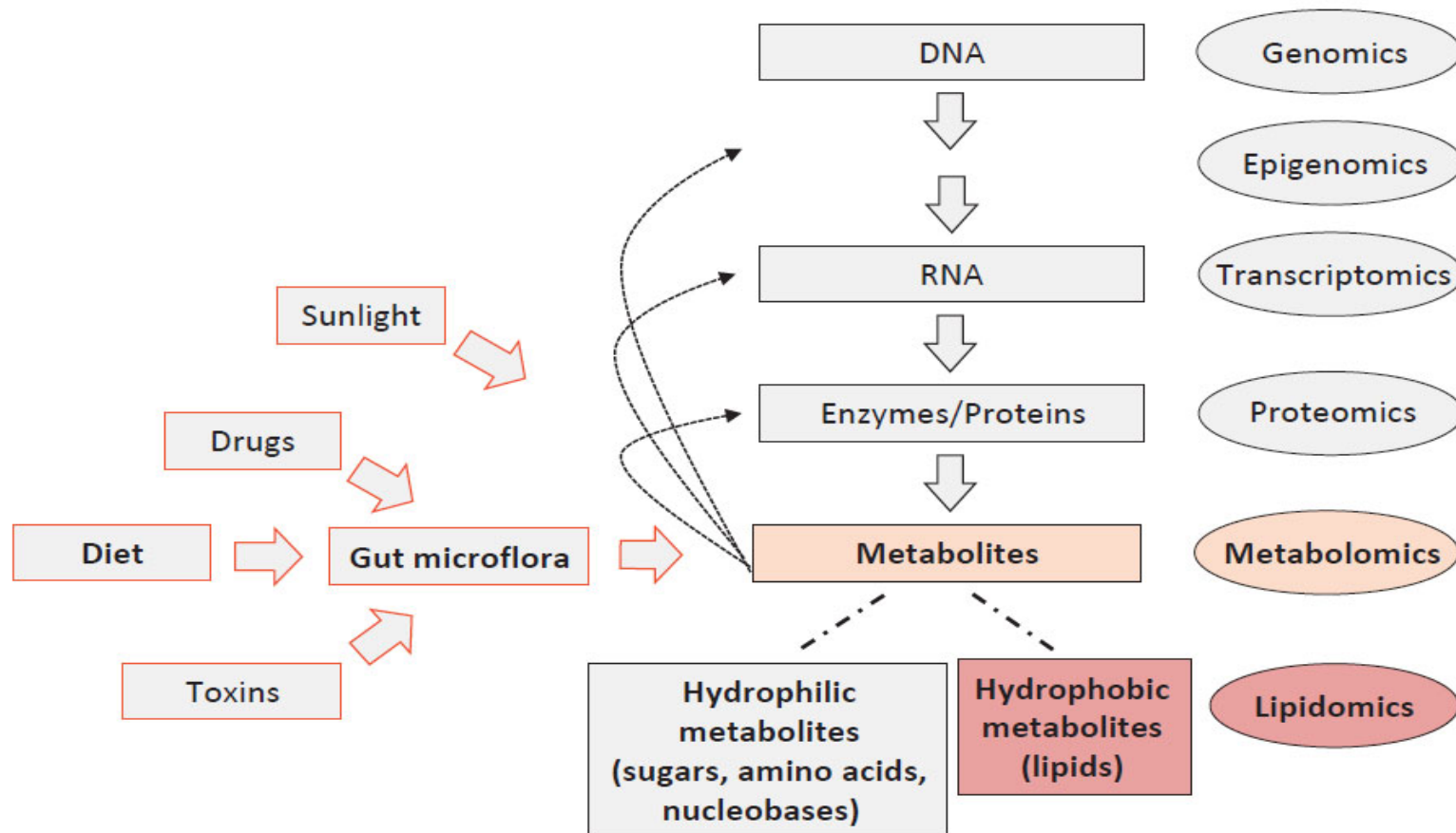
Introduction

- There are two major metabolic pathways that affect many health problems. The **Methylation** and the **Glutathione** pathway
- Nutritional supplements help improve symptoms

Thank You Human Genome Project!

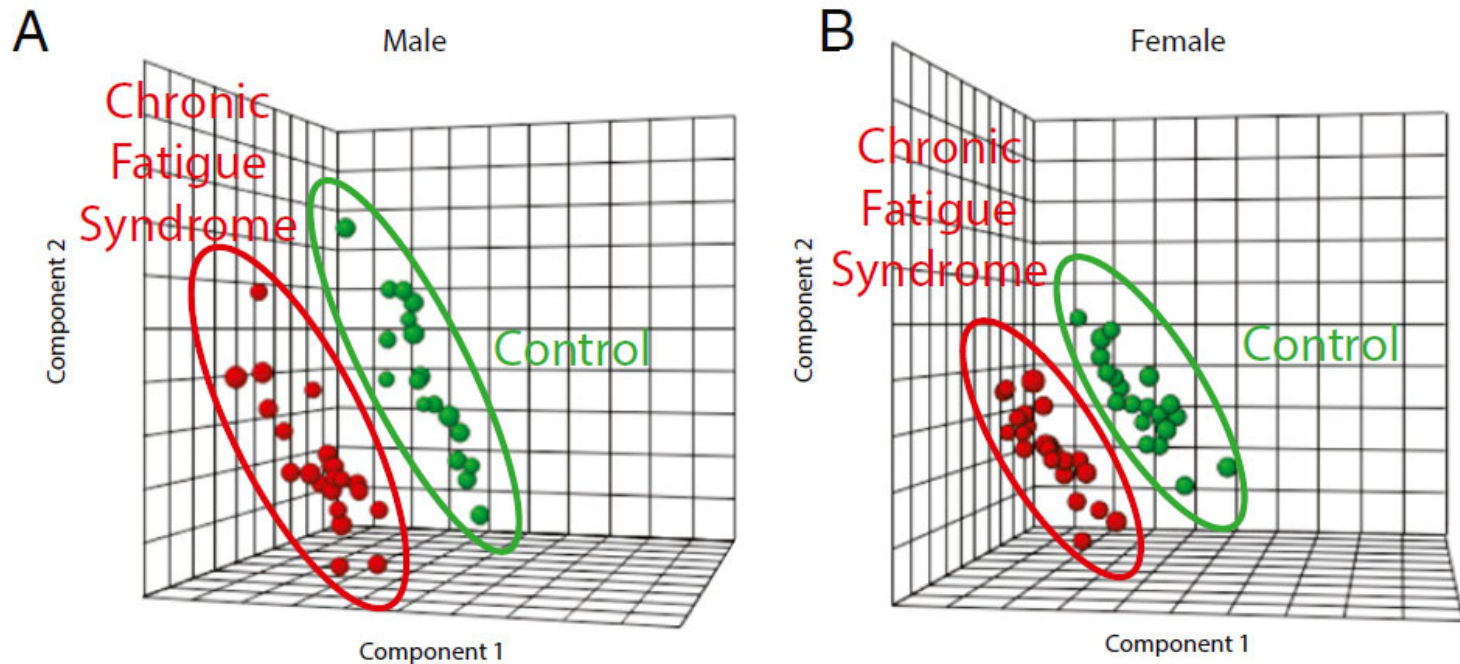


Many Factors affect your Health and Well Being



An emerging role for Metabolomics in Nutrition Science
J Nutrigenet Nutrigenomics 2013;6:181-200

Metabolomics for Chronic Fatigue It is Real!!!



Metabolic Features of Chronic Fatigue Syndrome. Naviaux et al.
www.pnas.org/cgi/doi/10.1073/pnas.1607571113



MTHFR Gene

The most studied

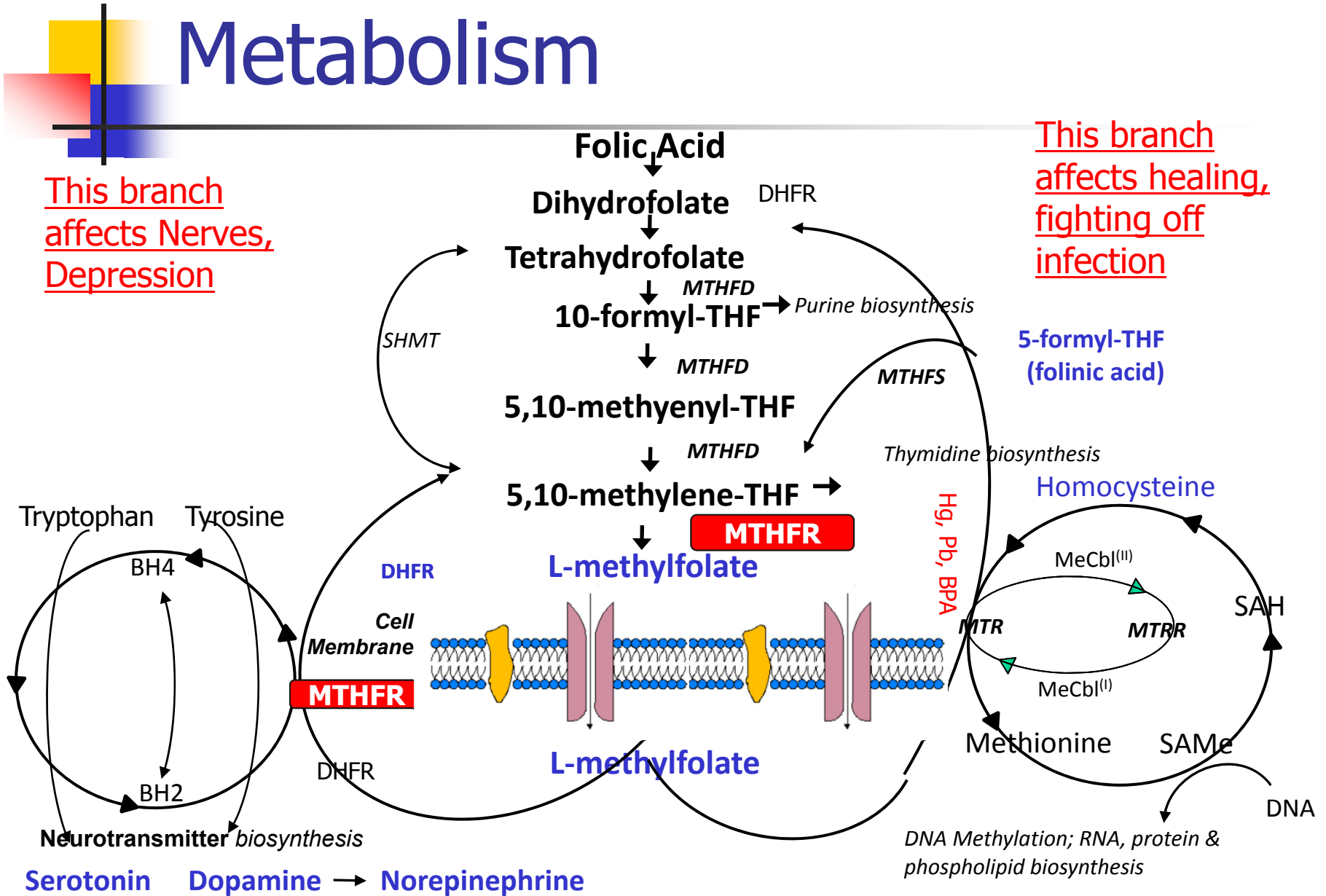
- Not everyone is born equal, as far as methylation is concerned
- Many toxins affect this pathway
- Nutritional treatments help most people

MTHFR

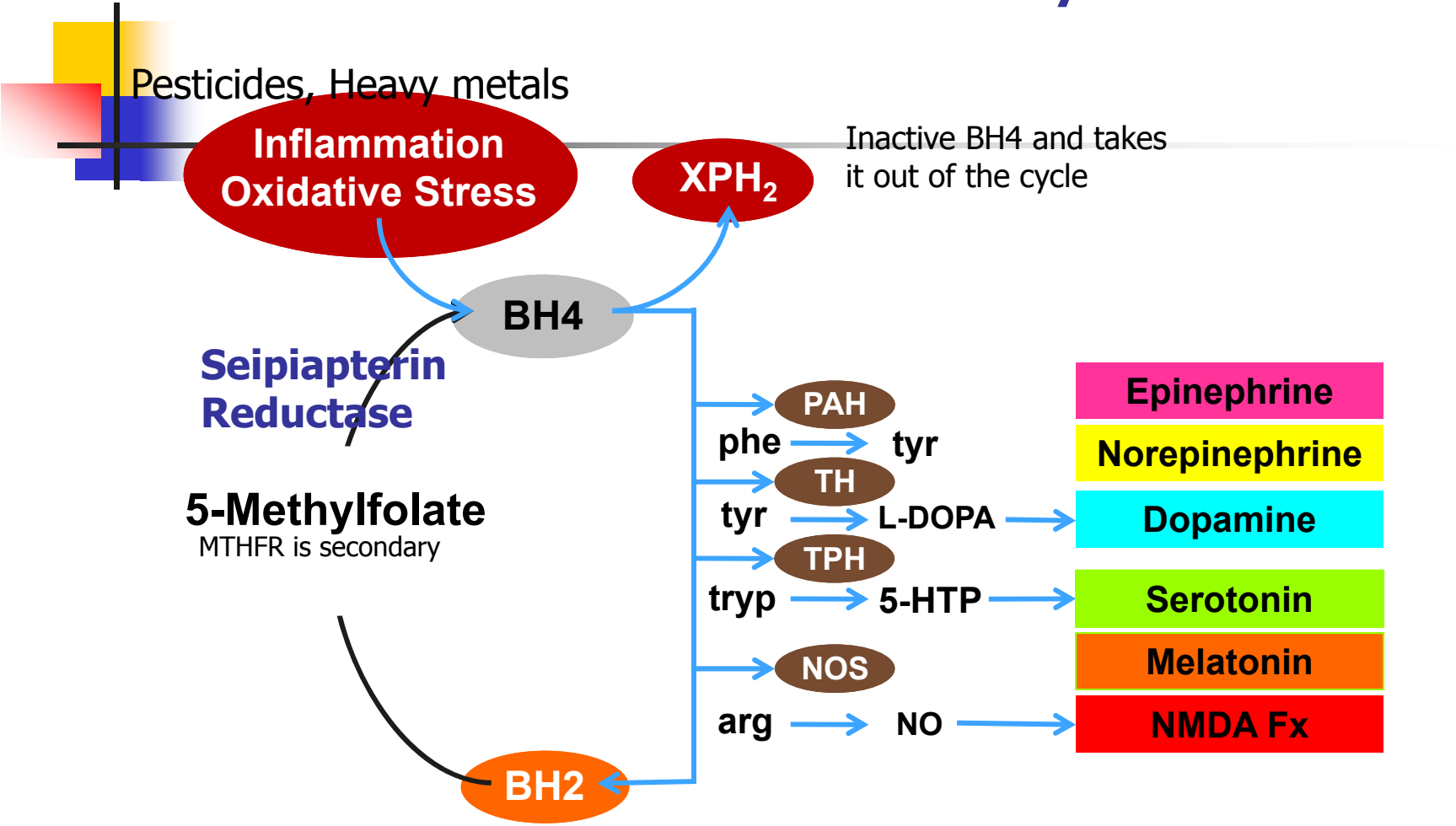
FDA reviewed treatments

- Depression (Deplin)
- Anxiety (Deplin)
- Memory Loss (CerefolinNAC)
- Diabetic neuropathy (MetaNX)
- High Risk Pregnancies (Neevo)

Genetic Variants of Folate Metabolism



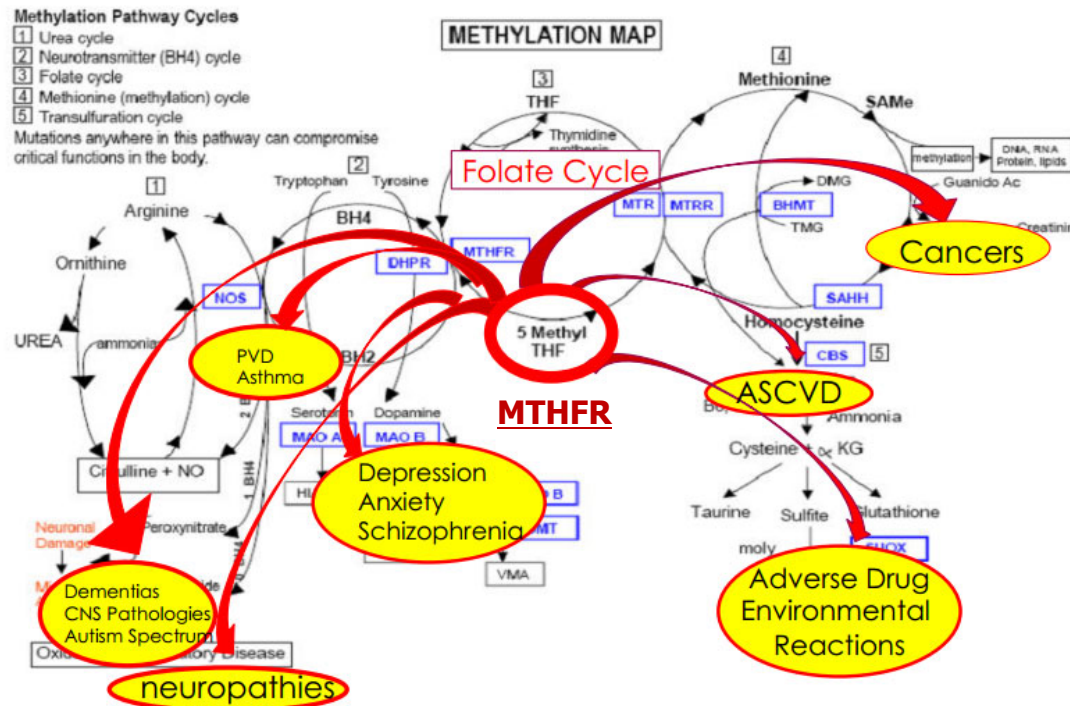
BH4 Pathway



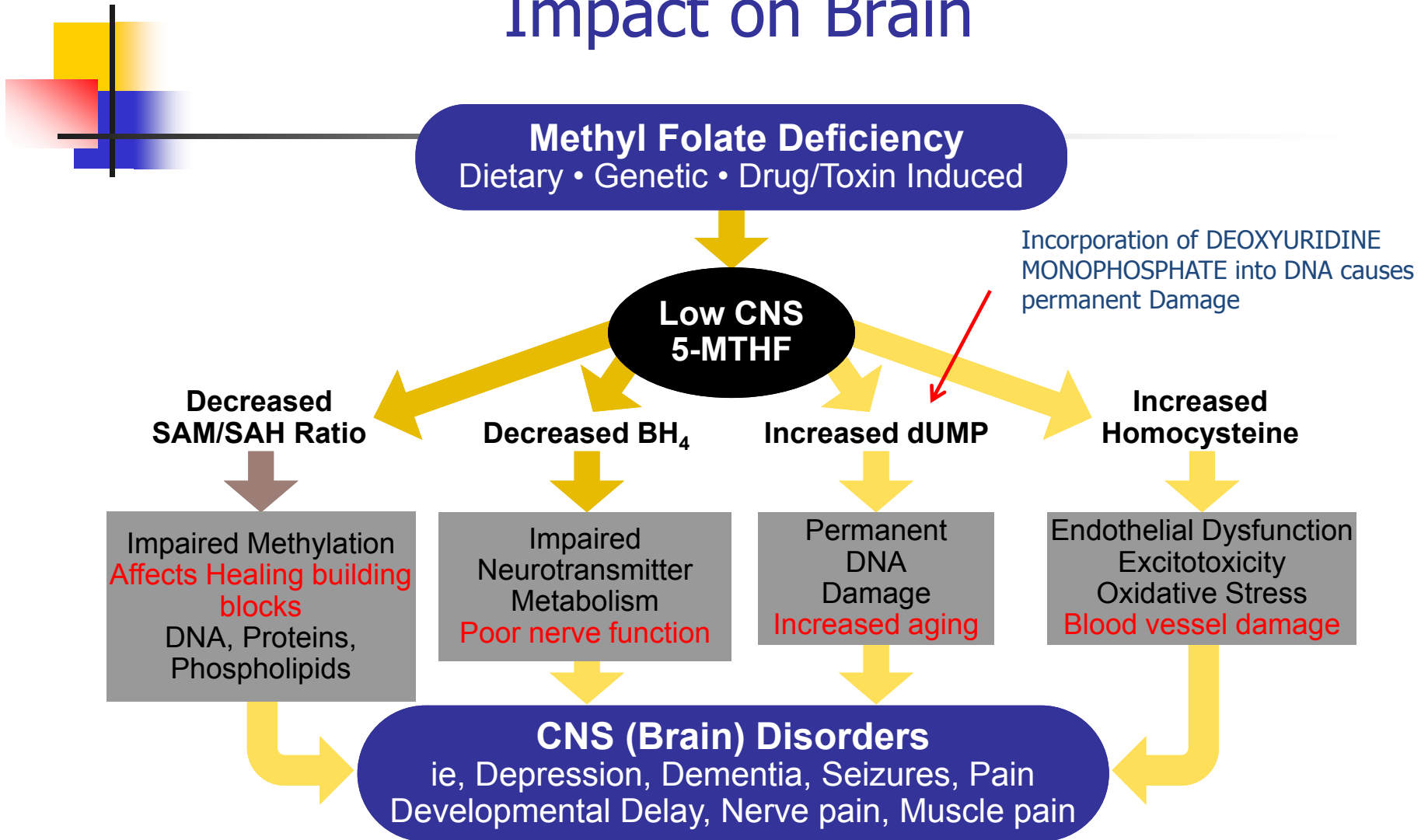
Haroon E, et al. *Neuropsychopharmacology*. 2012;37(1):137-162.

Methylfolate is the Key Pathway to many adverse reactions/Diseases

B-Vitamin Status and Methylation



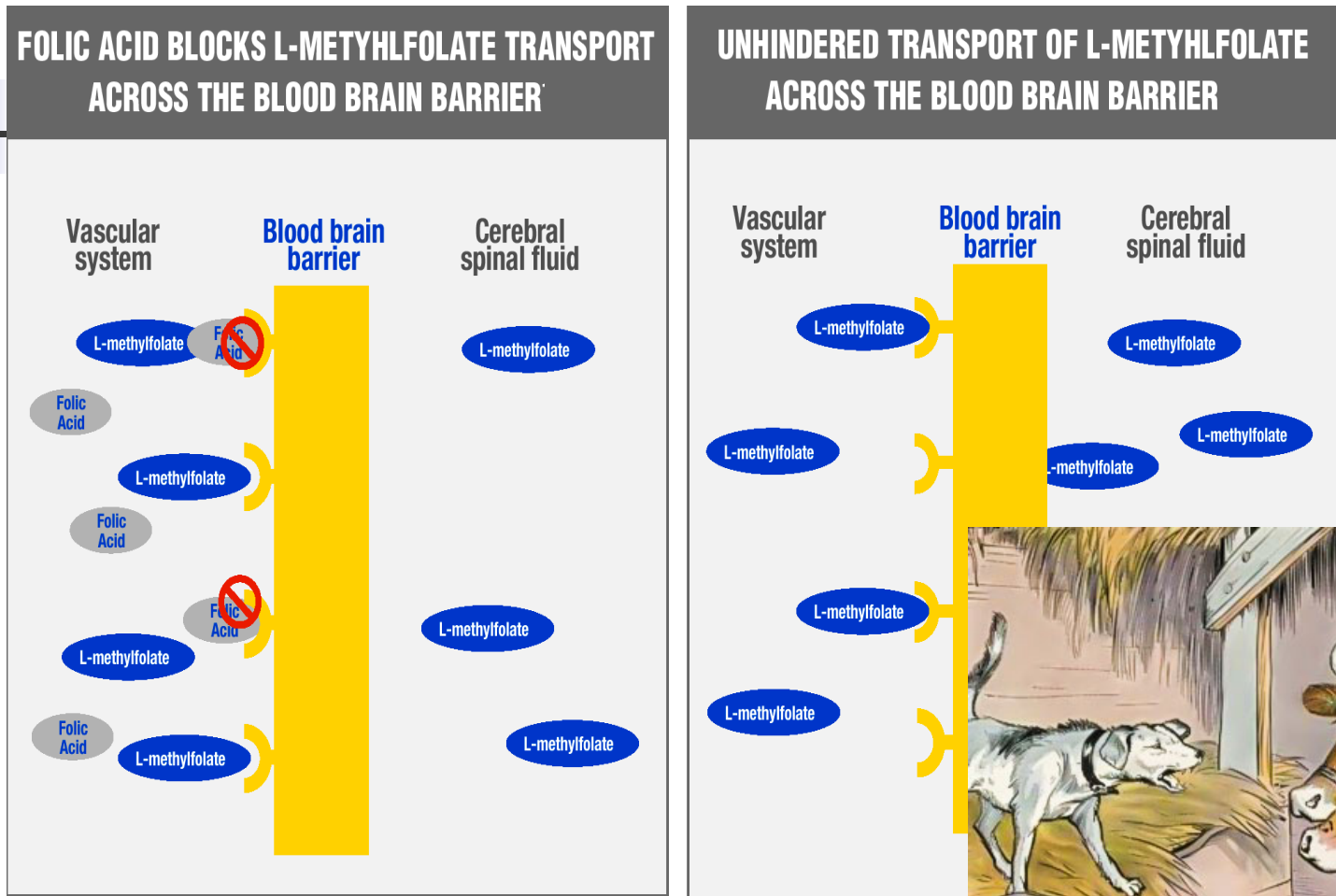
Methyl Folate Deficiency Impact on Brain



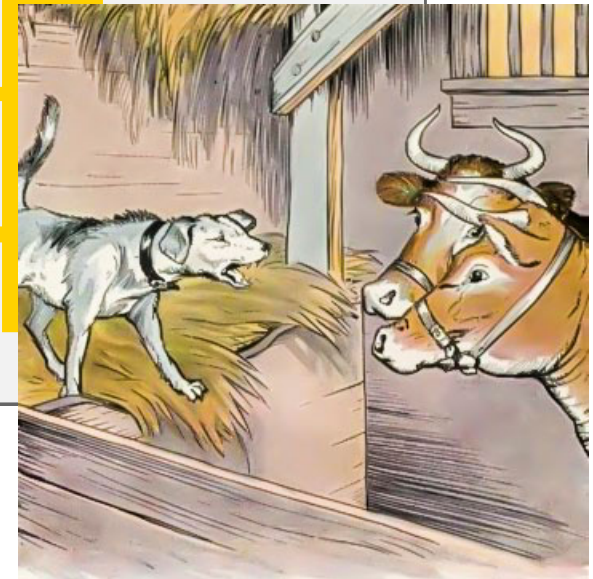
Bottiglieri T, Reynolds E. In: Bailey LB, ed. *Folate in Health and Disease, Second Edition*. Boca Raton, FL: Taylor & Francis Group; 2009:355-380.

Sedwick, D.W. et al Antifolate-induced misincorporation of dUMP into DNA. *Proc. Natl. Acad. Sci.* V78,2,pp 917-921 Feb 1981

The Folate form is crucial to make it effective



Regular folate is like the Dog in the Manger





Conditions Improved by Methylation/Glutathione

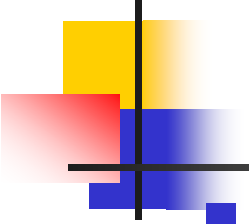
- Fibromyalgia
- Chronic Fatigue
- Irritable Bowel
- Migraines
- Bipolar, Schizophrenia, Parkinson's
- Autism, Autism spectrum disorders
- Prevention of Birth Defects



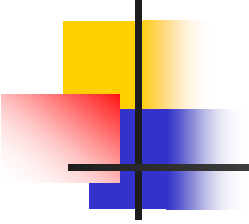
MTHFR and Autism Link

- Women not taking prenatal vitamins immediately before and during a pregnancy were **2X** as likely to have a child with autism
- If the women also had MTHFR, they were **7X** as likely to have a child with Autism
 - Epidemiology: July 2011 - Volume 22 - Issue 4 - pp 476-485

Risk factors for low L-Methylfolate

- 
1. Bottiglieri T. 2005. 29:1103-12.
 2. Stahl SM. *J Clin Psychiatry*. 2008; 69(9):1352-53.
 3. Sobczyriska-Malefora A et al. *Blood Coagul Fibrinolysis*. 2009; 20(4):297-302.
 4. Amilburu A, et al. *J Physiol Biochem*. 2201;57(2):71-80.
 5. PDR® For Nutritional Supplements, 2001. ISBN: 1-56363-364-7:157-67.
 6. Garg R, et al. *Am Heart J*. 1999;138:1082-7.
 7. Bolander-Gouaille C, Bottiglieri T. *Homocystiene Related Vitamins and Neuropsychiatric Disorders*. France: Springer-Verlag; 2003.
 8. Oskooilar N., et al. *J Clinincal Psychiatry*. 2009. 70(11):1609-10.
 9. Mahabir, S et al. *Eurpoean Journal of Clinical Nutrition*. 2008;62:644-650.

- **Meds:** Methotrexate, Antisiezure drugs, Metformin, Birth control pills, Antidepressants
- **Disease:** Diabetes, Crohns, Kidney failure, Thyroid disease
- **Lifestyle:** Smoking, Alcohol, BPA/toxin Exposure, Heavy metals
- **Aging:** Methylfolate more difficult to get in the brain
- **Genetics:** MTHFR, MTR, MTRR
- **Obesity:** BMI >30



MTHFR polymorphisms

What can I do?

- Testing? Not needed for most people
 - No great testing protocol yet
- Good nutrition necessary but not sufficient in this gene defect
- Reduce Toxins that affect this pathway
 - Heavy Metals (Lead, Arsenic, Cadmium)
 - Mercury(Dental filings, Fish)
 - BPA, Plastic stuff
 - Pesticides



Environmental concerns that can effect metabolic pathways

- Heavy Metal Toxicity is prevalent
 - Low level arsenic associated with diabetes
- BisPhenol A is common in plastics
 - Inhibits methylation pathway in rats and rat fetuses
 - Is associated with Diabetes, Heart disease, Stroke, Liver Disease
 - Estrogen disrupter, associated with PCOS, endometriosis



General Recommendations

1. Decrease exposure to toxins
 - Water filters, locally grown foods
2. Improve the body's Metabolism
 - Improve diet
 - Supplement around defects
3. Clear heavy metals if symptomatic



President's Cancer Panel Recommendations 2009

- Remove shoes when entering home
- Filter water, BPA free water bottles
- Don't drink from bottled water
- Microwave in glass or ceramic
- Use non-toxic cleaners
- Wash Fruits and vegetables
- Avoid pesticides
 - President's Cancer Panel annual report 2009.
"Reducing environmental cancer risk, What we can do now"
 - www.ourstolenfuture.org/basics/chemlist.htm



Other factors that help

- Dietary, vegetables, berries, fruits
 - Better if grown locally
- Mathematics, Accounting
 - Engineers, creative people
- Piano, Classical music
- Exercise
- Band (not rock band) participation (structured music)



Improve metabolism

General guidelines

- Only add one supplement at a time
- Drink/Cook with filtered Water
- Start with the combo Methylfolate, Methyl B 12 and NAC
- If mod/severe symptoms consider additional treatments and additional testing

Using this information to treat Memory Loss

We all have a
photographic memory.
Just some of us are
lacking the film. 🤔



JuicyQuotes.com

THE BEST JOKES TO SHARE

SD card

If you don't
remember film





Memory Loss, Brain loss

Current Treatment Option

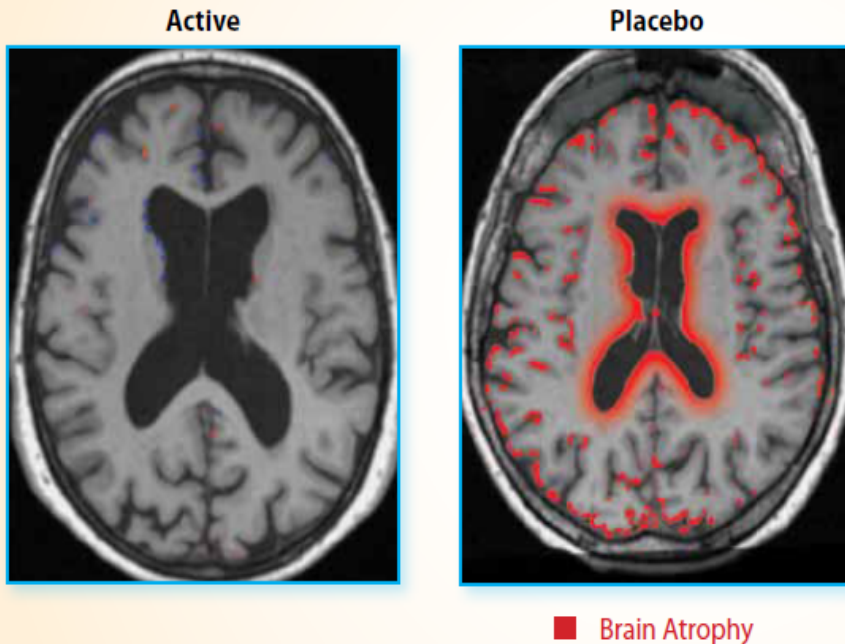
- Cerefolin NAC is a combination of
 - 5-L-Methylfolate 6 mg
 - Methylcobalamin 2 mg
 - N-Acetyl- Cysteine (NAC) 600 mg
- Helps with both Age related memory loss as well as Alzheimer's. AND.....

VITACOG Study

PET volume with Digital subtraction after 2Y

Preserve my brain!!!

Amount of brain loss depicted in RED!

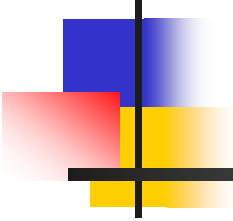


- 70 y/o with pre and Post PET volume
- Active group treated with Cerefolin NAC
- Randomized, Placebo controlled, n156
- As high as 53% neuro protection in the active treatment group compared to placebo
- Elevated Hcy strong prognostic marker for cognitive decline
- brain atrophy**

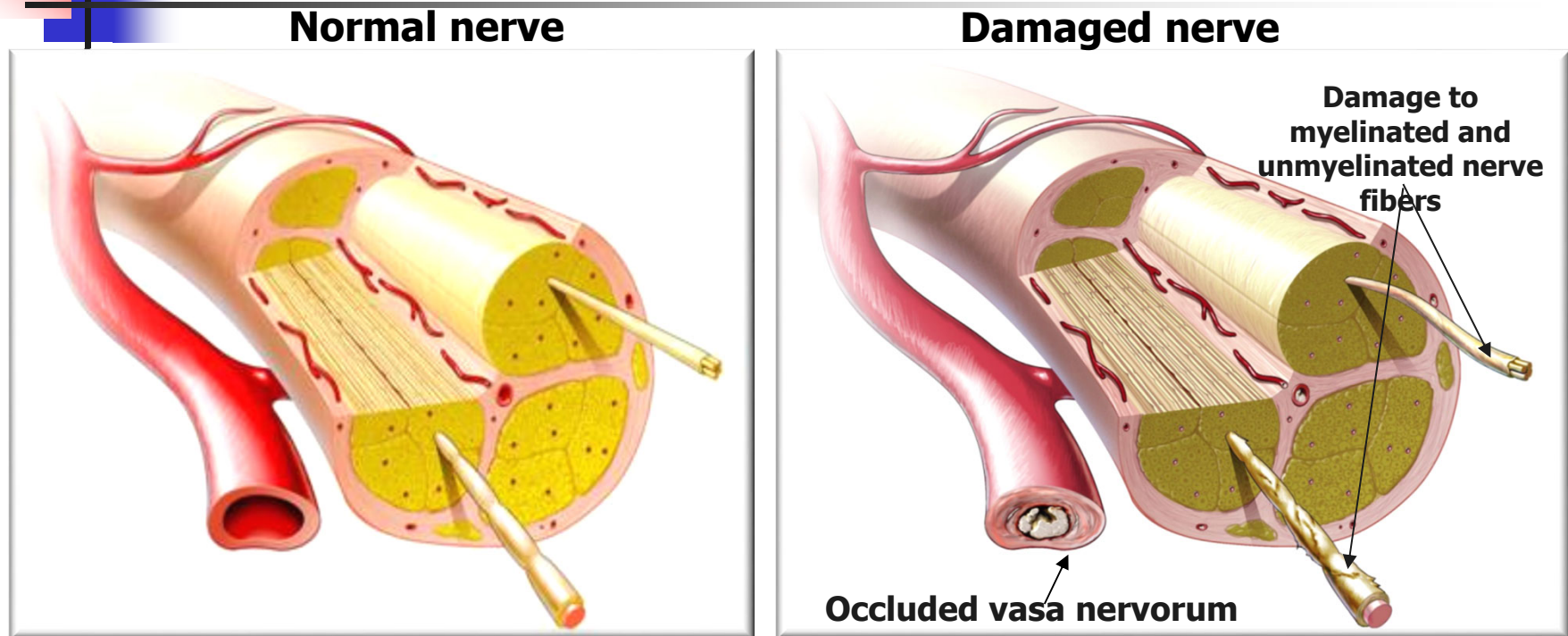
Jacoby, R et al, Oxford Project to investigate memory and ageing (OPTIMA Project) Int J Geriatr Psychiatry (2011) online 21 Jul 2011, DOI: 10.1002/gps.2758

Using this information to treat Nerve Pain

Diabetic and other nerve pain

- 
-
- Methylfolate 7.5-15 mg/d
 - Methyl B 12 5000 mcg/d
 - N-acetylcysteine (NAC)
 - 1000mg 1-3 X/ day
 - Active B6 (P5P) 25-50 mg/day
 - Stop intermittently because of toxicity (example 1 month on 1 month off)

Microvascular Damage Leads to Diabetic Peripheral Neuropathy



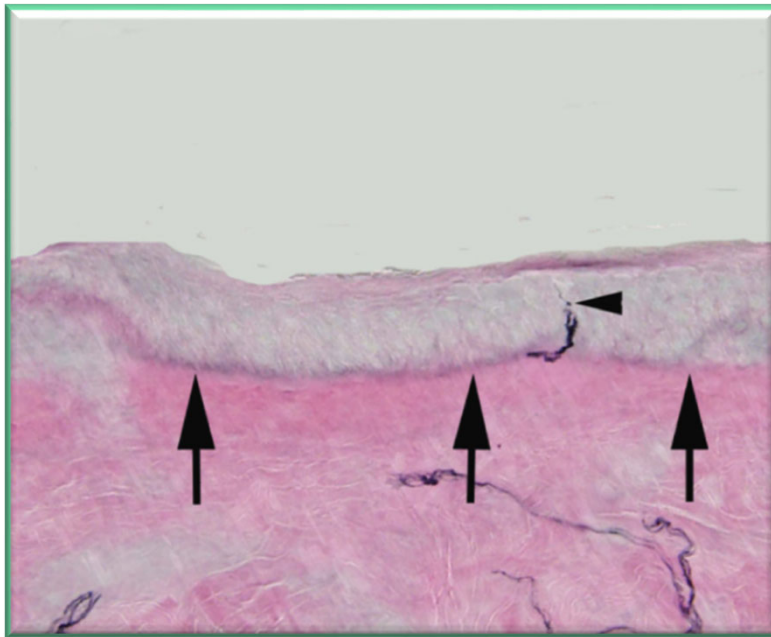
- Examination of tissues from patients with diabetes reveals capillary damage, including occlusion in the vasa nervorum
- Reduced blood supply to the neural tissue results in impairments in nerve signaling that affect both sensory and motor function

Dyck PJ, Giannini C. *J Neuropathol Exp Neurol.* 1996;55:1181-1193.

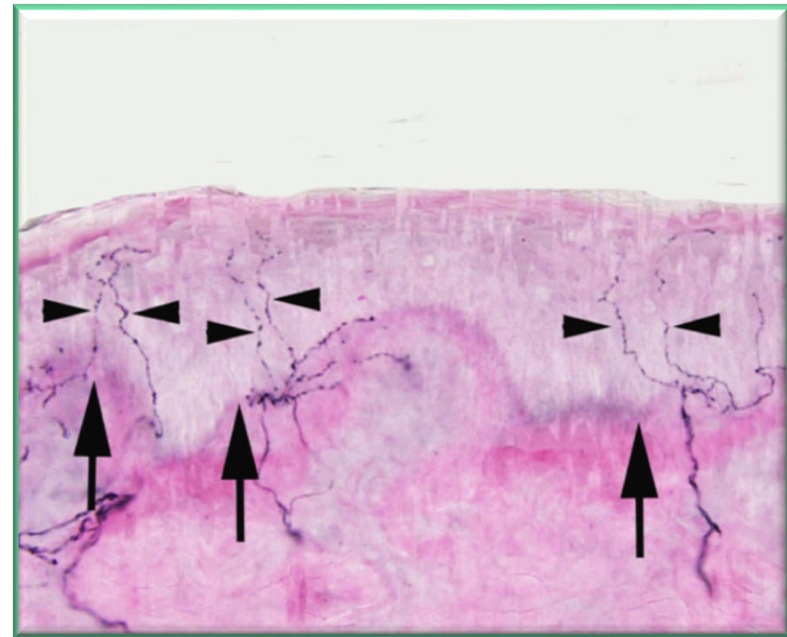
Sheetz MJ, King GL. *JAMA.* 2002;288:2579-2588.

Pathology Outcome

Baseline



6 months



Patient received baseline skin punch biopsy and given L-methylfolate, Me-Cbl , P-5-P (Metanx®) twice daily and followed for six months. Left image represents baseline skin punch biopsy at right calf. Right image represents six month follow up skin punch biopsy at right calf. Patient averaged an increase of .76 nerve fibers per mm. Skin Punch Biopsy Analysis and Images Performed by Therapath, LLC.

Summary

DPN TOTAL SYMPTOMS*						Disease State	
Modality	Onset	Reduced Burning Pain	Decreased Numbness	Reduced Tingling	Increased Thermal Sensations	Increased Sensory NCV	Increased ENFD
METANX^{®2-4} <i>(neurotrophic)</i>	1-12 WEEKS	✓	✓	✓	✓	✓	✓
PALLIATIVE⁵ <i>(pain masking)</i>	Acute	✓					

- Patients with Diabetic nerve pain experience TOTAL Symptoms
- Current therapies may have a quick onset, but are palliative only
- Treatment saved an average of \$2187 in diabetics that were treated with this vitamin combination

Ware JE et al. SF-36 Health Survey: Manual & Interpretation Guide 2000. Obrosova IF et al. Abstracts of the Experimental Biology Meeting. Oral Presentations 2011.

Am J Pharmacy Benefits 2012;4(5):218-225

Using this information to treat Depression/ Anxiety



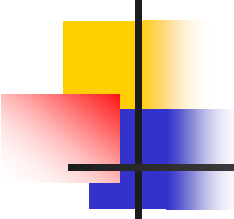


Using this information to treat Depression/ Anxiety Starting 3 supplements

- Methylfolate 15 mg /d
- Methyl B 12 5000 mcg /d
- N-acetylcysteine (NAC)
 - 1000 mg 1-3 times/d
- Add additional supplements if needed

Methylfolate Options

Some options not as stable

- 
- **Metafolin** from Merck (Best Studied)
 - Deplin, 7.5 or 15 mg, (prescription)
 - **EBM Medical** Methylfolate (equivalent to Deplin (prescription))
 - **Methyl-Life** methylfolate
 - Only other Crystalline formula
 - **Extrafolate, Extrafolate-S, Quatrefolate**
 - Made by Gnosis. Less stable
 - Many of the generics are this form



Methylfolate

- Doses
 - Treatment 7.5 or 15 mg
 - (15mg has the best data)
 - Sometimes require starting very low
- Depression treatment
 - Level A evidence*

1. Adjunctive Nutraceuticals for Depression: A Systematic Review and Meta-Analyses:
AJP in Advance (doi: 10.1176/appi.ajp.2016.15091228)

2. The Efficacy and safety of nutrient supplements in the treatment of mental disorders: Meta
review of Meta-analysis, World Psychiatry 2019;18:308-324



Methyl B12

(Oral dissolving tablets)

- Methylcobalamin B12 Level B evidence
 - Regular tablets not well absorbed
 - Oral Dissolving tablets improve absorption
 - Jarrow brand works well
 - Compounded Subcutaneous injections work very well but more expensive, limited pharmacy options
 - Light and Temperature control very important with injections
 - Oral drops for children with symptoms. (Malley's pharmacy)



N-Acetyl-Cysteine (NAC)

Level A evidence *

- **N Acetyl Cysteine** 1200- 1800mg
 - 2 capsules. 1-3 times daily
- This helps make **glutathione**, which clears heavy metals, helps with memory
- Recent study it helped PTSD**
- And much more!!

*J. Psychiatry Neurosci 2011;36(2):78-86

*Clinical trials of N-acetylcysteine in psychiatry and neurology: A systematic review: Neuroscience and Biobehavioral Reviews 55 (2015) 294–321

**A Double-Blind Randomized Controlled Pilot Trial of NAcetylcysteine in Veterans with PTSD and Substance Use Disorders: J Clin Psychiatry. 2016 November ; 77(11): e1439–e1446. doi:10.4088/JCP.15m10239

*The Efficacy and safety of nutrient supplements in the treatment of mental disorders: Meta review of Meta-analysis, World Psychiatry 2019;18:308-324



N Acetyl Cysteine (NAC)

Level of evidence (A the best-C OK)

- | | | | |
|----------------|-----|-------------------------|---|
| ■ Depression | A | ■ Trichotillomania | B |
| ■ Anxiety | B | ■ Hair pulling/twirling | |
| ■ ADHD | C | ■ Nail biting | C |
| ■ Bi-Polar | A | ■ Skin Picking | C |
| ■ Autism | B | ■ Schizophrenia | B |
| ■ Neuropathy | B | ■ OCD | B |
| ■ Brain injury | B | ■ Alzheimers | C |
| ■ Epilepsy | C | ■ ALS | B |
| ■ Surg Healing | A-B | ■ PTSD | B |



Additional things to treat Depression/ Anxiety

Items to add if the first 3 don't
give sufficient relief



Supplement Options

- **Vitamin B6 P5P, 25 mg** daily for the first 3 mo then use one week on, one week off
- **Epsom Salt bath** Soak feet or body with 1-2 cup of salts 2/3 times/week
- **Vitamin C**, 1,000 mg, 1-3 times a day (helps with constipation, regenerates glutathione)
- **DMG-Dimethylglycine or TMG-trimethylglycine**
200-250mg/day
- **Zinc** 20-40 mg/ day
 - Especially important in eye sensitivity



Supplement Options (cont'd)

- **Omega 3**
 - Flax seed, Chia Seeds, Fish oil
 - *Some of the fish oil tablets don't have the mercury removed.*
- **Silymarin** 150mg twice a day - improves glutathione usage and protects the liver.
- **Glutathione** (usually destroyed by stomach)
 - Sustained release option by Thorne
 - 2 capsules/day helps with detoxification.
 - SafeCell from TESSMED
 - 1 capsule a day



Additional Problems treated by these protocol

Autism

Chronic Fatigue

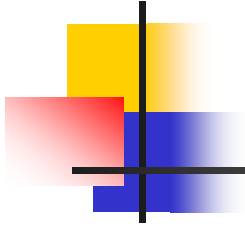
Fibromyalgia

Other Nerve problems



Summary

- Methylation and glutathione pathways have important roles and uses, especially with new insight gained by the human genome project to incorporate the use of active forms
- Supplements are a trial and error, No test to guide therapy
- Easy to try, May have very beneficial effects with low if any toxicity
- Consider trying to reduce toxins if symptoms may suggest toxins are affecting the methylation pathways
- Future: More to discover.....



"Before I came here I was confused about this subject. Having listened to your lecture I am still confused. But on a higher level. "

Enrico Fermi (Developed first nuclear reactor)



LOST

CONFUSED

UNSURE

UNCLEAR

PERPLEXED

DISORIENTED

BEWILDERED

QUESTIONS?

