“Clinicians will be central to helping consumer-patients use genomic information to make health decisions.” – NEJM
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I am President and CEO of SeekingHealth.com, SeekingHealth.org and founder of MTHFR.Net

I am compensated for this presentation.

I am on the Xymogen Board of Advisors.

My kids aren’t perfect.
HUSBAND, I’VE DECIDED TO NOT FEED YOU ANYMORE. INSTEAD, I’M GIVING YOU THIS FISHING ROD...

“GIVE A MAN A FISH, AND HE’LL EAT FOR A DAY--TEACH A MAN TO FISH, AND HE’LL EAT FOR THE REST OF HIS LIFE.”

AT THE RATE I’M CATCHING FISH MY LIFE WON'T LAST ANOTHER WEEK!
Genetic and Epigenetic Contributions to Human Nutrition and Health: Managing Genome–Diet Interactions

PATRICK J. STOVER, PHD; MARIE A. CAUDILL, PHD, RD

ABSTRACT
The Institute of Medicine recently convened a workshop to review the state of the various domains of nutritional genomics research and policy and to provide guidance for further development and translation of this knowledge into nutrition practice and policy. Nutritional genomics holds the promise to revolutionize both clinical and public health nutrition practice and facilitate the establishment of (a) genome-informed nutrient and food-based dietary guidelines for disease prevention and healthful aging, (b) individualized medical nutrition therapy for disease management, and (c) better targeted public health nutrition interventions (including micronutrient fortification and supplementation) that maximize benefit and minimize adverse outcomes within genetically diverse human populations. As the field of nutritional genomics matures, which will include filling fundamental gaps in knowledge of nutrient–genome interactions in health and disease and demonstrating the potential benefits of customizing nutrition prescriptions based on genetics, registered dietitians will be faced with the opportunity of making genetically driven dietary recommendations aimed at improving human health.


Public health nutrition continues to be challenged by increasing expectations from the food supply on one hand, and fundamental gaps in nutrition knowledge on the other, which can constrain the development and implementation of nutrition and food policy (1). Current demands on the food supply are no longer limited to ensuring general safety and preventing micronutrient deficiencies. Increasingly, there is interest in engineering medicinal qualities into the food supply to enable diets that promote health and “nurture” a sense of well-being that transcends the mere absence of disease by improving biological functions and even increasing lifespans. Unquestionably, nutrition is one of the primary environmental exposures that determines health. Common human chronic diseases, including type 2 diabetes, metabolic syndrome, cardiovascular and neurological disease, and many cancers are initiated and/or accelerated by nutrient/food exposures. However, it is also recognized that chronic diseases are complex in their etiology and include a substantial genetic component; individuals respond differently to foods and even individual nutrients. Investigation in this new field of nutrition research, often referred to as nutritional genomics, focuses on deciphering the biological mechanisms that underlie both the acute and persistent genome-nutrient interactions that influence health.

Nutritional genomics, while centered on the biology of individuals, distinguishes itself from other “omics” fields by its unique focus on disease prevention and healthy aging through the manipulation of gene–diet interactions. Nutritional genomics promises to revolutionize both clinical and public health nutrition practice and facilitate the establishment of (a) genome-informed nutrient and food-based dietary guidelines for disease prevention and healthful aging, (b) individualized medical nutrition therapy for disease management, and (c) better targeted public health nutrition interventions that maximize benefit and minimize adverse outcomes within genetically diverse human populations.
What is Methylation?

The addition of a single carbon group with three hydrogens onto a compound

(Klug & Cummings 1997)
Methyl Donors support Methylation

Methyl Donors assist S-adenosylmethionine (SAM) production

1. Methylfolate
2. Methylcobalamin
3. Serine
4. Glycine
5. Choline
6. Betaine (TMG)
7. DMG
FIGURE 1. Major reactions involved in transmethylation flux and methyloneogenesis. The total transmethylation flux is equivalent to the total flux occurring through reactions that convert S-adenosylmethionine to S-adenosylhomocysteine. The 3 S-adenosylmethionine-dependent reactions thought to contribute quantitatively to this flux are methylation of guanidinoacetate by guanidinoacetate methyltransferase (GAMT) to form creatine; methylation of phosphatidylethanolamine by phosphatidylethanolamine methyltransferase (PEMT) to form phosphatidylcholine; and methylation of glycine by glycine N-methyltransferase (GNMT) to form sarcosine (N-methylglycine). A large number of additional S-adenosylmethionine-dependent methyltransferases also occur in mammals [see Katz et al (3)], but their collective quantitative contribution to transmethylation flux may be small compared with those mentioned above. The final steps in methyloneogenesis are the reduction of a methylene group of 5,10-methylenetetrahydrofolate (methylene-THF) by methylenetetrahydrofolate reductase (MTHFR) to form 5-methyltetrahydrofolate (methyl-THF), followed by transfer by methionine synthase of the newly formed methyl moiety to homocysteine, forming methionine and tetrahydrofolate (THF). Sarcosine is formed not only by GNMT, but also by oxidation of choline to betaine, formation of dimethylglycine by betaine homocysteine methyltransferase (BHMT), and oxidation of dimethylglycine to sarcosine. Sarcosine is oxidized by sarcosine dehydrogenase (SDH). During the reaction, glycine is produced, and a 1-carbon unit is transferred to THF, forming methylene-THF. MAT, methionine adenosyltransferase; CBS, cystathionine β-synthase; CG, cystathionine γ-lyase; SAHH, S-adenosylhomocysteine hydrolase.
S-Adenosylmethionine (SAM): Functions

- Cofactor for Methyltransferases
  - COMT, PEMT, HMT, PNMT, GNMT, GAMT, DNMT...
- Binds to CpG Sites and Islands to block gene transcription
- Maintains normal liver function
- Induces apoptosis in liver cancer cells
- Modulates iNOS synthesis
- ↑ viral latency
- ↓ NFk-B
- ↑ CBS ➔ cysteine, hydrogen sulfide, taurine, pyruvate and glutathione

<table>
<thead>
<tr>
<th>Study, [Ref.],</th>
<th>Design</th>
<th>Subjects (n)</th>
<th>SAMe dose (g/day)</th>
<th>Duration</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Nicastri et al., 1998 [113]</td>
<td>RCT</td>
<td>32 women at 30-37 wk gestation</td>
<td>800 mg/day po vs. UDCA vs. SAMe + UDCA vs. placebo</td>
<td>20 d</td>
<td>Combination SAMe and UDCA better than either alone or placebo for bile salts, bilirubin, ALT, ALP, pruritus, neonatal and maternal outcome</td>
</tr>
<tr>
<td>*Ribalta et al., 1991 [114]</td>
<td>RCT</td>
<td>18 women before 32 wk gestation</td>
<td>800 mg/day iv vs. placebo</td>
<td>20 d</td>
<td>No benefit of SAMe for bile salts, bilirubin, ALT, ALP, pruritus, neonatal and maternal outcome</td>
</tr>
<tr>
<td>*Frezza et al., 1990 [115]</td>
<td>RCT</td>
<td>30 women</td>
<td>800 mg/day iv vs. placebo</td>
<td>Until delivery (mean 18 d)</td>
<td>SAMe improved bile salts, bilirubin, ALT, ALP, pruritus, neonatal and maternal outcome</td>
</tr>
<tr>
<td>*Frezza et al., 1984 [116]</td>
<td>RCT</td>
<td>18 women at 28-32 wk gestation</td>
<td>200 mg/day po vs. 800 mg/day po vs. placebo</td>
<td>Until delivery</td>
<td>SAMe 800 mg/day improved clinical biochemistry, pruritus, neonatal and maternal outcome</td>
</tr>
<tr>
<td>*Floreani et al., 1996 [117]</td>
<td>RCT</td>
<td>20 women before week 34 gestation</td>
<td>1 g/day im vs. UDCA</td>
<td>&gt;15 d</td>
<td>SAMe had no effect on bile salts, bilirubin, ALT, ALP, pruritus, neonatal and maternal outcome</td>
</tr>
<tr>
<td>Lafuenti et al., 1988 [118]</td>
<td>Open label</td>
<td>17 patients</td>
<td>1800 mg/day po and 600 mg/day po</td>
<td>n.a.</td>
<td>Manuscript out of print</td>
</tr>
<tr>
<td>Catalino et al., 1992 [119]</td>
<td>Open label</td>
<td>55 patients, no comparator</td>
<td>800 mg/day iv</td>
<td>10-30 d</td>
<td>Improved bile salts, bilirubin, ALT, ALP, pruritus vs. baseline</td>
</tr>
<tr>
<td>Roncaglia et al., 2004 [72]</td>
<td>RCT</td>
<td>46 patients, before 36 wk gestation</td>
<td>SAMe 1 g/day po vs. UDCA 600 mg/day</td>
<td>until delivery</td>
<td>UDCA was more effective than SAMe in lowering bile acid levels. Both improved pruritus</td>
</tr>
</tbody>
</table>

* included in Cochrane systematic review [73].
S-Adenosylmethionine (SAM): Functions

**Biosynthesis**
- Serotonin → Melatonin
- Norepinephrine → Epinephrine

**Degradation**
- Histamine
- Dopamine
- Catechol estrogens
- Epinephrine
- Arsenic

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S-Adenosylmethionine (SAM): Pain Reduction

**Dopamine**

- \( \uparrow \) Dopamine \( \rightarrow \) \( \downarrow \) Pain Tolerance
- SAM = cofactor for COMT
Functions of Methylation

Several Functions of Methylation:
1. Turn on and off genes (gene regulation)
2. Process chemicals, endogenous and xenobiotic compounds (biotransformation)
3. Build neurotransmitters (norepinephrine → epinephrine, serotonin → melatonin)
4. Metabolize neurotransmitters (dopamine, epinephrine)
5. Process hormones (estrogen)
6. Build immune cells (T cells, NK cells)
7. DNA and Histone Synthesis (Thymine aka 5-methyluracil)
8. Produce energy (CoQ10, carnitine, creatine, ATP)
9. Produce protective coating on nerves (myelination)
10. Build and maintain cell membranes (phosphatidylcholine)

“Methylation is a common but generally minor pathway of xenobiotic transformation.” – Toxicology, 8th ed.
How is Methylation Disturbed?

Methylation is often disturbed by various mechanisms

1. Lack of cofactors/substrate driving methylation forward (zinc, B2, magnesium, cysteine, B6, methylcobalamin)
2. Medications (antacids, methotrexate, metformin, nitrous oxide)
3. Specific nutrients depleting methyl groups (high dose Niacin)
4. Environmental toxicity, heavy metals, chemicals (acetylaldehyde, arsenic, mercury, high copper)
5. Excessive end product (feedback inhibition – eg. DMG, SAMe, Methylfolate)
6. Genetic mutations/polymorphisms (MTHFR, GSTM1, PEMT, MAT, GAMT, CBS)
7. Mental state (stress, anxiety, lack of sleep, ‘can’t do it’, pessimist, optimist)
Methylation Genetics

Pathways Supporting Methylation (not comprehensive)
- Folate
- B12
- Methionine
- ROS
- Biotransformation

Folate
- DHFR
- MTHFD
- MTHFR
- SHMT
- FOLR
- TYMS
- SLC19A1

B12
- TCN2 and TCN3
- MMAB (aka cblB)

Methionine Cycle
- MTR/MTRR
- MAT1
- AHCHY
- CBS

Benjamin Lynch, ND

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http://www.ornl.gov/sci/techresources/Human_Genome/project/info.shtml
Mitochondrial Genetics

Mitochondrial DNA (mtDNA)
- Inherited only from Maternal side (family hx Important)
- Majority of ATP produced in mitochondria
- Require importing nDNA gene products to function
- Mitochondrial dysfunction $\rightarrow$ cell dysfunction $\rightarrow$ methylation dysfunction
- SNPS/mutations in mtDNA may be pathological
  - Cancer
  - Diabetes
  - Cardiovascular Diseases
  - Neurodegenerative Diseases
  - Aging
  - Degenerative Diseases
- mtDNA copy number ↑ cell survival and function


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Genetics: Mitochondria

Mitochondrial DNA (mtDNA)
- Sperm – 700 molecules of mitochondria
- Oocytes – 200,000 molecules of mitochondria

Cell Division and Mitochondria:
- Mitochondria ‘float’ in cytoplasm
- Lack of Spindles
- Randomized
Cell Division and Replication of ‘Sick’ Cells?

Stimulate DNA Bases and ↑ Cell Proliferation
- “New” cells created:
  - ↓ Glutathione
  - Oxidized cell membrane
  - ↓ Potassium
  - ↑ ROS
  - ↑ Cell death

Flare of Patient Symptoms with addition of Folate / B12.

Necessitates Treatment Flow
“As an organism grows and develops, carefully orchestrated chemical reactions activate and deactivate parts of the genome at strategic times and in specific locations.

Epigenetics is the study of these chemical reactions and the factors that influence them.”

“Epigenetic changes are environmentally responsive mechanisms that can modify gene expression independently of the genetic code.”
Epigenetics 1st → Identify Causation of Dysfunction

- Environment
- Lifestyle
- Diet
- Pathogens
- Heavy Metals
- Xenobiotics
- Oxidative Stress
- Nutrient Deficiencies
- Nutrient Excess
- SNPs

System-Wide Dysfunction
Most stable epigenetic alteration at CpG islands
Epigenetic Example: Inflammatory Bowel Disorders

High monozygotic twin discordant rates in Crohn disease and UC.
70+ loci associated with CD. 40+ for UC = epigenetic control.

High monozygotic twin concordant rates in Celiac disease.
Single HLA locus linked to 40% of heritability = genetic control

Epigenetic Control in Crohn’s Disease and UC

Source: Epigenetics and the developmental origins of inflammatory bowel diseases.
Epigenetics in Action

a) Lab Setting

- Variable methylation region
- Agouti gene
- Methylated
- Not methylated
- agouti mRNA briefly made during development
- agouti gene silenced remainder of mouse life
- Healthy mouse with brown fur
- Mouse with yellow fur; develops obesity and diabetes during adulthood

b) Environment

http://www.hudsonalpha.org/education/outreach/basics/epigenetics
MTHFR increasing in the population.

- Folic acid fortification
  - ↑ Full-Term Pregnancies
  - ↑ Folate SNPs
  - ↑ Methylation SNPs
  - ↑ Inferior SNPs
  - ↑ Metabolic Issues

↑ Susceptibility to Environmental Exposures

Natural DeSelection:
Survival of the ‘Unfittest’

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Folic Acid Fortification, Increase in MTHFR and Rise in Autism?

by Dr. Lynch on May 11, 2012 in MTHFR and Pregnancy

If we sit back and evaluate the dates when folic acid fortification began and the fast rise of autism – do they correlate?

“In Spain, the prevalence of the MTHFR 677TT genotype has reportedly approximately doubled in the population since the introduction in 1982 of folic acid supplements for women in early pregnancy”...

“Folic acid fortification and supplement use might be “a genetic time bomb.” The first premise of this dramatic claim, that folic acid use increases the proportion of children born with the T allele of MTHFR, is as yet poorly documented and is clearly in urgent need of further study.

Studies of the MTHFR genotype frequencies in children before and after fortification should be carried out in countries planning fortification of food with folic acid. Thus, saving fetuses that have a genetic constitution that favors abortion or nonsurvival could lead to children being born with genotypes that favor increased disease during life”[1]

Folic acid fortification started heavily in 1992.[2]

Autism began to quickly rise in 1993.

In the early 1990s, autism diagnoses began to soar. In the 10 years between 1993 and 2003, the number of American schoolchildren with autism diagnoses increased by over 800%. In 2006, the CDC noted a slight decrease in the number of new cases diagnosed.[3]

Autism began to rise at the same time folic acid fortification began.

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Is the rise of autism due to an increased survival rate of babies with MTHFR defects?
The impact of the lacto-ovo vegetarian diet on the erythrocyte superoxide dismutase activity: a study in the Romanian population

M M Boancă, H A Colosi and E C Crăciun

Background/Objectives:

Recent studies have shown that vitamin B12 scavenges superoxide anion as effectively as superoxide dismutase (SOD), and has a key role in the defense against oxidative stress. The status of vitamin B12 is suboptimal in a substantial number of vegans and even vegetarians. We therefore evaluated in lacto-ovo vegetarians (LOVs) who did not take vitamin B12 supplements the impact of the duration of this diet on the vitamin B12 status, the erythrocyte SOD activity and the serum malondialdehyde (MDA) concentration.
SAM Deficiency via MATI/III Inhibitors

Oxidative Stress
- NO
- TNFα
- IL-6

Causes vicious cycle
↓ SAM → ↓ CBS activity → ↓ GSH, ↓ H₂S & ↑ Hcy → ↑ SAH

Methionine intake may NOT ↑ SAM

Homocysteine

- Methionine = Methyl-Homocysteine

- Breakdown product of SAM $\rightarrow$ SAH via AHCY
Homocysteine Kinetics

Methionine cycle $\rightarrow$ low Km / high affinity for sulfur-containing substrate
  - $\uparrow$ methionine (sulfur) $\downarrow$ methionine cycle

Betaine-Homocysteine Methyltransferase (BHMT) $\rightarrow$ low Km for Hcy

Transsulfuration cycle $\rightarrow$ high Km for sulfur-containing substrate
  - $\uparrow$ methionine (sulfur) $\uparrow$ transsulfuration cycle
    - $\uparrow$ GSH
    - $\uparrow$ H2S
    - $\uparrow$ Taurine
    - $\downarrow$ Hcy
  - $\uparrow$ demand of P5P, cysteine and serine
Homocysteine Metabolism

**Tissue Specific**

Plasma homocysteine is a ‘gross’ average.
Not tissue specific.

Ex. CBS
- Brain
- Liver
- Pancreas
- Muscle

Ex. BHMT
- Liver
- Oocyte
- Kidney

Ex. MTR
- Brain
- Oocyte

Support ALL Routes

Regulation of homocysteine metabolism and methylation in human and mouse tissues and http://www.procrelys.fr/telechargement/publications/hcy_fertilSteril.pdf
Low homocysteine (< 6) is an important finding
What did the doctor do? What happened here?

**Methylation Profile; plasma**

<table>
<thead>
<tr>
<th>PRIMARY &amp; INTERMEDIATE METABOLITES</th>
<th>RESULT/UNIT</th>
<th>REFERENCE INTERVAL</th>
<th>2.5th</th>
<th>16th</th>
<th>50th</th>
<th>84th</th>
<th>97.5th</th>
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<tbody>
<tr>
<td>Methionine</td>
<td>3.2 (\mu\text{mol/dL})</td>
<td>1.6-3.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cysteine</td>
<td>34 (\mu\text{mol/dL})</td>
<td>20-38</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>S-adenosylmethionine (SAM)</td>
<td>409 (\text{nmol/L})</td>
<td>86-145</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-adenosylhomocysteine (SAH)</td>
<td>20.1 (\text{nmol/L})</td>
<td>10-22</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Homocysteine</td>
<td>8.2 (\mu\text{mol/L})</td>
<td>&lt;11</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cystathionine</td>
<td>0.01 (\mu\text{mol/dL})</td>
<td>&lt; 0.05</td>
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**METHYLATION INDEX**

<table>
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<tr>
<th>RESULT</th>
<th>REFERENCE INTERVAL</th>
<th>PERCENTILE</th>
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<tbody>
<tr>
<td>SAM : SAH</td>
<td>&gt; 4</td>
<td>68th-95th</td>
</tr>
</tbody>
</table>
Here is the consequence. What happened? How to restore?

**Methylation Profile; plasma**

<table>
<thead>
<tr>
<th>PRIMARY &amp; INTERMEDIATE METABOLITES</th>
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<th>16th</th>
<th>50th</th>
<th>84th</th>
<th>97.5th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methionine</td>
<td>2.0 µmol/dL</td>
<td>1.6 - 3.6</td>
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<tr>
<td>Cysteine</td>
<td>50 µmol/dL</td>
<td>20 - 38</td>
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<tr>
<td>S-adenosylmethionine (SAM)</td>
<td>205 nmol/L</td>
<td>86 - 145</td>
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<tr>
<td>S-adenosylhomocysteine (SAH)</td>
<td>46.1 nmol/L</td>
<td>10 - 22</td>
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<td></td>
<td></td>
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<tr>
<td>Homocysteine</td>
<td>20.6 µmol/L</td>
<td>&lt; 11</td>
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<td></td>
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<tr>
<td>Cystathionine</td>
<td>0.30 µmol/dL</td>
<td>&lt; 0.05</td>
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**METHYLATION INDEX**

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<tbody>
<tr>
<td>SAM : SAH</td>
<td>4.5</td>
<td>&gt; 4</td>
<td></td>
</tr>
</tbody>
</table>
Low Alkaline Phosphatase

- ↓ Phosphate
- ↓ Magnesium
- ↓ Zinc
- Celiac
- Malnutrition
- Hypothyroid
- Pernicious anemia
CBS and CDO

CBS
• Cofactor: B6
• Requires: Serine or Cysteine & Hcy
• Inhibited by: NO
• Promoted by: SAM
• Product: H$_2$S & Cystathionine

CDO
• Cofactor: Iron & Zinc
• Requires: Cysteine
• Inhibited by: α-ketoglutarate, TNFα
• Promoted by: Sulfur/Cysteine
• Product: Cysteinesulfinate

CDO Inhibition may lead to Cysteine Excitotoxicity
- Support CDO  - Support COMT  - Remove Pathogens
- Support IDO  - Support MAO  - Remove Metals

Signs (sensitive to cysteine intake):
↑ Cysteine:Sulfate  ↑ Cysteine:Taurine  ↑ Sulfite:Sulfate  ↑ Hydrogen Sulfide

http://www.wikigenes.org/e/gene/e/1036.html and
http://www.ncbi.nlm.nih.gov/pubmed/11059810 and
http://ajpendo.physiology.org/content/early/2011/06/15/ajpendo.00151.2011
Figure 1. Schematic representation of the classical proposed mechanisms by which quinolinic acid (QUIN) exerts toxicity in the Central Nervous System. Firstly, increased levels of QUIN in the extracellular domain are achieved after inflammatory-induced glial activation. QUIN can then act in several non-excluding ways: (1) stimulating NMDAr and, together with other endogenous excitatory agents (glutamate), to induce excitotoxic events further leading to exacerbated intracellular calcium-mediating signaling and recruiting more calcium from internal storages (mitochondria and endoplasmic reticulum). QUIN can then act with other inner toxic signals, including mitochondrial dysfunction, cytochrome c release, reactive oxygen and nitrogen species (ROS/RNS) formation, protease activation, etc. Altogether, the above interactions lead to necrotic and apoptotic cell death. (2) QUIN directly interacts with free iron ions to form toxic complexes that exacerbate ROS/RNS formation, oxidative stress and excitotoxic events already in course. Eventually, these toxic signals can be extended, thus reaching adjacent cells, either glial or neuronal, hence starting a degenerative chain in the brain. 

Abbreviations: AA, arachidonic acid; COX, cyclooxygenase; L-KYN, L-kynurenine; LOX, lipooxygenase; SOD, superoxide dismutase.
Folates: Which are off?
<table>
<thead>
<tr>
<th>AMINOACIDS IN PLASMA</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrotyrosine</td>
<td>2.87 µg/l</td>
<td>1.1 - 6.8 µg/l</td>
</tr>
<tr>
<td>Glutathione (oxidised)</td>
<td>0.51 µmol/L</td>
<td>0.16 - 0.50 µmol/L</td>
</tr>
<tr>
<td>Glutathione (reduced)</td>
<td>3.0 µmol/L</td>
<td>3.8 - 5.5 µmol/L</td>
</tr>
</tbody>
</table>

| MISCELLANEOUS                |                  |                  |
| Ammonia (plasma)             | 50 µmol/L        | 8 - 40 µmol/L    |
| NO (Nitric oxide)            |                  | 18.0 - 35.0 ng/mL |

| Derivatives                   |                  |                  |
| S-Adenosylmethionine (RBC)    | 225 µmol/dl       | 221 - 256 µmol/dl |
| S-Adenosylhomocysteine (RBC)  | 52.8 µmol/dl      | 38.0 - 49.0 µmol/dl |

| FOLIC ACID DERIVATES         |                  |                  |
| 5-CH3-THF                     | 6.9 nmol/l        | 8.4 - 72.6 nmol/l |
| 10-Formyl-THF                 | 2.9 nmol/l        | 1.5 - 8.2 nmol/l |
| 5-Formyl-THF                  | 3.80 nmol/l       | 1.20 - 11.70 nmol/l |
| THF                           | 0.53 nmol/l       | 0.60 - 6.80 nmol/l |
| Folic Acid                    | 14.0 nmol/l       | 8.9 - 24.6 nmol/l |
| Folinic Acid (WB)             | 15.3 nmol/l       | 9.0 - 35.5 nmol/l |
| Folic Acid, active (RBC)      | 326 nmol/l        | 400 - 1500 nmol/l |

| BIOLOGICAL AMINES             |                  |                  |
| CATACHOLAMINES IN PLATELETS   |                  |                  |
| Histamine (whole blood)       |                  |                  |

| NUCLEOSIDE                    |                  |                  |
| Adenosine                      | 24.8 10^-8 M     | 16.8 - 21.4 10^-8 M |

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http://www.hdri-usa.com/tests/methylation/
Keep to the Basics

- History
- Lifestyle
- Diet
- Compliance
- Motivation
- Mindset
- Environment
- Water
- Exercise
When your patient feels good...
Do NOTHING!

Look for the Apex of the “Bell Shape Curve”

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Stay Informed

Great ways to stay informed:
• Newsletter Available at www.MTHFR.net
• Facebook: https://www.facebook.com/drbenjaminlynch

Thank You