Autism and Metabolic Disorders—A continuing story. Part III OAA/FOD July 31, 2010

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Thanks to

- Bill Nyhan
- Neil Kirkman
- Art Aylsworth
- Charlie Roe
- Kalle Reichelt
- Elizabeth Cooper
- James Pitt
- Jill James
- Nancy O'Hara
- Richard Kelly
- Paul Shattock
- Dave Gaylor
- Sydney Baker
- Bernie Rimland
- Martha Herbert
- Jane El-Dahr
- Susan Owens
- Jill Fussell
- Maya Lopez
- Terry Harville

What we'll talk about

- Autism
  - Define/diagnostic criteria
  - Biomedical aspects
- Inborn errors
  - How can they affect brain function
  - Why would someone with an IEM have autistic features?

What we'll talk about--2

- What can we learn from children with autism about inborn errors, and vice versa?
- How can we treat the autistic features of our children with metabolic errors?
- What might be worth studying further?

FEATURES OF AUTISM

- Impaired/inappropriate social interactions
- Impaired communication
- Restricted repertoire of activities/interests
- Onset in childhood
- ?Lack of concept of mind?
- Sensory distortion/dysregulation
- Mental retardation, seizures

Be careful when you put a label on something--it may prevent you from thinking about it.

Art Aylsworth, MD

To be classified as autistic, an individual simply has to meet a set of carefully delineated criteria in three domains. That is all. As there are no biological markers for autism, so also there are no biological criteria for autism. There is nothing in the definition of autism that either prescribes or excludes any specific type of biology or any disease course.

Martha Herbert, 2006

AUTISM IS A DESCRIPTION OF WHAT WE SEE

- There is nothing in the description about causation, untreatability, irreversibility, etc.
- Age of onset is biological; other criteria are behavioral.
- Various diagnostic criteria—points on a scorecard—reflect attempts to quantify something we don’t understand how to measure very well.

Ditto learning problems

- Does developmental testing/IQ testing measure something “real” (g factor)
- Or do these tests measure the ability to take the Denver/Stanford-Binet, etc. (circular definition)

ALTERED CONNECTIVITY AND BRAIN TIMING CAN HELP EXPLAIN DIVERSE OBSERVATIONS

Where have we gotten so far?

- Single genes
  - Not many—TS., inborn errors, nucleotide disorders, Rett syndrome,
- Recognizable disorders-
  - Fragile X, Down syndrome, Williams, Angelman and P-W,
- 2-40% of autism-- ‘known etiology’—
  - Perhaps, depending on ascertainment

THE SCALE PROBLEM

- Looking at single metabolites—hard to discern relationship to
- Genes→protein→pathway→where located→cell→ brain circuit→what else is going on?→behavior
- Where does metabolite act?
- How can this action lead to altered brain function and altered behavior.

GENETIC ASPECTS OF AUTISM—Relatives

- Increased incidence of
  - Affective disorders;
  - Auto-immune problems;
  - Intelligence?
  - Organizing skills?
  - Migraine?

Comparisons at each step.

- Autism as I see it.
- How these features relate to patients with IEMs.
- What we can learn.
- IF YOU SEE SOMETHING THAT MIGHT APPLY TO YOUR CHILD'S STORY, PLEASE LET ME KNOW.

There are more things in heaven and earth, Horatio, Than are dreamt of in your philosophy.

W. Shakespeare

Autism Spectrum Disorders

- Typical autism
- Pervasive Developmental Disorder (PDD-NOS)
- Asperger Syndrome
- Related conditions--co-morbidities
  - Seizures
  - Mental retardation
  - ADHD
  - OCD

Syndromic associations

- Chromosome disorders—Down syndrome
- Single-gene syndromes—tuberous sclerosis, fragile X, Williams
- Preceded by infantile spasms, encephalitis, other brain injury.

Learning difficulties/differences

- Selected—
  - Input (sensory) differences—hearing, vision, tactile, etc.
  - Output (motor) differences—speech dypraxia, clumsiness

SET AND SETTING

- Try to cast your mind back to what you remember about the ’60’s, Timothy Leary, experimental and experiential pharmacology

The anatomy of autism

- Hippocampus (imaging, encephalitis)
- Cerebellum (imaging, autopsy)
- Frontal lobes (metabolic imaging, autopsy)
- White matter abnormalities (Herbert)
- Head circumference/brain size INCREASED--failure to remodel apppropriately? Why? Timing.
- Abnormalities of mirror neurons?

Some functional aspects of autism

- ‘Noisy’ brain circuits—hard to concentrate, hard to process things quickly.
- Inability to regulate sensations—too much/too little light, sounds, touch, smells, textures. (Sensory integration disorder?)
- Areas of expertise/skill can be missed by global IQ tests.

“STANDARD” THERAPIES

- Behavioral
- Learning techniques, (ABA, etc.)
- SSRIs, anti-psychotics, etc.
- (Opiate antagonists)

RECURRING THEMES in the Enigmatology Clinic

- Onset
- unusual/difficult infancy
- multiple infections and antibiotics
- febrile event
- Food observations
- Course—can include UPS and DOWNS
- sudden loss of speech
- Unexplained tachycardia

THESE ARE OFTEN PART OF THE HISTORY OF IEMs.

Cherish your exceptions.

Barton Childs

The expanding phenotype of autism/the autisms

Autism--
which organs are involved?

- Brain and nervous system
- Gut
- Immune System

G.I.--First observations

- Feeding problems in infancy
- Abnormal bowel movements
- Food intolerances/allergies
- Restricted diet
- Response to fasting, TPN

BOWEL FUNCTION--1

- Abnormal bowel movements--constipation, diarrhea, paradoxical diarrhea
- Pancreas function--response to hormones
- Response to pancreatic enzymes--why?
- Amount/character of digestive juices

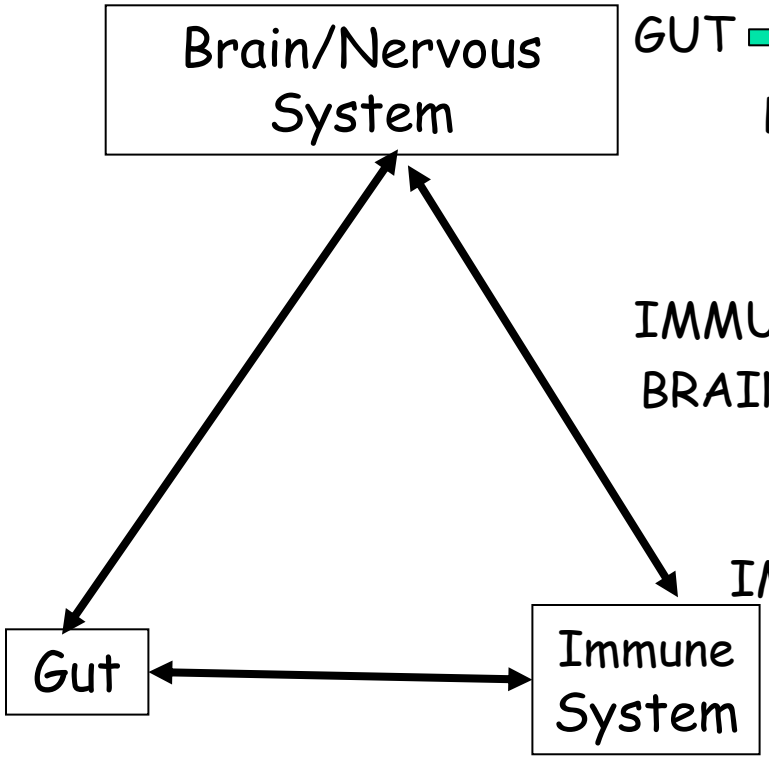
IMMUNE SYSTEM--1

- No suggestion of major inherited immune deficiency.
- Genetic aspects of immune response--do they play a role? No prospective studies yet.
- Acquired immune problems--often found
- “Auto-immune”???

Neuroimmune interactions

- Nervous system and immune system have similar duties--
- MEMORY AND RESPONSE
- Therefore they MUST communicate
- Brain-->Immune system ENDORPHINS, NEUROPEPTIDES (systemic, local)
- Immune system--> Brain INTERLEUKINS, CYTOKINES, ABD. LYMPH NODES, VAGUS

The Autism Triad: Brain-Gut-Immune Axis



GUT ➡ BRAIN: Vagus afferents; Gut neuropeptides

BRAIN ➡ GUT: Endorphins; Neuropeptides

IMMUNE ➡ BRAIN: Cytokines; microglia activation

BRAIN ➡ IMMUNE: Endorphins; Neuropeptides; Cortisol

IMMUNE ➡ GUT: Cytokines; leukotrienes

GUT ➡ IMMUNE: Gut neuropeptides; microbial products

All 3 systems highly vulnerable to chronic oxidative stress

WHAT'S BIOCHEMICAL ABOUT AUTISM?

- Simple answer--all behavior and neurological function has a biochemical basis--neural transmission, receptors, responses, memory, etc.
- [Persistent theme in autism--Serotonin has something to do with the story
- Platelet serotonin content (cf migraine)
- Response to SSRIs]

THE LESSON OF PKU

- Completely genetic if you don’t know about phenylalanine
- Prevention of disease by changing the diet (environment)
- Damage is progressive and irreversible. Treatment must be started before damage occurs.

Autistic behavior in patients with nameable inborn errors--1

- PKU
- Disorders of biopterin metabolism—’malignant hyperphenylalaninemia’ (defective neurotransmitter synthesis)

Autistic behavior in patients with nameable inborn errors--2

- Disorders of folate metabolism
- Disorders of B12 metabolism
- ORGANIC ACIDEMIAS, esp
  - Propionic acidemia
  - MMA
  - SSADH

Autistic behavior in patients with nameable inborn errors--3

- D2HGA
- NOT GA I.
- Disorders of energetics—Krebs cycle problems (deficiency of PDH, E3, fumarase, mitochondrial ox-phos problems)

Some other metabolic aspects

- Lactic acidosis/mito dysfunction?
  - Richard Kelley, John Shoffner, others
- Hyperuricosuria--pyrimidine depletion?--response to uridine (Page)
- Hyperammonemia?

Autistic behavior in patients with nameable inborn errors—3.5

- Hanna Poling
  - Sudden onset after multiple immunizations
  - Fever
  - Evidence for impaired mitochondrial function—increased lactate, alanine.
  - Evidence for biochemical problem—increased transaminases, abnormal mito function (muscle biopsy)

Autistic behavior in patients with nameable inborn errors—3.6

- Hanna Poling
  - No abnormal genes (nuclear or mitochondrial) identified
  - Possibility of mitochondrial IMPAIRMENT (not due to genetic problem)→ inability to withstand stressor. (Too much stress? Not enough resistance to stress?)

Autistic behavior in patients with nameable inborn errors--4

- Fatty Acid Oxidation disorders
  - SCAD?
  - GA II?
  - Long-chain defects?
  - NOT MCAD def. (?)

Autistic behavior in patients with nameable inborn errors--5

- Urea cycle disorders—OTC, citrullinemia, ASAuria. ?Arginase deficiency?
- Disorders of creatine synthesis/transport
- Disorders of purine and pyrimidine metabolism

Other ‘inborn errors’

- Sanfilippo (MPS III)—perhaps.

Small molecules and brain function

- Successes
  - Phenylalanine
  - Glucose
- Not so successful
  - Lesch-Nyhan syndrome
- Interpretation of some observations will change (numerous)
  - e.g., Glutaric aciduria I—insufficient glucose during stress is the biggest problem. Toxicity is from glutamate.
  - What is toxic in PA? MMA?

Looking through the wrong end of the telescope

- Lumping all patients together will blur distinctions
- Identifying discrete groups can generate hypotheses that can be tested prospectively
  - (e.g.,food dyes and ADHD—Kathy Rowe, 1994)
  - IEMs and autistic behavior?

Anecdotes vs data

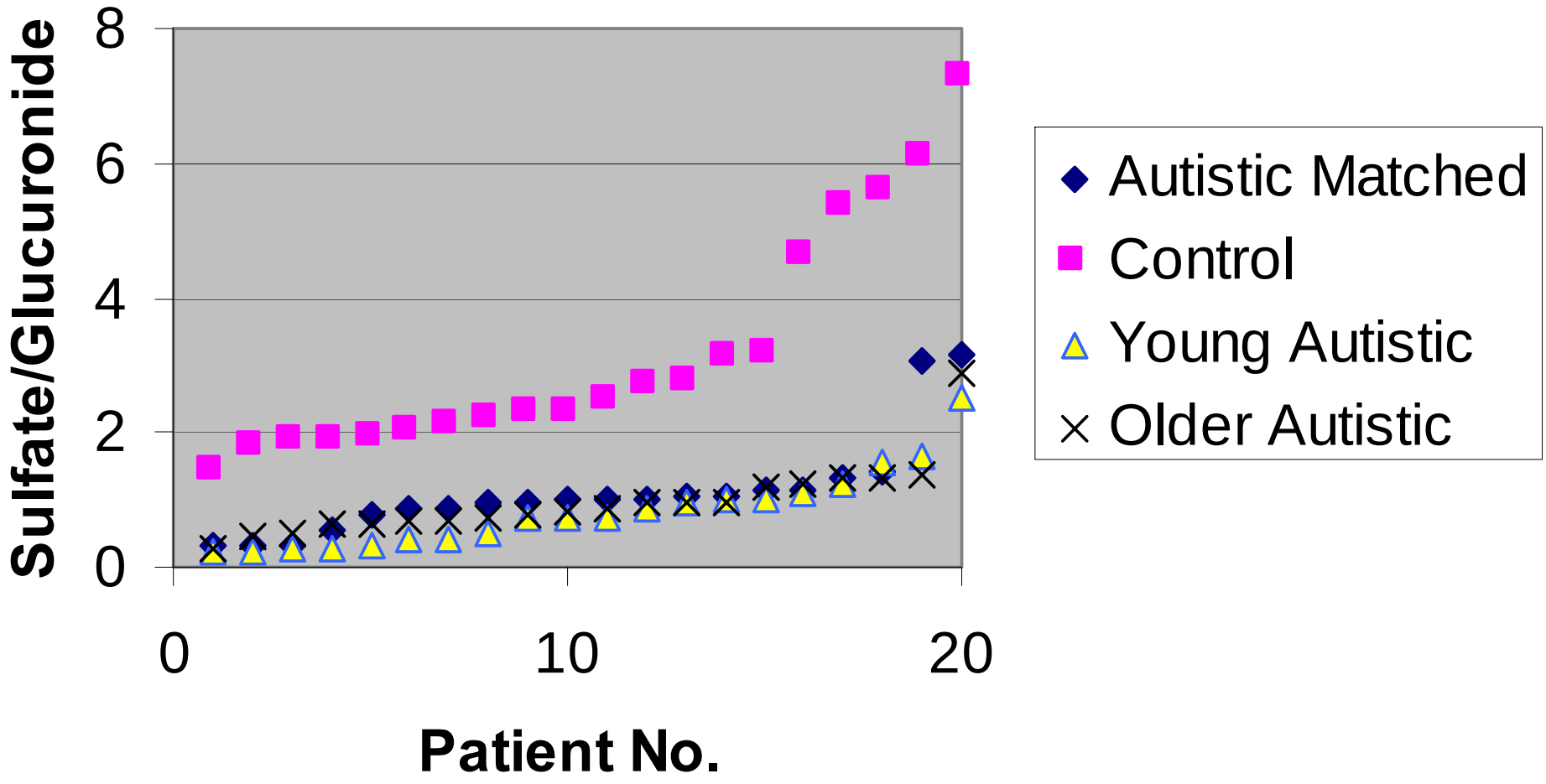
- CAN BE MISINTERPRETED—
  - Anecdote vs N of 1 study (on-off-on)
  - Data vs poor study design

- 1 case
- 2 cases
- 3 cases

Sudden onset disorders

- Rett syndrome
- Vanishing white matter syndrome
- Sydenham chorea
- PANDAS and PITANDS
- Schizophrenia
- Pink disease (acrodynia)
- Glutaric aciduria I

Paracetamol Sulfate/Glucuronide (Alberti et al., 2000)



Environmental factor(s)

- Persistent or hit-and-run?

SULFATION DEFECT?

- Polymorphisms in xenobiotic metabolism/detoxification
- Importance of sulfation and glucuronidation
- Glucuronidation defects
- Sulfation defects?
- Sulfation of xenobiotics, neurotransmitters?

Abnormalities of sulfur AAs

- Low methionine
- Low cysteine
- Low glutathione, total and reduced
- Vulnerability of methionine synthase
- Response to methylcobalamin, folinic acid, and betaine
- Inborn errors with sulfation vulnerability
  - HCYS, PA/MMA, cbl defects

Deficient glutathione, Impaired methionine synthase

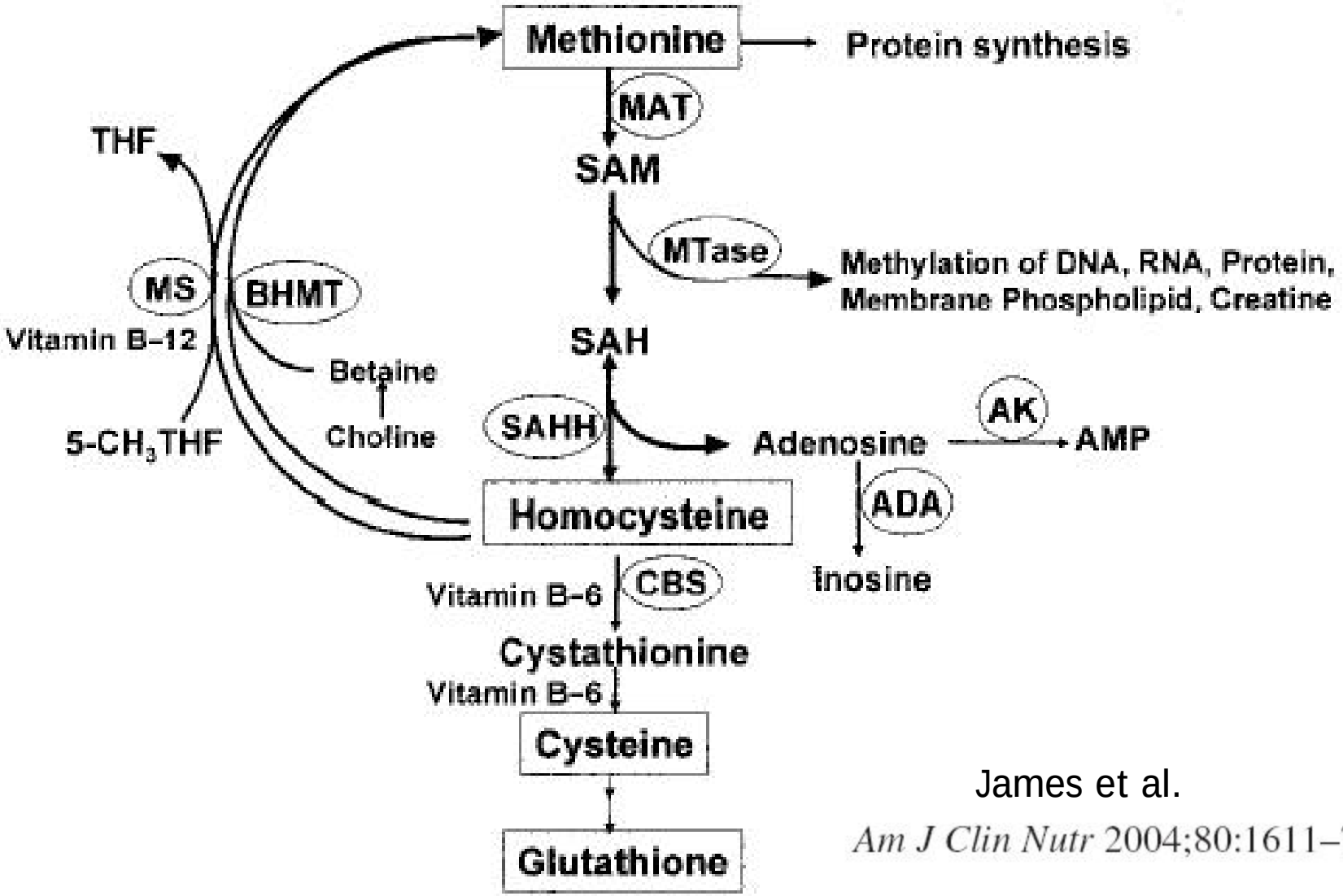
S. Jill James (U of Arkansas)

R. Deth (Northeastern U.)

Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism[1,2]

S Jill James, Paul Cutler, Stepan Melnyk, Stefanie Jernigan, Laurette Janak, David W Gaylor, and James A Neubrander

Am J Clin Nutr 2004;80:1611–7.

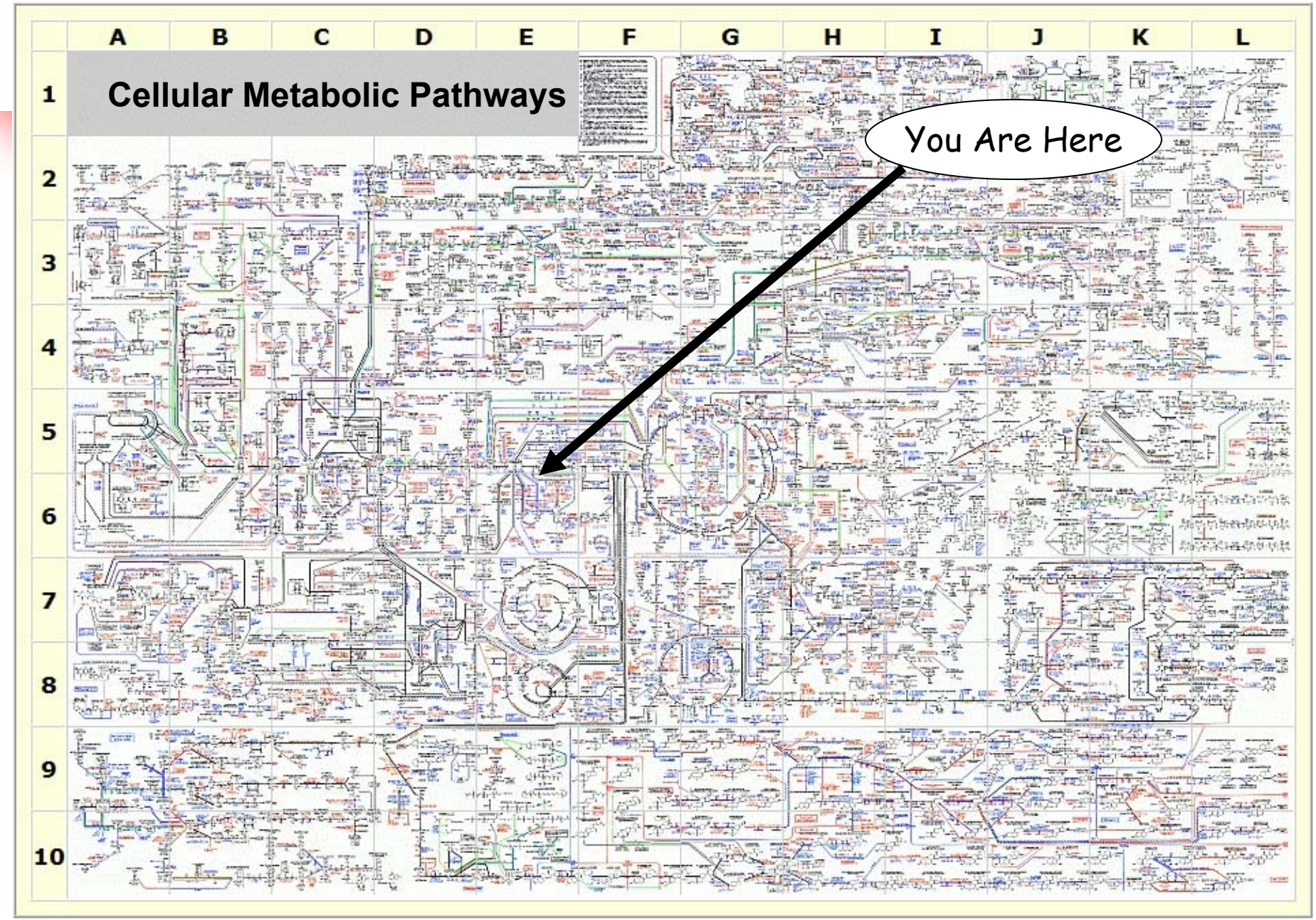


James et al.

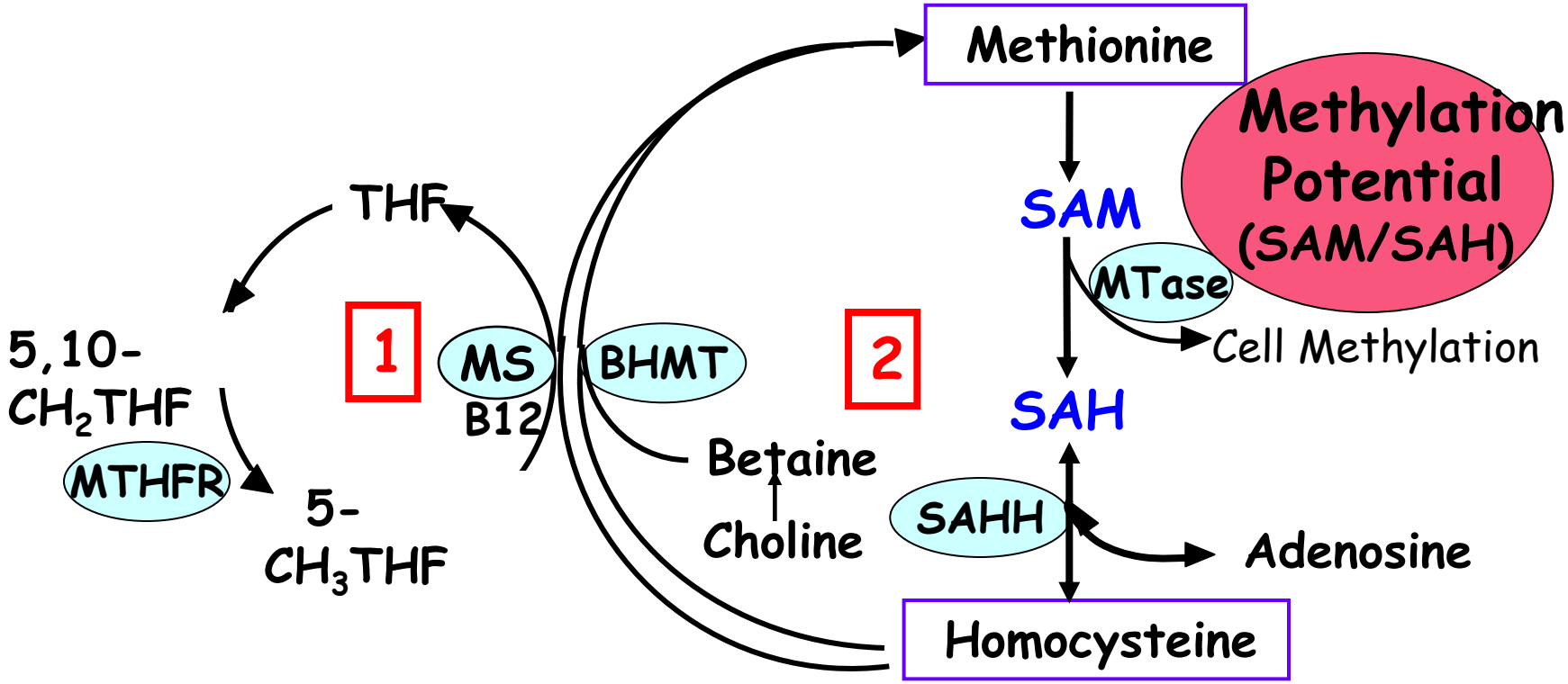
Am J Clin Nutr 2004;80:1611–7.

FIGURE 1. The methionine cycle involves the remethylation of homocysteine to methionine by either the folate–vitamin B-12–dependent methionine synthase (MS) reaction or the folate–vitamin B-12–independent betaine homocysteine methyltransferase (BHMT) reaction. Methionine is then

Putting it all into Perspective……we see what we know



Methionine Transsulfuration to Cysteine and Glutathione



THF: tetrahydrofolate

Enzymes

Comparison of methionine cycle and transsulfuration metabolites between autistic children and control children[1]

	Control children (n = 33)	Autistic children (n = 20)
Methionine (μmol/L)	31.5 ± 5.7 (23–48)	19.3 ± 9.7 (15–25)[2]
SAM (nmol/L)	96.9 ± 12 (77–127)	75.8 ± 16.2 (68–100)[3]
SAH (nmol/L)	19.4 ± 3.4 (16–27)	28.9 ± 7.2 (14–41)[2]
SAM:SAH	5.2 ± 1.3 (4–8)	2.9 ± 0.8 (2–4)[2]
Adenosine (μmol/L)	0.27 ± 0.1 (0.1–0.4)	0.39 ± 0.2 (0.17–0.83)[4]
Homocysteine (μmol/L)	6.4 ± 1.3 (4.3–9.0)	5.8 ± 1.0 (4.0–5.8)[3]
Cystathionine (μmol/L)	0.17 ± 0.05 (0.1–0.27)	0.14 ± 0.06 (0.04–0.2)[5]
Cysteine (μmol/L)	202 ± 17 (172–252)	163 ± 15 (133–189)[2]
tGSH (μmol/L)	7.6 ± 1.4 (3.8–9.2)	4.1 ± 0.5 (3.3–5.2)[2]
Oxidized glutathione (nmol/L)	0.32 ± 0.1 (0.11–0.43)	0.55 ± 0.2 (0.29–0.97)[2]
tGSH:GSSG	25.5 ± 8.9 (13–49)	8.6 ± 3.5 (4–11)[2]

[1] All values are $\bar{x}$ ± SD; range in parentheses. SAM, *S*-adenosylmethionine; SAH, *S*-adenosylhomocysteine; tGSH, total glutathione; GSSG, oxidized glutathione.

[2–5] Significantly different from control children: [2] $P < 0.001$, [3] $P < 0.01$, [4] $P < 0.05$, [5] $P < 0.002$.

James et al., 2004 *Am J Clin Nutr* 2004;80:1611–7.

Folinic Acid, Betaine, and Methyl B-12 Supplementation in Children with Autism

Eight of the children participated in an intervention trial and were given 800 μg folinic acid and 1000 mg betaine b.i.d. for 3 months and the plasma metabolites were re-measurec

The children were then given injectible methyl-B12 (75 μg/Kg 2x/week) and the plasma profile was repeated after 4 weeks of combined folinic acid, betaine, and methyl B12

American Journal of Clinical Nutrition 80:611-17, 2

Proportion of Autistic Children within Normal Range Before and After Supplementation

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

[a] Range estimated to include 90% of control children

Does this apply to IEMs?

- Low intake of methionine in PA, MMA, HCYSuria
- RECOGNITION OF GLUTATHIONE DEFICIENCY WHEN IT GETS SEVERE ENOUGH.
- No information about oxidative stress, glutathione needs in most patients

Things to think about

- We are much better at recognizing high levels than low
- We can only measure
  - what we CAN measure
  - What we DO measure

Possible survey questions--1

Parents' information:

Have you heard of autism? The autism spectrum disorders?

Do you think your child with IEM has some features that made you think of autism? Or the autism spectrum disorders?

Do you think any of your child's relatives have features of an autism spectrum disorder?

Possible questions--2

- Has your child had a developmental evaluation?
- Did it include an autism assessment? (CARS, ADOS, etc.)
- Did your child receive a diagnosis of an autism spectrum disorder?

Possible questions--3

Which features of autism have concerned you?

Impaired/inappropriate social interactions

- Impaired communication
- Restricted repertoire of activities/interests
- Lack of concept of mind
- Sensory distortion/dysregulation
- Mental retardation, seizures

Possible questions--4

- Does your child have ups and downs of behavior?
- Does your child have times with greater or lesser autistic features?

Possible questions--5

Do you think ups and downs are related to:

- Illness?
- Feeding?
- Not feeding?
- Fever?
- TPN?
- Medications?
- Seizures?
- Something else?

Does this apply to IEMs?

- Parents as observers—absolutely!
- Internet—a wonderful resource!
- Do metabolic physicians listen? I hope so.

Does this apply to IEMs?--2

- Diet responsiveness?
- Food dyes/colored foods?
- Response to fasting/TPN?

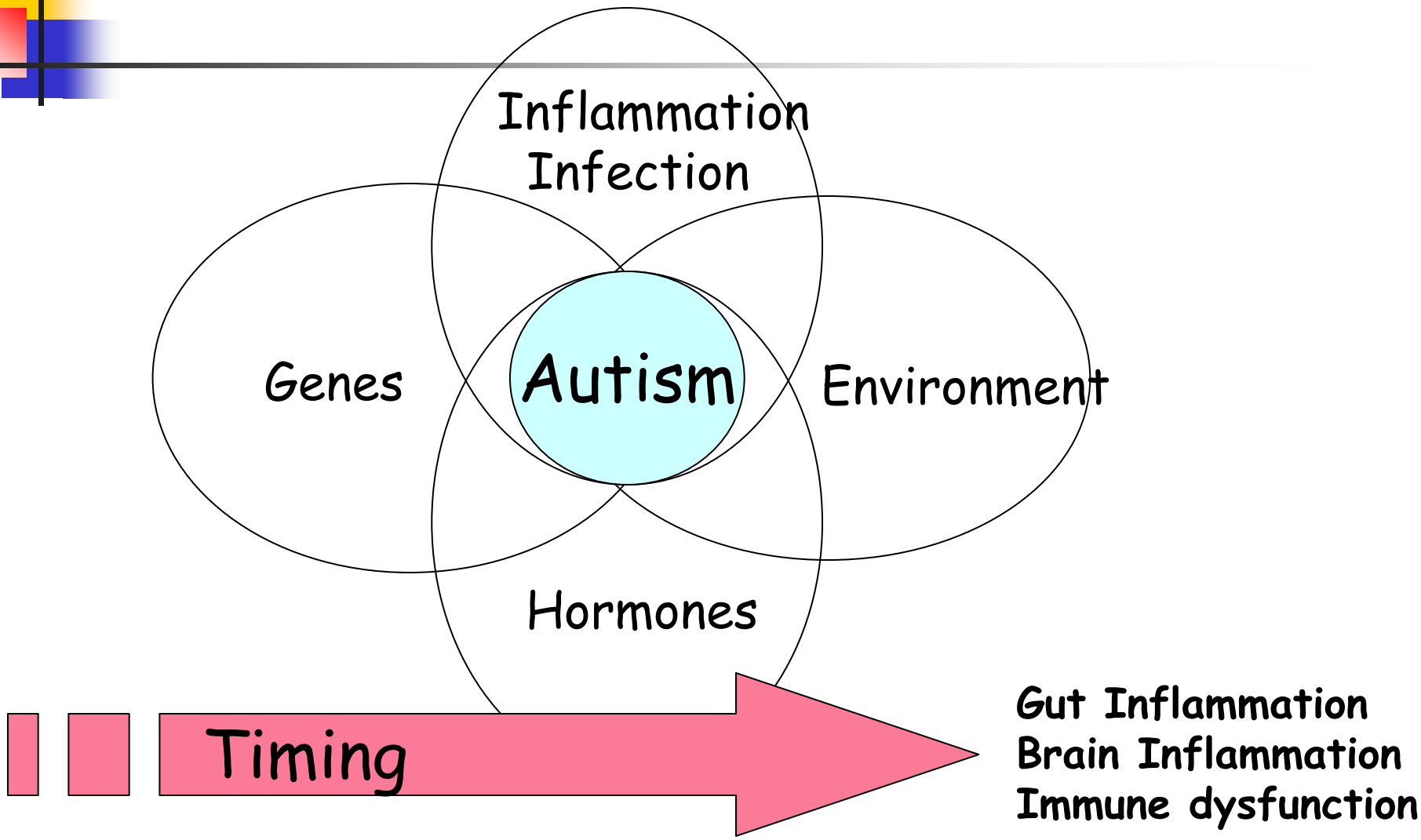
Parents as observers

- “Listen to your patient. He’s trying to tell you something.” Gene Stead, Duke.
- Crepe-hanging--> patients don’t return. They get on the internet and go somewhere else.

Have we seen anything similar in our IEM patients?

- PARENTS ARE THE BEST OBSERVERS!

Factors Contributing to Oxidative Stress in Autistic Children



WORKING HYPOTHESIS June 2006 (James)

The abnormal metabolic profile in children with autism strengthens the hypothesis that an <u>inability to maintain glutathione redox status and to control oxidative stress</u> may contribute to the development of neurologic, immunologic,and gastrointestinal dysfunction that occurs with autism.

UNIFYING CONCEPTS—HOW DOES THIS APPLY TO IEMs?

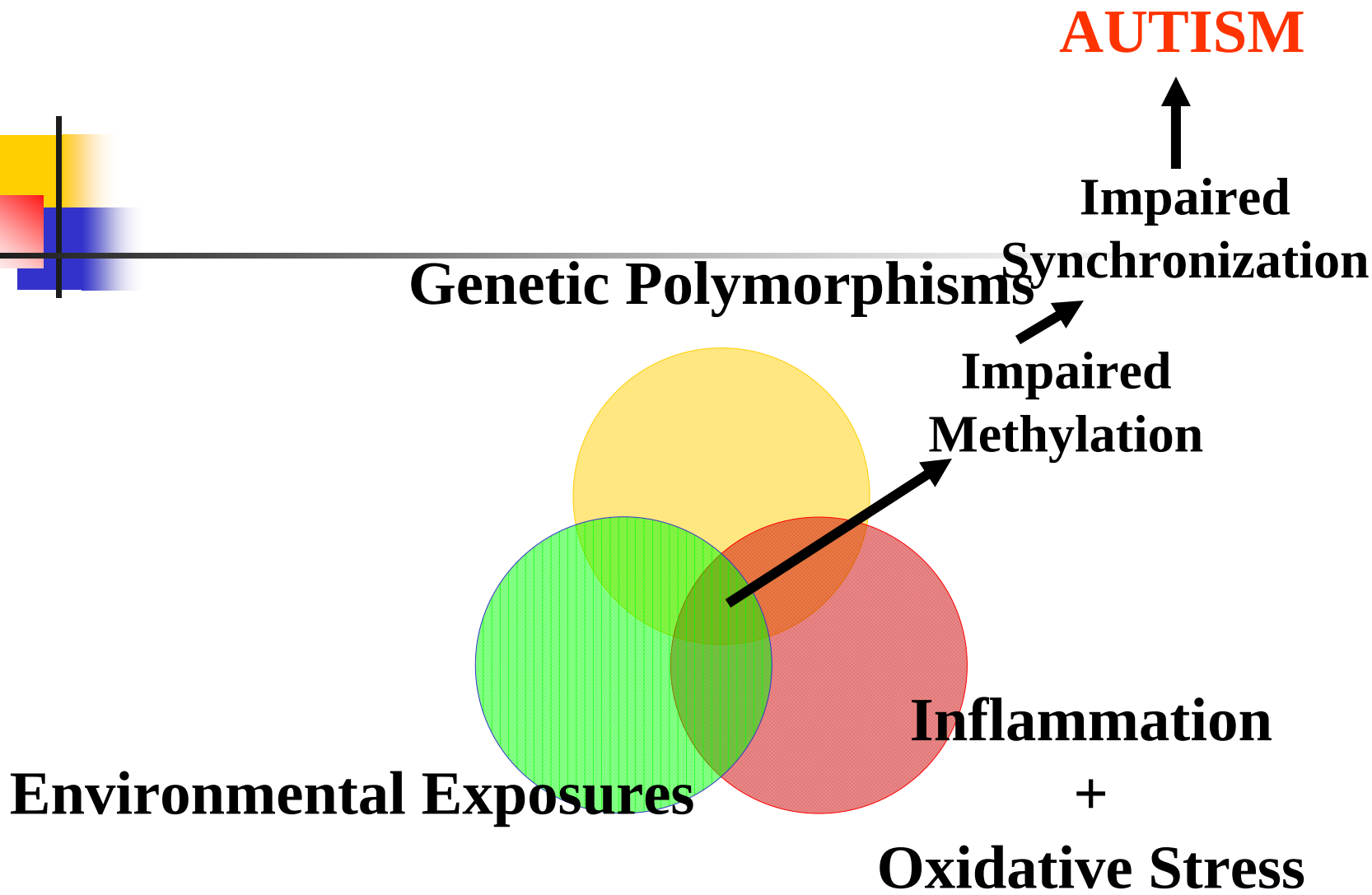
- Any suggestion of ups and downs?
- Any idea what causes them?
- How do ‘metabolic strokes’ cause damage? Probably different for each disorder.
- How can we prevent/ameliorate/treat these events?
- Which of the ideas from idiopathic autism should be explored first?

Pink Disease (Calomel—mercurous chloride)

- 140 years of mercury toxicity—first suspicion after 50 years (1870). Convincing proof more than 70 years later (1940s)
- Out of babies' lives by 1961.
- 500-fold range of sensitivity (Josef Warkany)

Mercury--

- Multiple forms--interconversions
- Variable vulnerability; age
- Blood half-life isn’t the whole story
- Boluses vs averages
- Thimerosal toxicity plausible at achievable concentrations
- Testosterone enhances toxicity
- CDC Simpsonwood



Modified from original source

OTHER GENETIC TESTS--4

- Biochemical testing for metabolites that may indicate genetic weakness or toxicity
  - Amino acids (plasma and urine)
  - Organic acids (urine)
  - Complete blood count, basic metabolic profile, ammonia,
  - Vitamin levels (thiamine, glutathione, pyridoxine and pyridoxal 5-phosphate, B12, folate, etc.) Carnitine level, acylcarnitine profile.
  - Evidence for mitochondrial dysfunction—increased anion gap, increased lactate in urine or plasma, increased alanine.
    - Any primary mitochondrial or nuclear DNA mutations found in patients with autism yet?
- Gene testing for variants of vulnerable enzyme systems (MTFR, etc.)

Elimination Diet

- Casein (Dairy)
- Gluten (Wheat, oats, barley, rye)
- Chocolate
- Nuts and Peanuts
- Food dyes/colored foods
- Tomatoes and peppers
- Yeasts, fermented foods, simple sugars
- LOOKS LIKE MIGRAINE AND FOOD INTOLERANCE LIST!

Celiac disease as a model

- Genetic—HLA DR2, DQ8
- Environmental—gluten
- Immune-mediated, at least in part
- Gut pathology
- Immune derangement; rash, arthritis, lymphoma
- Brain effects--depression, ataxia, calcifications, seizures, schizophrenia

“COMPLEMENTARY THERAPY”--1

- Pyridoxine and Magnesium
- Epsom salts ($MgSO_4$)
- Diet changes--‘Feingold diet.’ *
- Pancreatic enzymes
- Anti-fungal medication; elimination of yeast and simple sugars in diet. Specific carbohydrate diet (Haas, Gotschall)

“COMPLEMENTARY THERAPY”--2

- Dimethylglycine, betaine; folates;
- B12 (methylcobalamin) *
- Fish oils, other sources of n-3 fatty acids EPA, HEPA
- vitamin A (beta carotene)/bethanechol
- Thiamine tetrahydrofurfuryl disulfide (TTFD)
- Chelation--DMSA, DMPS *

Biochemical Aspects needing further investigation--3

- Serotonin--platelet content, response to SSRIs. Is there a promoter of uptake?
- Alteration of brain serontonin synthesis
- Hyper- or hypouricosuria
- Thiamine-responsiveness?
- Hyperbaric oxygen? Does it work by re-normalizing brain perfusion?

Other investigations--1

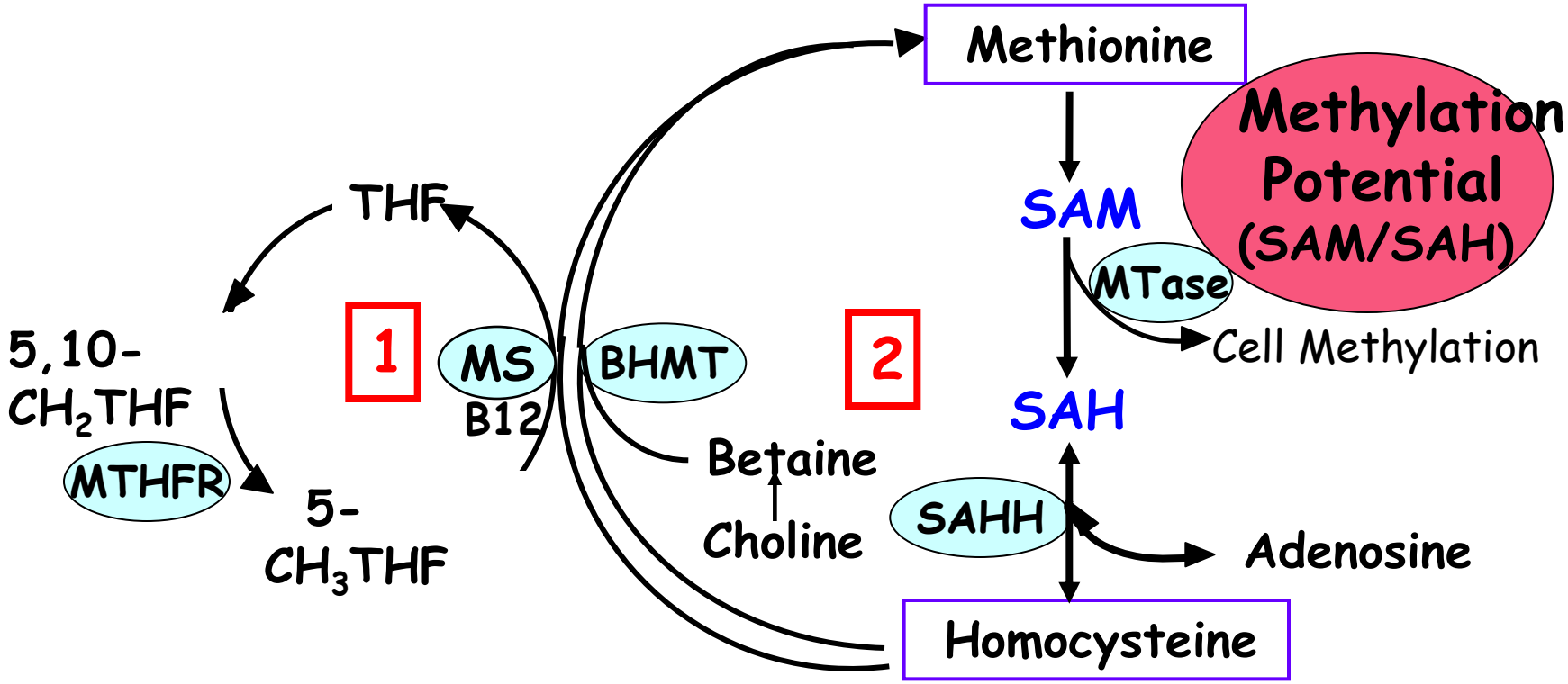
- Gut flora
- Immune function
- Heavy metal accumulation and excretion
- identification of gene-environment interactions. Recurring observation of vulnerability to environmental stressors.

Other investigations--2

- Brain function-perfusion relationships
- mechanism of response to effective therapies
- Single-blind studies can allow collaboration between treaters and investigators
- Video tapes are invaluable

Some details about the glutathione problem—S. Jill James

Methionine Transsulfuration to Cysteine and Glutathione



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Enzymes

Pharmacologic doses of nutrient cofactors can release metabolic blocks and restore normal flux by mass action

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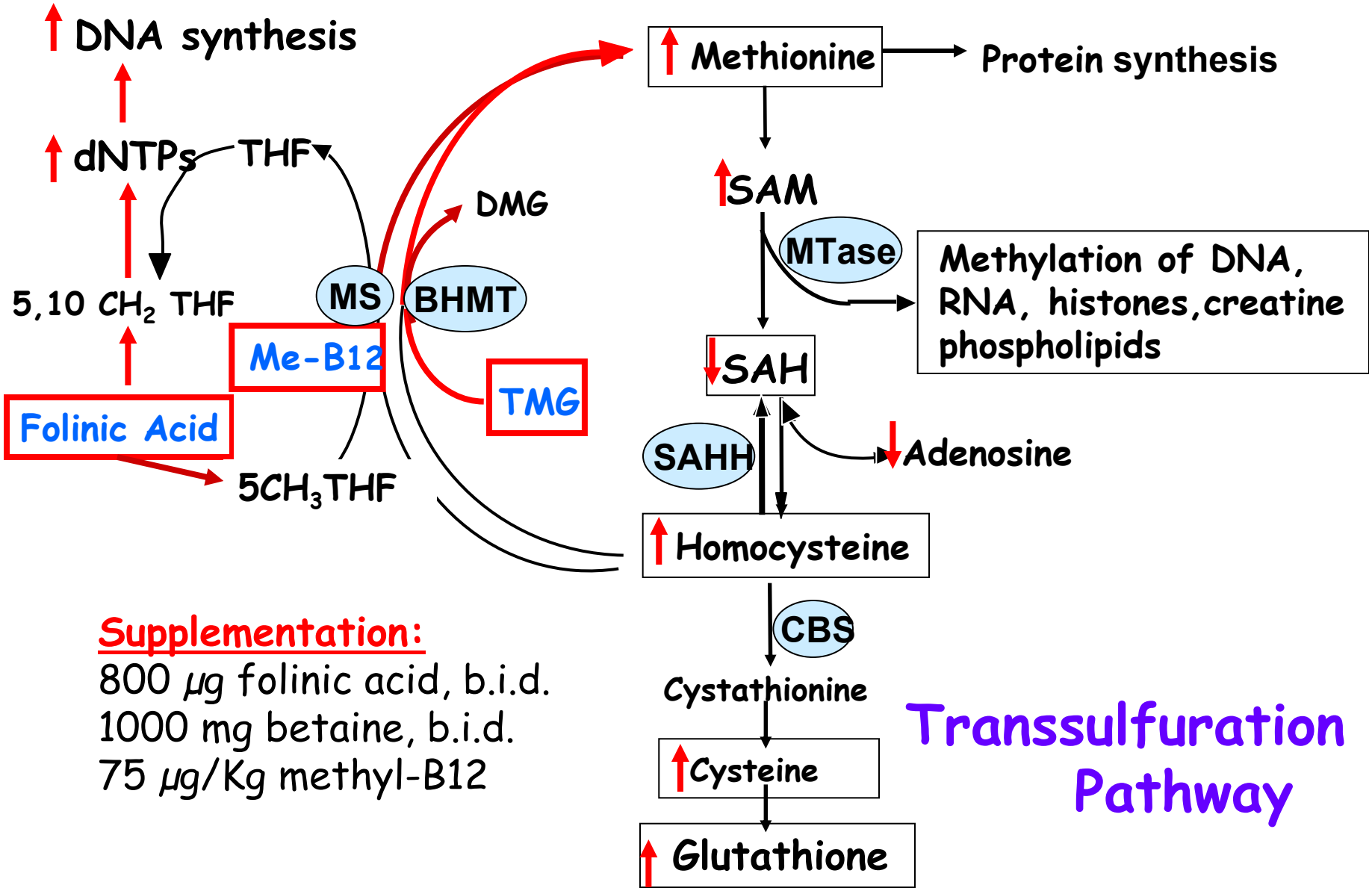

Supplementation:

800 μg folinic acid, b.i.d.
1000 mg betaine, b.i.d.
75 μg/Kg methyl-B12

Transsulfuration Pathway

Proportion of Autistic Children within Normal Range Before and After Supplementation

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INTERPRETATION

Folinic Acid and Betaine brought all the methionine cycle metabolites into normal range.

The combined regimen of Folinic Acid, Betaine, and Methyl B12 brought all the transsulfuration metabolites into the normal range.

Best predictors of impaired methylation are low methionine and SAM/SAH ratio OR elevated adenosine.

Best predictors of impaired antioxidant defense are low cysteine, and low glutathione (low GSH/GSSG ratio).

Is there a genetic basis for increased vulnerability to oxidative stress?

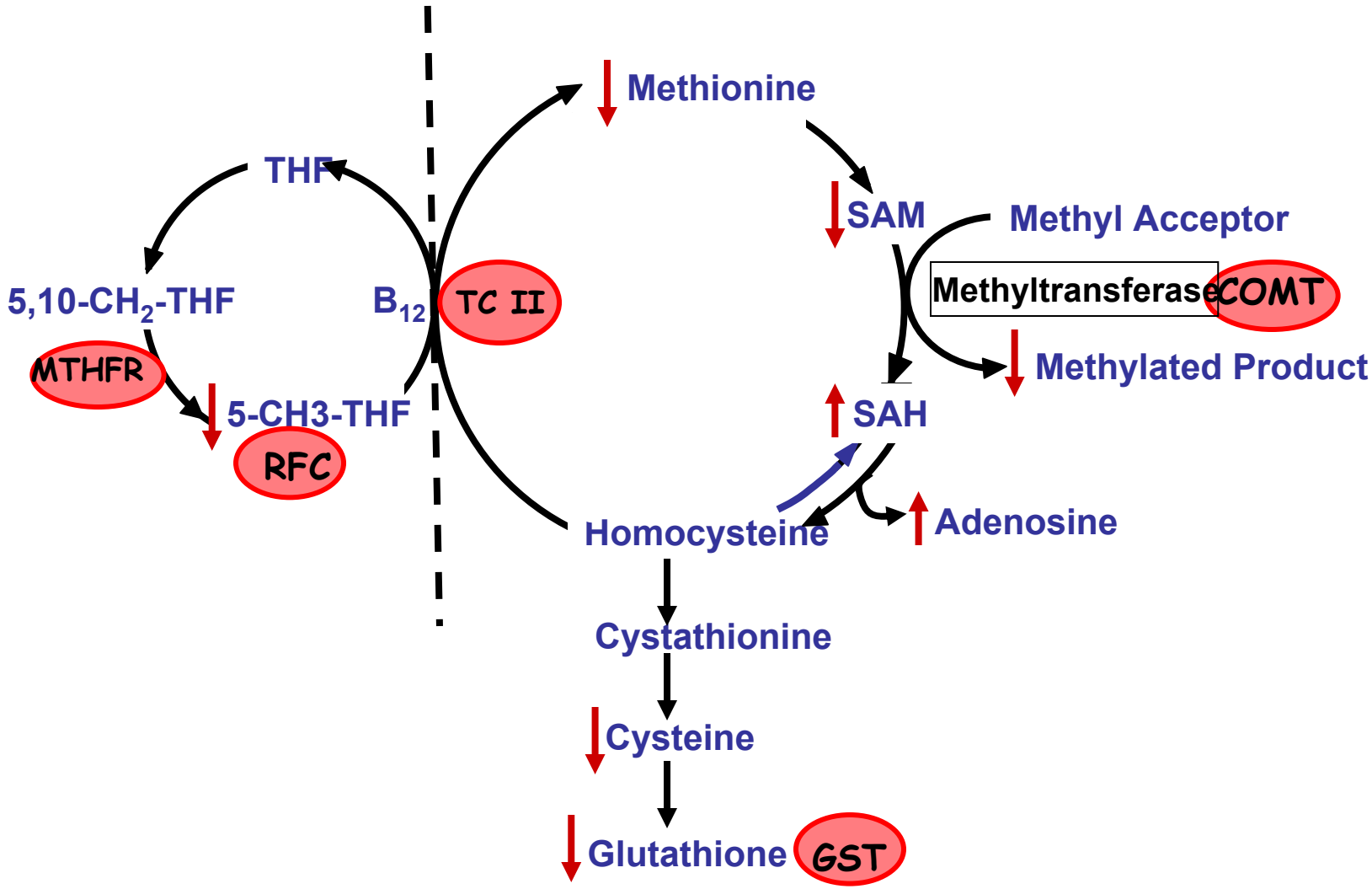
e.g., Mercury and other heavy metal toxicity; cell death

Autoimmunity: increased T helper2 cells

Gut Inflammation: increased inflammatory cytokines

Redox imbalance in the brain: inflammation; cell death

A Targeted Approach to Genetic Polymorphisms; The Metabolic Phenotype



Important Caveat

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

The metabolic phenotype provides a targeted approach to autism genetics.

Difficulties with purely genetic approach to autism

More than 10 genes will be required for the autistic phenotype.

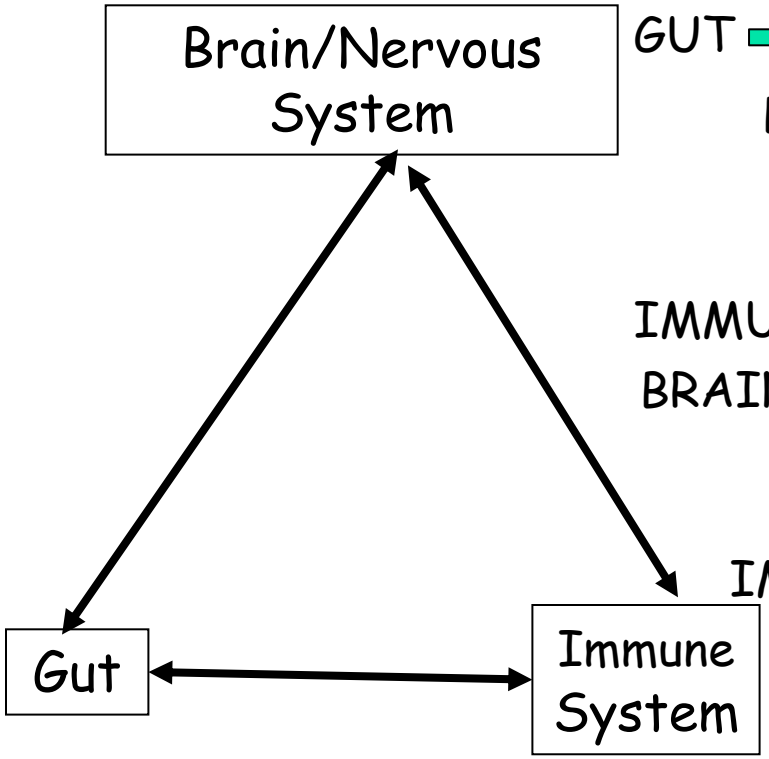
Different combination of genes in different individuals

Genetic susceptibility likely to require an environmental trigger

Same genetic risk factors may be present in unaffected individuals

Differences in timing and/or severity of environmental exposures plus different combinations of susceptibility genes will produce heterogeneous phenotypes.

The Autism Triad: Brain-Gut-Immune Axis



(Steve Kahler)

GUT ➡ BRAIN: Vagus afferents; Gut neuropeptides

BRAIN ➡ GUT: Endorphins; Neuropeptides

IMMUNE ➡ BRAIN: Cytokines; microglia activation

BRAIN ➡ IMMUNE: Endorphins; Neuropeptides; Cortisol

IMMUNE ➡ GUT: Cytokines; leukotrienes

GUT ➡ IMMUNE: Gut neuropeptides; microbial products

All 3 systems highly vulnerable to chronic oxidative stress

New Questions

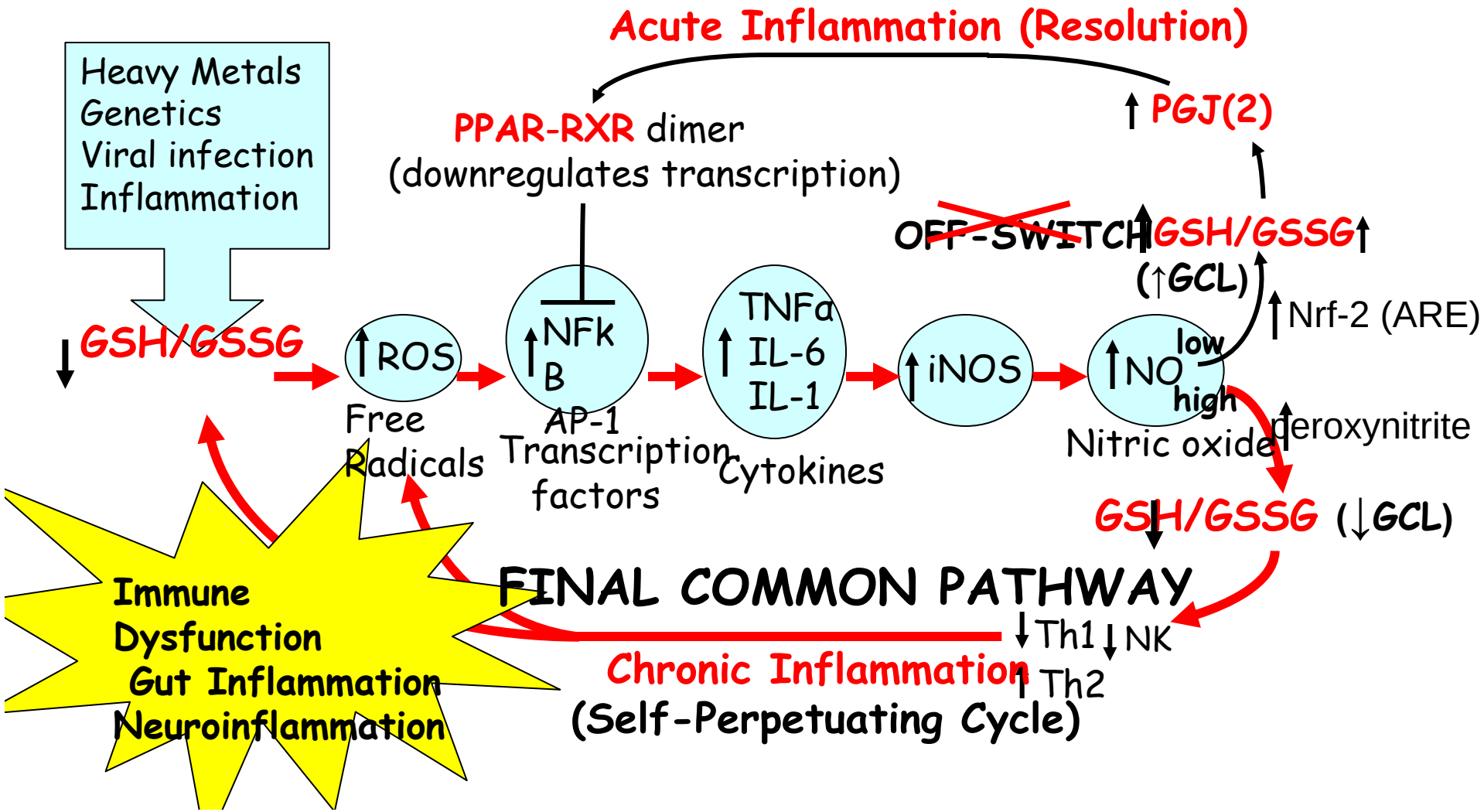
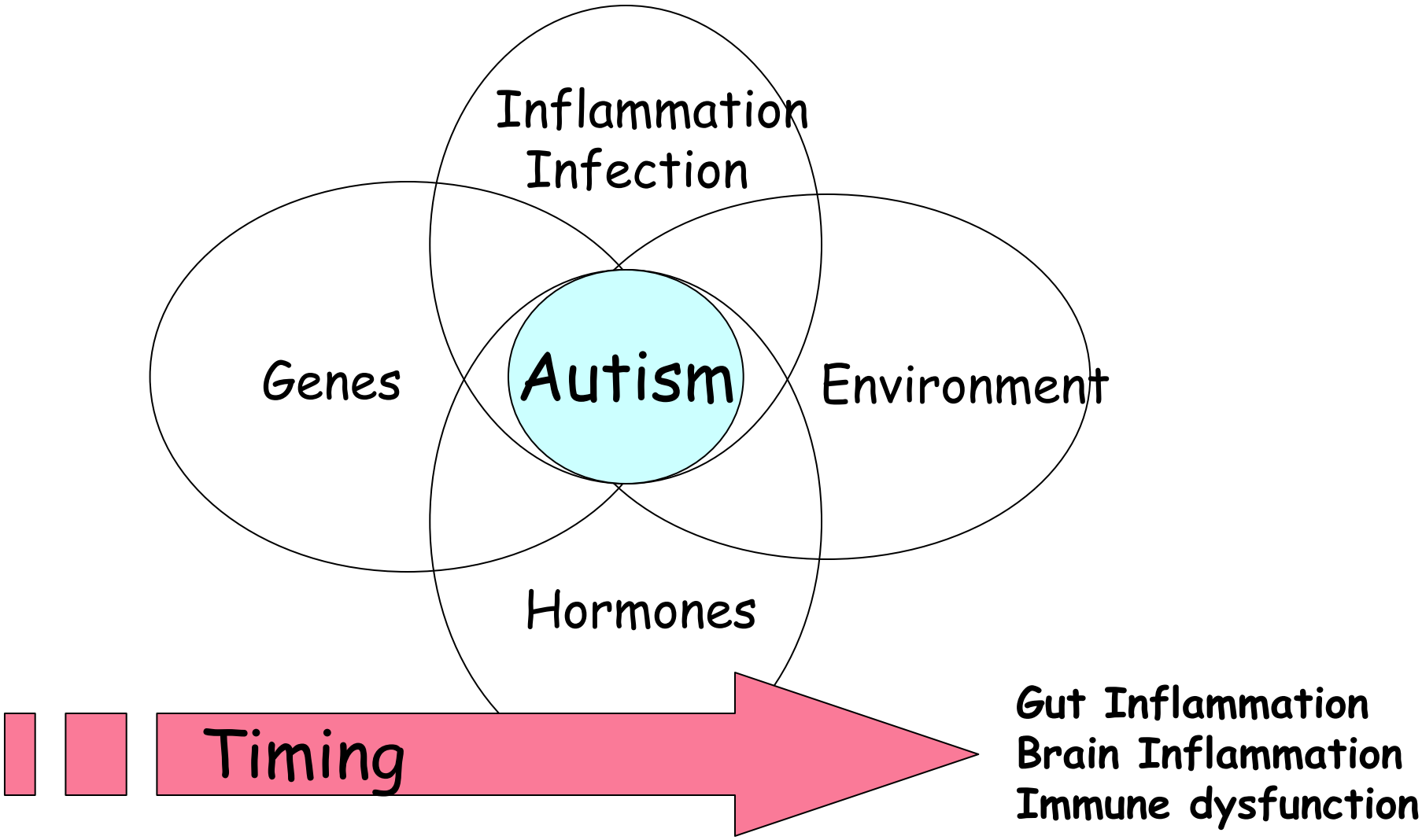
Do we need a broader paradigm for autism pathogenesis ?

A more systemic approach beyond brain genes?

Could there be a component of metabolic encephalopathy?

The oxidative stress hypothesis encompasses the gut-brain-immune axis and gene-environment interactions

The failure to maintain GSH/GSSG redox balance and to resolve acute inflammatory stress promotes a self-perpetuating cycle of chronic inflammation



Factors Contributing to Oxidative Stress in Autistic Children