Biomedical Therapies for Autism

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What is Autism?

- DSM 4 definition of Autism:
  - Qualitative impairments in social interaction
  - Qualitative impairments in communication
  - Repetitive, restrictive, or stereotyped interests and behaviors
  - Symptoms present before age 3
- PDD-NOS is similar with less severe symptoms

Clinicians see what we are looking for.

Not every child who looks autistic has the same issues.

How does a biomedical clinician see autism?

- Developmental symptoms reflect brain dysfunction
- Brain dysfunction reflects cellular dysfunction
- Cellular dysfunction involves metabolic insufficiencies, toxic overload, oxidative stress, and immunological overreactivity.

What do we see when we look at an autistic child?

- Aloofness, lack of interest in others
- Language delays and abnormalities
- Cognitive delays
- Sensory hyper-reactivities and under-responsiveness
- Hyperactivity or lethargy
- Irritability or emotional reactivity
- Obsessiveness and persistence

Are there physical symptoms present?

- At least half of children with autism seem to have an intestinal problem chronic loose smelly stool or constipation
- Seizures are eventually diagnosed in about 25%
- Feeding disorders common
- Some of these children look sick

Frequent Regression

- 10-50% of children with autism have history of significant developmental regression in the second year.
- Regressions anecdotally associated with episodes of significant illness or immunizations.
- Regression frequently associated with the development of physical symptoms

Asperger Syndrome

- Asperger Syndrome is a distinct but related presentation of symptoms including:
  - No significant language delay
  - Qualitative impairment in social interaction
  - Repetitive, restrictive, or stereotyped interests and behaviors
  - No significant mental retardation
- Depression, OCD, etc. are common comorbidities

Modes of inheritance

- Chromosomal – 5%
- Mendelian -- 5%
- Conditional Mendelian -- ?%
- Mitochondrial -- ?%
- Multi-factorial -- ?%
- Epigenetic – Maternal hypomethylation
- Transplacental -- 10% of moms
- Autism higher in assisted pregnancies

What about treatment?

- Behavioral Therapies
- Educational Therapies
- Occupational Therapies
- Conventional Medical Therapies
- Biomedical therapies (e.g. DAN)
- Alternative therapies (Energy medicine)

Behavioral Therapies

- The most important thing in therapy is to make a connection. Quantity Counts.
  - ABA - DTT –Therapist directed
    - Skill acquisition is the goal
  - Relationship based – Child directed
    - Parents learn the skills and do the work
    - Connection is the Goal
    - Floortime, Son-Rise, Play to Talk, Others
- More than 24 hours a week needed

Educational Therapies

- Individual Educational Plan (IEP)
- Speech, PECS, etc.
- Academic skills
- Managing classroom behavior

- Consider a consultant

Occupational therapies

- Activities of Daily Living
- Fine motor skills
- Feeding therapy
- Assistance with regulation
  - Parenting and teacher guidance
- Sensory Integration Therapy
  - Helps to cope with brain dysfunction
- Adaptations to the overstimulating world

Conventional medical therapies

- Medications can affect irritability, aggressiveness, hyperactivity, sleep, repetitiveness, and self-injurious behavior.
  - Risperidal and Abilify are only FDA approved medications to treat irritability and aggressiveness in children with autism.
  - SSRI's not significantly effective in studies
  - Stimulants can improve attention, hyperactivity, and interaction

However…

- Studies do a poor job of capturing individual responses.
- The effect sizes are often not impressive.
- Studies are all short term.
- Side effects can be significant.
- In my opinion, dramatic clinical responsiveness is as valuable as a randomized trial.
- But, don’t be surprised if meds don’t help.

What can biomedical therapies treat?

- Core autistic symptoms
- Developmental delays
- Behavioral problems
- Feeding choices and behaviors
- Medical issues such as diarrhea, constipation, and sleep
- We can improve the child and family's "Quality of Life"

What do I see everyday?

- Children waking up
- Children calming down
- Irritability disappearing
- Bowels normalizing
- Language flowing
- Affection growing
- Worsening can be a sign of healing

Problems

- I have also seen treatments not work
- Minimal good data exist
- Assessing developmental progress in a developmental disorder with a variable course
- Sorting out the individual factors affecting symptoms
- RCT vs N = 1 Trial

Is this child treatable?

- Predictive tests do not yet exist.
- The more problems there are, the more likely that there are problems that can be improved (e.g. Maybe we can at least improve the diarrhea).
- The more quickly a child responds to therapies, the more likely they will be responsive and potentially curable.

The hardest question

- If a particular child is not responding to therapy, is it because that child is “incurable”?
- Or have we just not found the cure?

How do supplements help?

An introduction to biochemistry

- Biochemistry is the study of the transformation of small molecules such as sugars, amino acids, and fatty acids into each other and into macromolecules such as DNA, proteins, and cell membranes

- Enzymes are the proteins that catalyze these chemical reactions.
- Proteins are made as strings of amino acids that then fold into a 3-dimensional structure
- The function of enzymes is determined this structure and the specific amino acids that are brought together in its “active site”

- One of the most common amino acids in active sites is cysteine, which has a sulfur group sticking out. If this cysteine is damaged, say by having a mercury atom attached to it, the enzyme will no longer work.
- That is how heavy metals do their damage.

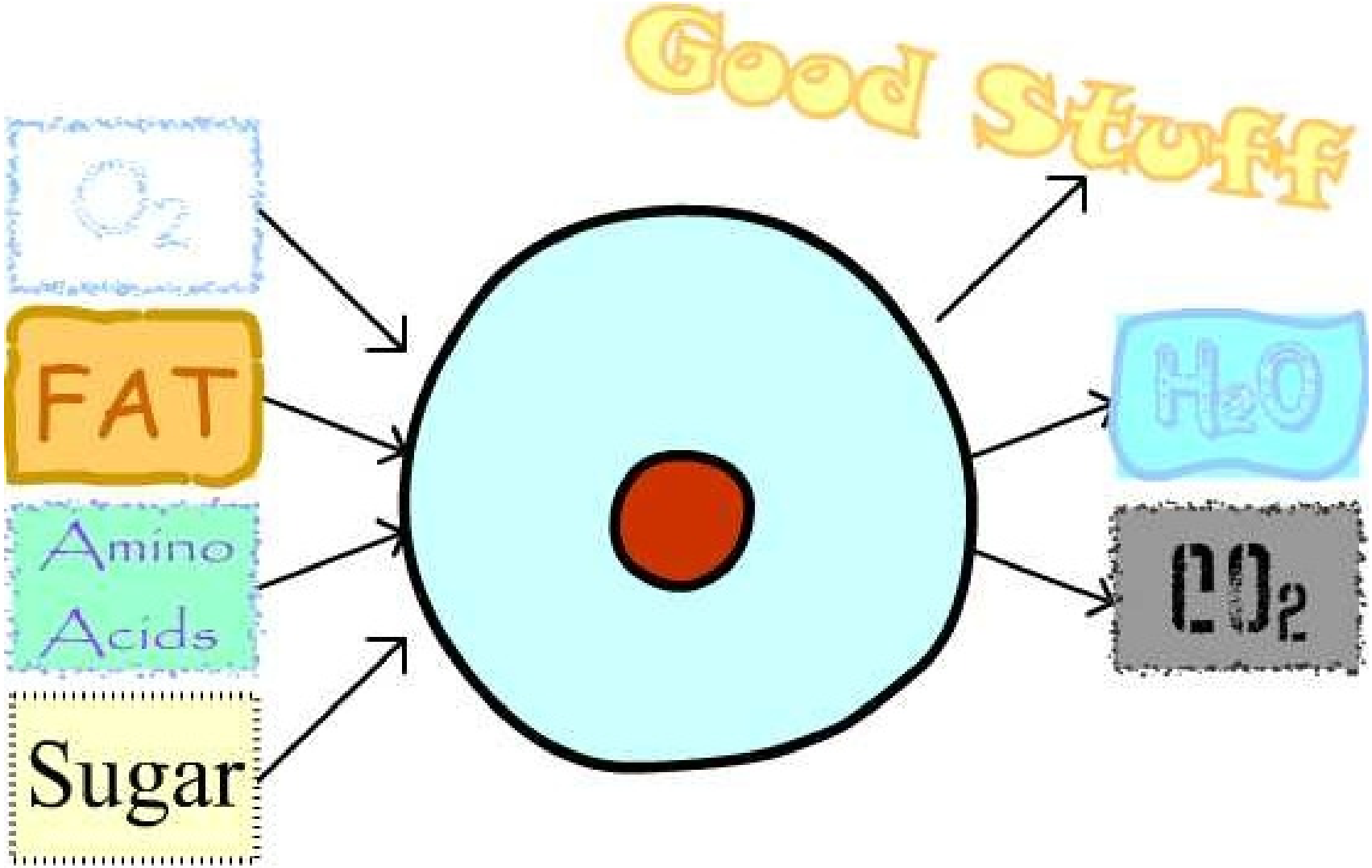
Vitamins and Minerals

- Vitamins are small molecules found in foods that the body cannot make itself.
- Some, like vitamin C and E absorb oxidative stress.
- Some like vitamin A and D are hormones
- Some, like B vitamins act as cofactors for enzymes
- There are some like coQ10 and carnitine that the body can’t make enough of.

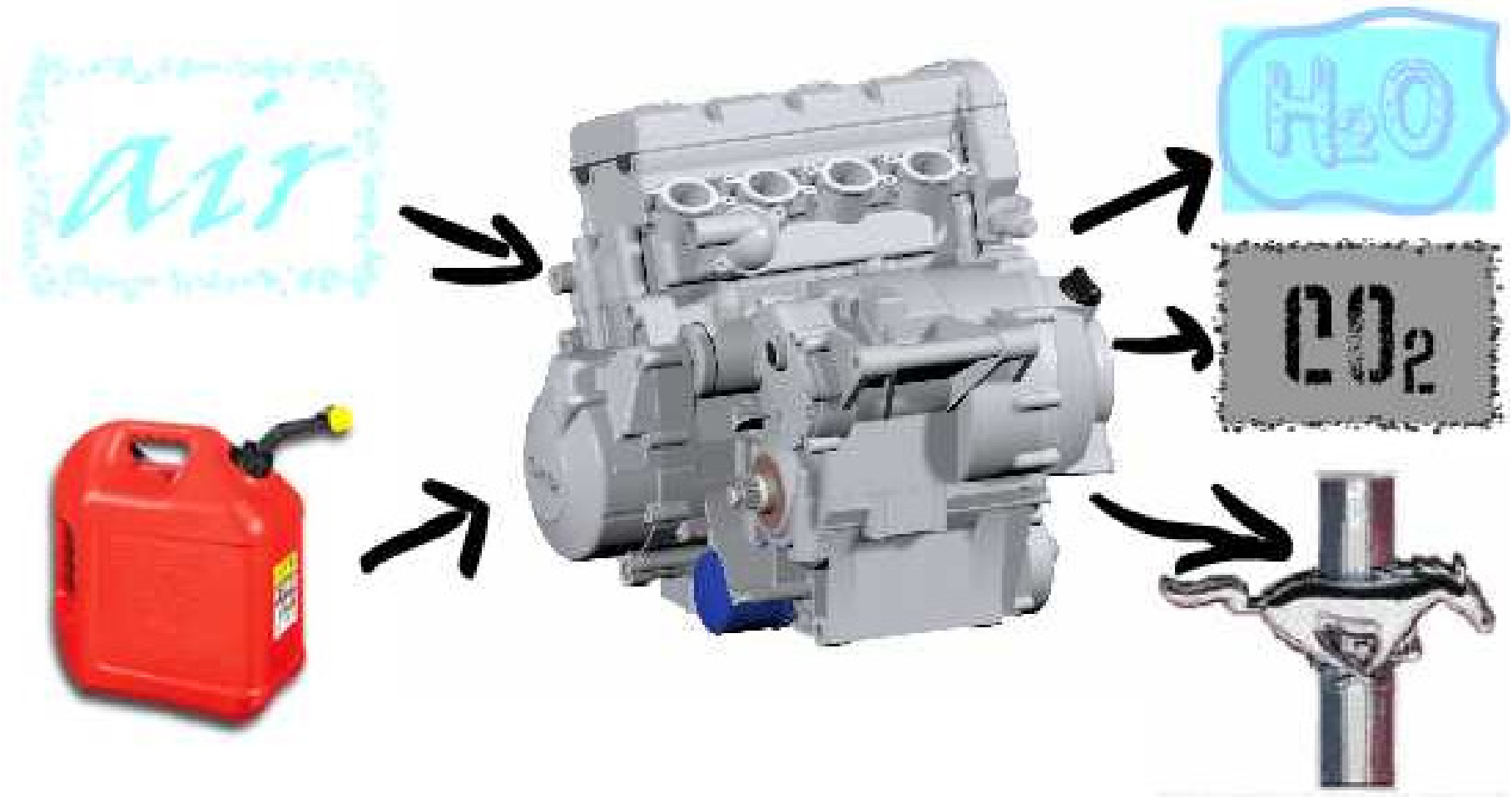
- Many enzymes require cofactors to function, like a power drill and a drill bit.
- Some people have genetic variant enzymes (SNP's) or damaged enzymes that do not bind the cofactors well.
- These people need more vitamins than the "RDA"

- Some people need more anti-oxidants to absorb and reverse damage. This is a major role for vitamins in autism.
- For example vitamin C and E are needed to recycle glutathione.
- Zinc is a cofactor for hundreds of enzymes and can be hard to absorb.

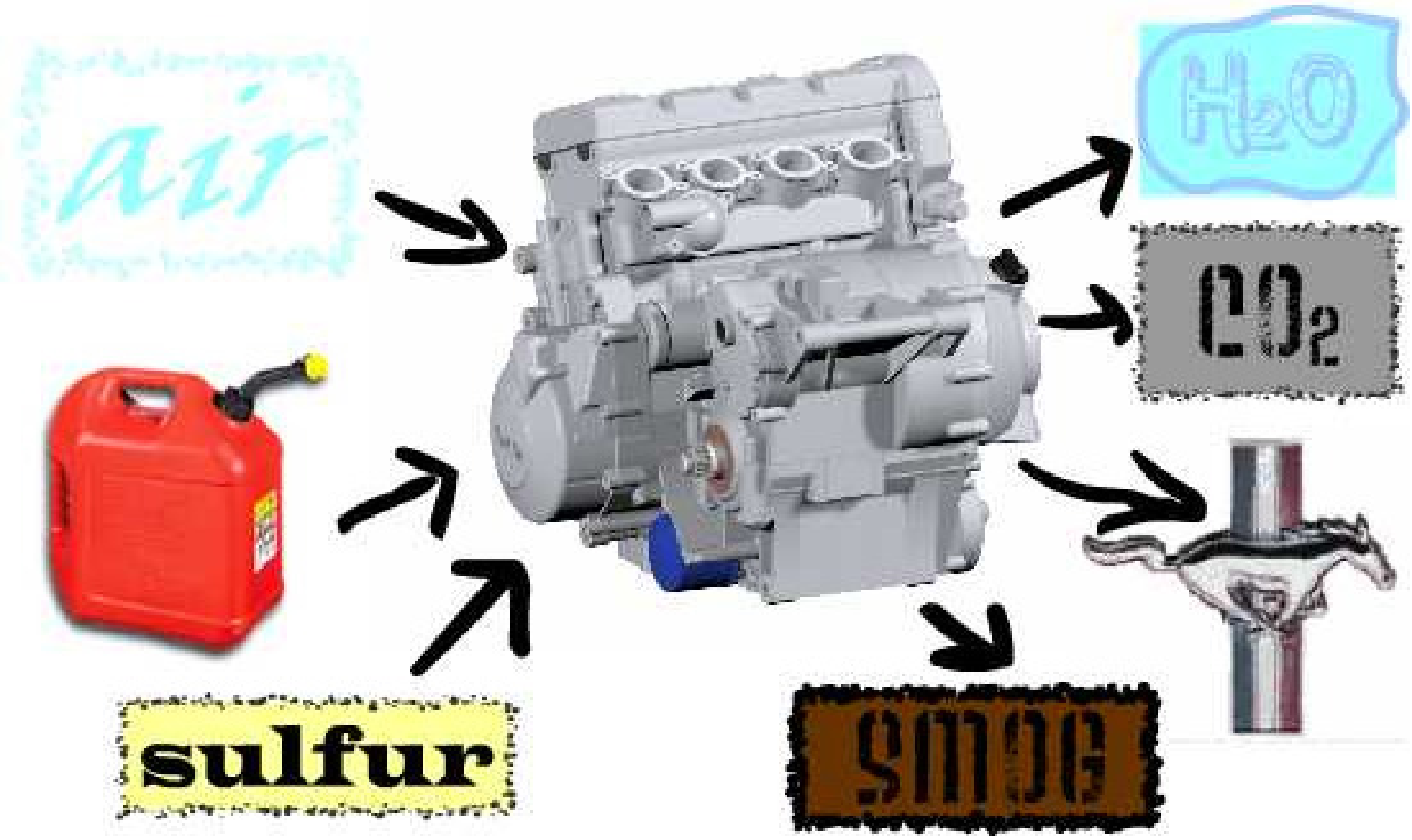
A Schematic View of a Cell



So, a cell is like an engine



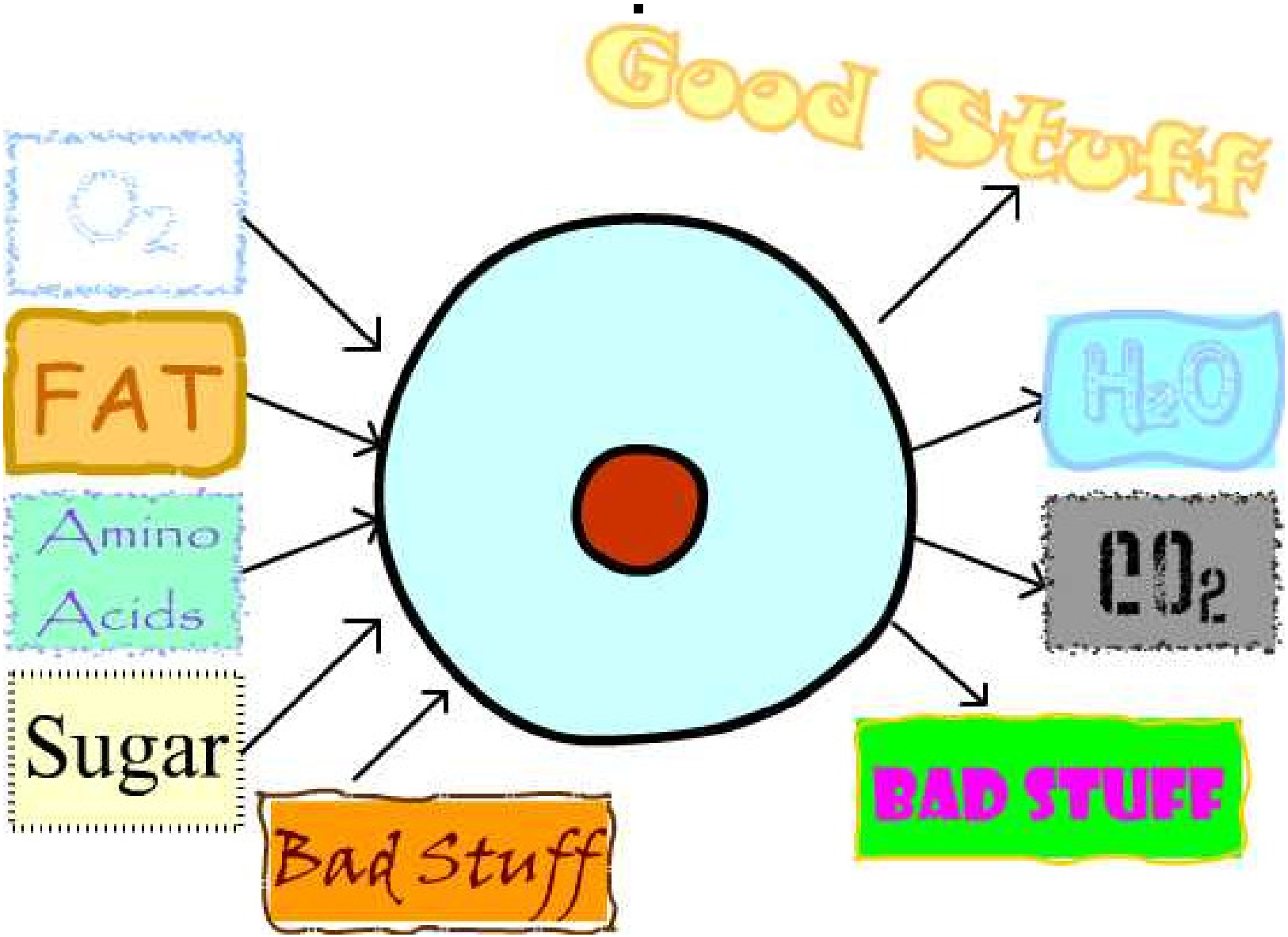
Engines don’t always run clean



Similarly--

- A cell that is lacking in sufficient vitamins and partially poisoned by heavy metals like lead and mercury will run rough, losing horsepower and making smog.

- This is called “Oxidative Stress”


Good Stuff
O_2
FAT
Amino Acids
Sugar
Bad Stuff
H_2O
CO_2
BAD STUFF

Inefficiency makes more toxins

- Partially metabolized biochemicals
- Activated oxygen species
- Interrupted Detox pathways
  - Phase 1: activation of toxins-free radicals
  - Phase 2: conjugation and clearance
  - Conjugation substrates:
    - Glutathione, sulfate, glucaronic acid, SAM

Handful of Tylenol,anyone?

What is the effect of toxins?

- Increased oxidative load
- Biochemical modification of important macromolecules
  - Enzymes, lipids, DNA
- Molecular mimicry
  - Hormones, neurotransmitters

Toxins make more inefficiency

Inefficiency leads to the accumulation of more toxins

Heavy metals are pervasive toxins

- Mercury, lead, cadmium, arsenic all modify and inactivate enzymes
- Mercury causes increased oxidative stress
- Mercury inactivates enzymes involved in detoxification and antioxidant synthesis
- Heavy metals interfere with heme biosynthesis – urine porphyrins
- Heme is required for all oxygen transfer

Oxidative Stress

- Deficiencies in Antioxidant Metabolism

	Autistic Patients	Controls	P value
Reduced/oxidized Glutathione	8.6 +/-3.9	25.5 +/- 8.5	<0.001
Glutathione Peroxidase	29 +/- 3	38 +/- 5	<0.05
Superoxide Dismutase	724 +/- 90	993 +/- 118	<0.05

James et al. 2004, Yorbik et al. 2002

- Elevations in Oxidative Injury

	Autistic Patients	Controls	P value
Nitric Oxide Products	1.6 +/- 0.5	0.9 +/- 0.22	<0.0001
Lipid Peroxides	32 +/- 8	15 +/- 3	<0.001
Lipid Peroxides	33 +/- 2	6 +/- 1	<0.001

Sogut et al. 2003, Zoroglu et al. 2004, Ming 2005

Specific sulfation deficiencies in autistic children

		Autistic	Control	
Sulfation/ Glycosylation Ratio	High	2	19	
	Low	18	1	
Mean ratio		1.1	3.1	P<.00002

This might go with genetic abnormalities in sulfate intake

Autistic children seem to have less mercury in their hair

"Baby" Hair Results
Average Mercury Level

Autistic Children	Normal Children
0.47 mcg/g	3.8 mcg/g

$P < 0.01$

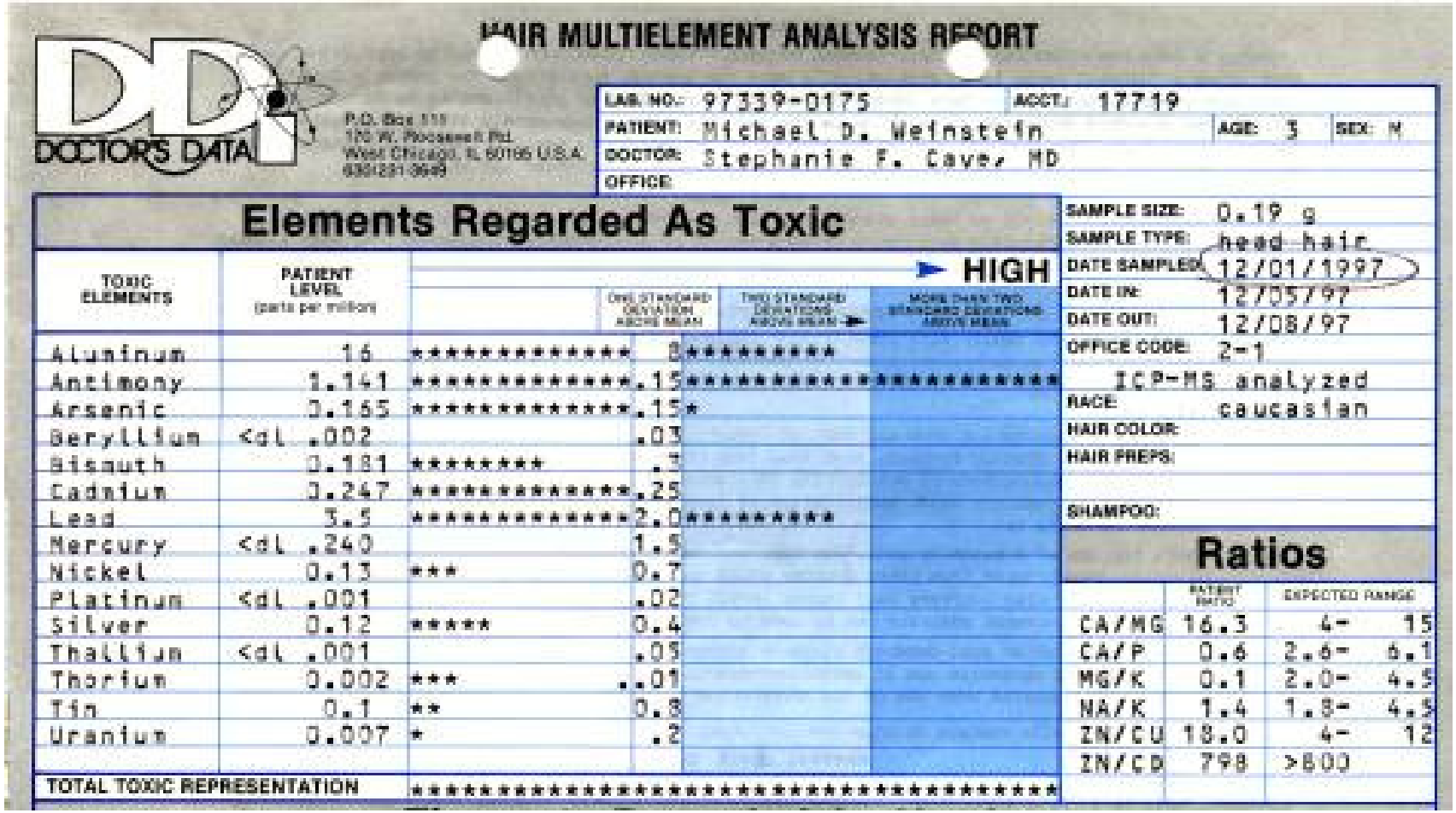
But they also can have more mercury in their urine if chelated.

		mcg/g creatinine
• Autistic children	(n=221)	4.06 +/- 8.59
• Controls	(n=18)	1.29 +/- 1.24

  – AM urine collection after DMSA

- So, maybe autistic kids just have trouble getting mercury out.

Autistic Child (MW) 3 year-old Hair Hg = < dl (0.03 mcg/g)



HAIR MULTIELEMENT ANALYSIS REPORT

DOCTOR'S DATA

P.O. Box 111
170 W. Roosevelt Rd.
West Chicago, IL 60185 U.S.A.
630/231-3649

LAB. NO.: 97339-0175 ACCT.: 17719
PATIENT: Michael D. Weinstein AGE: 3 SEX: M
DOCTOR: Stephanie F. Cave, MD
OFFICE:

SAMPLE SIZE: 0.19 g
SAMPLE TYPE: head hair
DATE SAMPLED: 12/01/1997
DATE IN: 12/05/97
DATE OUT: 12/08/97
OFFICE CODE: 2-1
ICP-MS analyzed
RACE: caucasian
HAIR COLOR:
HAIR PREPS:
SHAMPOO:

Elements Regarded As Toxic

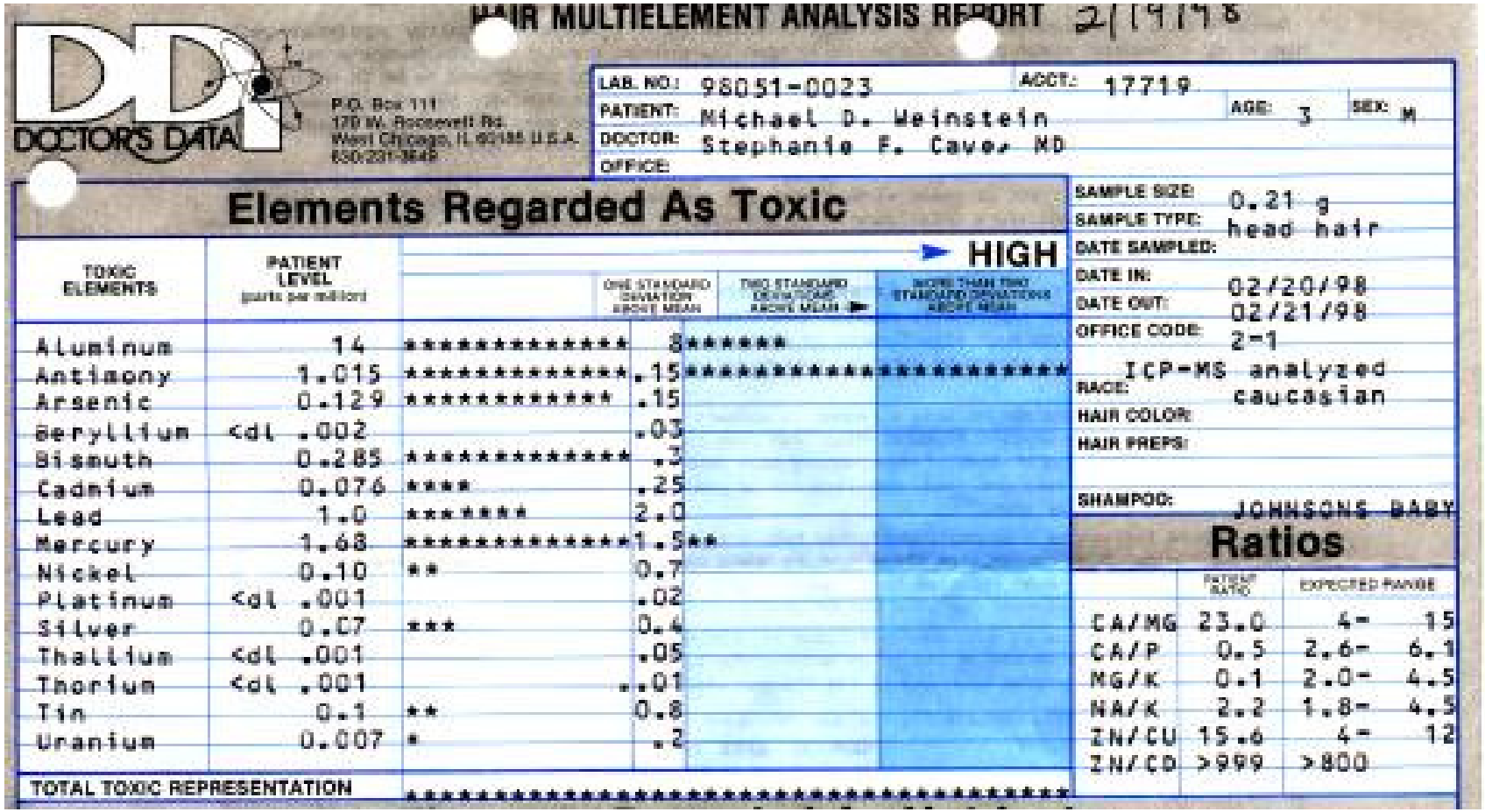
TOXIC ELEMENTS	PATIENT LEVEL (parts per million)	ONE STANDARD DEVIATION ABOVE MEAN	TWO STANDARD DEVIATIONS ABOVE MEAN → HIGH	MORE THAN TWO STANDARD DEVIATIONS ABOVE MEAN
Aluminum	16	********** 8	**********	
Antimony	1.141	********** .15	**********	**********
Arsenic	0.165	********** .15	*	
Beryllium	<dl .002	.03		
Bismuth	0.181	******** .3		
Cadmium	0.247	********** .25		
Lead	3.5	********** 2.0	**********	
Mercury	<dl .240	1.5		
Nickel	0.13	*** 0.7		
Platinum	<dl .001	.02		
Silver	0.12	***** 0.4		
Thallium	<dl .001	.05		
Thorium	0.002	*** .01		
Tin	0.1	** 0.8		
Uranium	0.007	* .2		
TOTAL TOXIC REPRESENTATION		**********	**********	**********

Ratios

	PATIENT RATIO	EXPECTED RANGE
CA/MG	16.3	4- 15
CA/P	0.6	2.6- 6.1
MG/K	0.1	2.0- 4.5
NA/K	1.4	1.8- 4.5
ZN/CU	18.0	4- 12
ZN/CD	798	>800

Autistic Child (MW) 2 months after DMSA
Hg = 1.43 mcg/g

Same child, 2 mo later after DMSA
Hg = 1.43 mcg/g



HAIR MULTIELEMENT ANALYSIS REPORT 2/19/98

DOCTOR'S DATA
P.O. Box 111
170 W. Roosevelt Rd.
West Chicago, IL 60185 U.S.A.
630/231-3649

LAB. NO.: 98051-0023 ACCT.: 17719
PATIENT: Michael D. Weinstein AGE: 3 SEX: M
DOCTOR: Stephanie F. Cave, MD
OFFICE:

Elements Regarded As Toxic

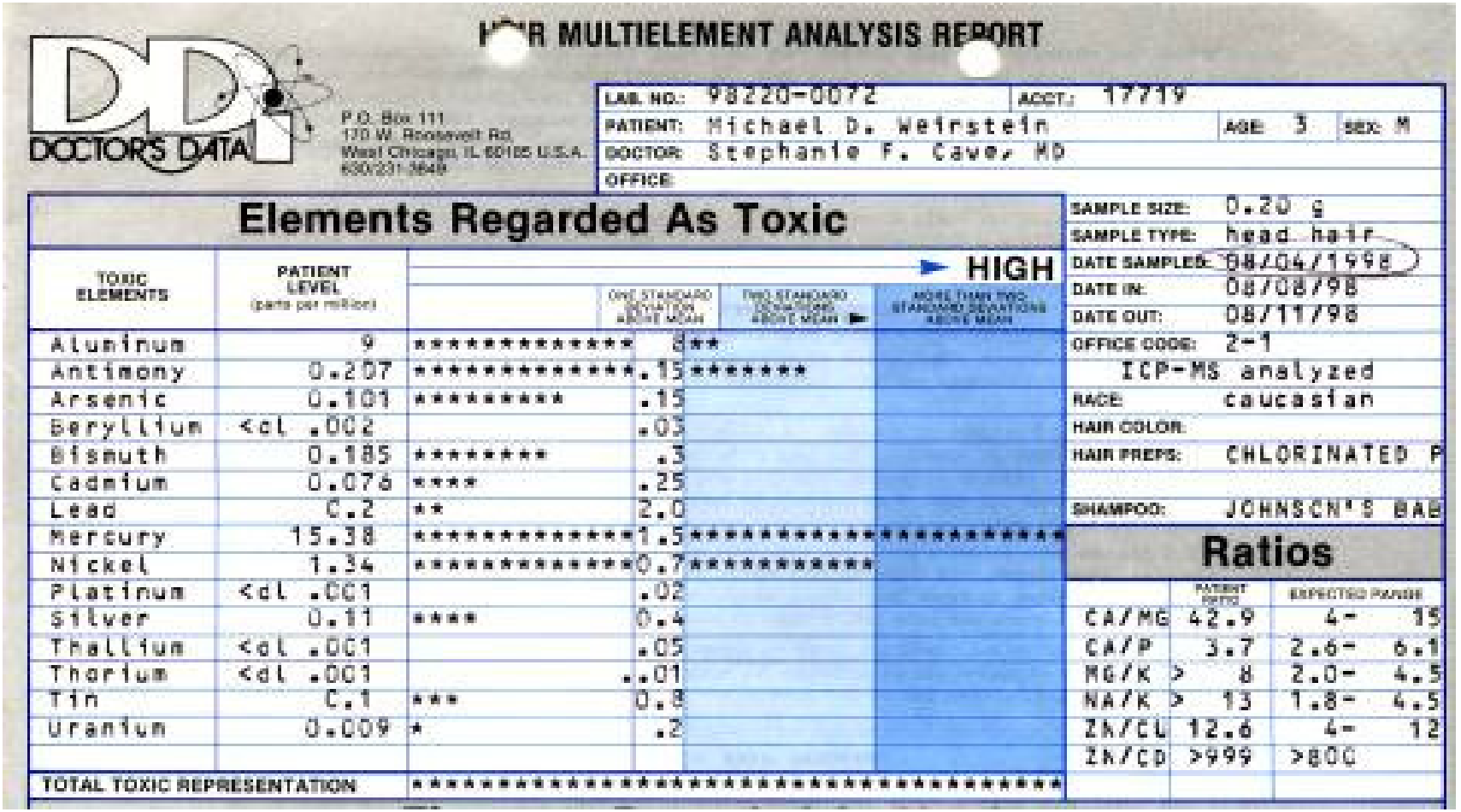
TOXIC ELEMENTS	PATIENT LEVEL (parts per million)	HIGH → ONE STANDARD DEVIATION ABOVE MEAN	TWO STANDARD DEVIATIONS ABOVE MEAN	MORE THAN TWO STANDARD DEVIATIONS ABOVE MEAN
Aluminum	14	**********	8	******
Antimony	1.015	**********	.15	**********
Arsenic	0.129	**********	.15	
Beryllium	<dl .002		.03	
Bismuth	0.285	**********	.3	
Cadmium	0.076	****	.25	
Lead	1.0	*******	2.0	
Mercury	1.68	**********	1.5	**
Nickel	0.10	**	0.7	
Platinum	<dl .001		.02	
Silver	0.07	***	0.4	
Thallium	<dl .001		.05	
Thorium	<dl .001		.01	
Tin	0.1	**	0.8	
Uranium	0.007	*	.2	
TOTAL TOXIC REPRESENTATION		**********	**********	**********

SAMPLE SIZE: 0.21 g
SAMPLE TYPE: head hair
DATE SAMPLED:
DATE IN: 02/20/98
DATE OUT: 02/21/98
OFFICE CODE: 2-1
ICP-MS analyzed
RACE: caucasian
HAIR COLOR:
HAIR PREPS:
SHAMPOO: JOHNSONS BABY

Ratios

	PATIENT RATIO	EXPECTED RANGE
CA/MG	23.0	4- 15
CA/P	0.5	2.6- 6.1
MG/K	0.1	2.0- 4.5
NA/K	2.2	1.8- 4.3
ZN/CU	15.6	4- 12
ZN/CD	>999	>800

Same child, 8 mo later after DMSA
Hg = 15.4 mcg/g



HAIR MULTIELEMENT ANALYSIS REPORT

DOCTOR'S DATA

P.O. Box 111
170 W. Roosevelt Rd.
West Chicago, IL 60185 U.S.A.
630/231-3649

LAB. NO.: 98220-0072 ACCT.: 17719
PATIENT: Michael D. Weirstein AGE: 3 SEX: M
DOCTOR: Stephanie F. Cave, MD
OFFICE:

Elements Regarded As Toxic

TOXIC ELEMENTS	PATIENT LEVEL (parts per million)	HIGH: ONE STANDARD DEVIATION ABOVE MEAN	TWO STANDARD DEVIATIONS ABOVE MEAN	MORE THAN TWO STANDARD DEVIATIONS ABOVE MEAN
Aluminum	9	********** 8	**	
Antimony	0.207	********** .15	*******	
Arsenic	0.101	********* .15		
Beryllium	<dl .002	.03		
Bismuth	0.185	******** .3		
Cadmium	0.076	**** .25		
Lead	C.2	** 2.0		
Mercury	15.38	********** 1.5	**********	
Nickel	1.34	********** 0.7	**********	
Platinum	<dl .001	.02		
Silver	0.11	**** 0.4		
Thallium	<dl .001	.05		
Thorium	<dl .001	.01		
Tin	C.1	*** 0.8		
Uranium	0.009	* .2		
TOTAL TOXIC REPRESENTATION		**********		

SAMPLE SIZE: 0.20 g
SAMPLE TYPE: head hair
DATE SAMPLED: 08/04/1998
DATE IN: 08/08/98
DATE OUT: 08/11/98
OFFICE CODE: 2-1
ICP-MS analyzed
RACE: caucasian
HAIR COLOR:
HAIR PREPS: CHLORINATED P
SHAMPOO: JOHNSON'S BAB

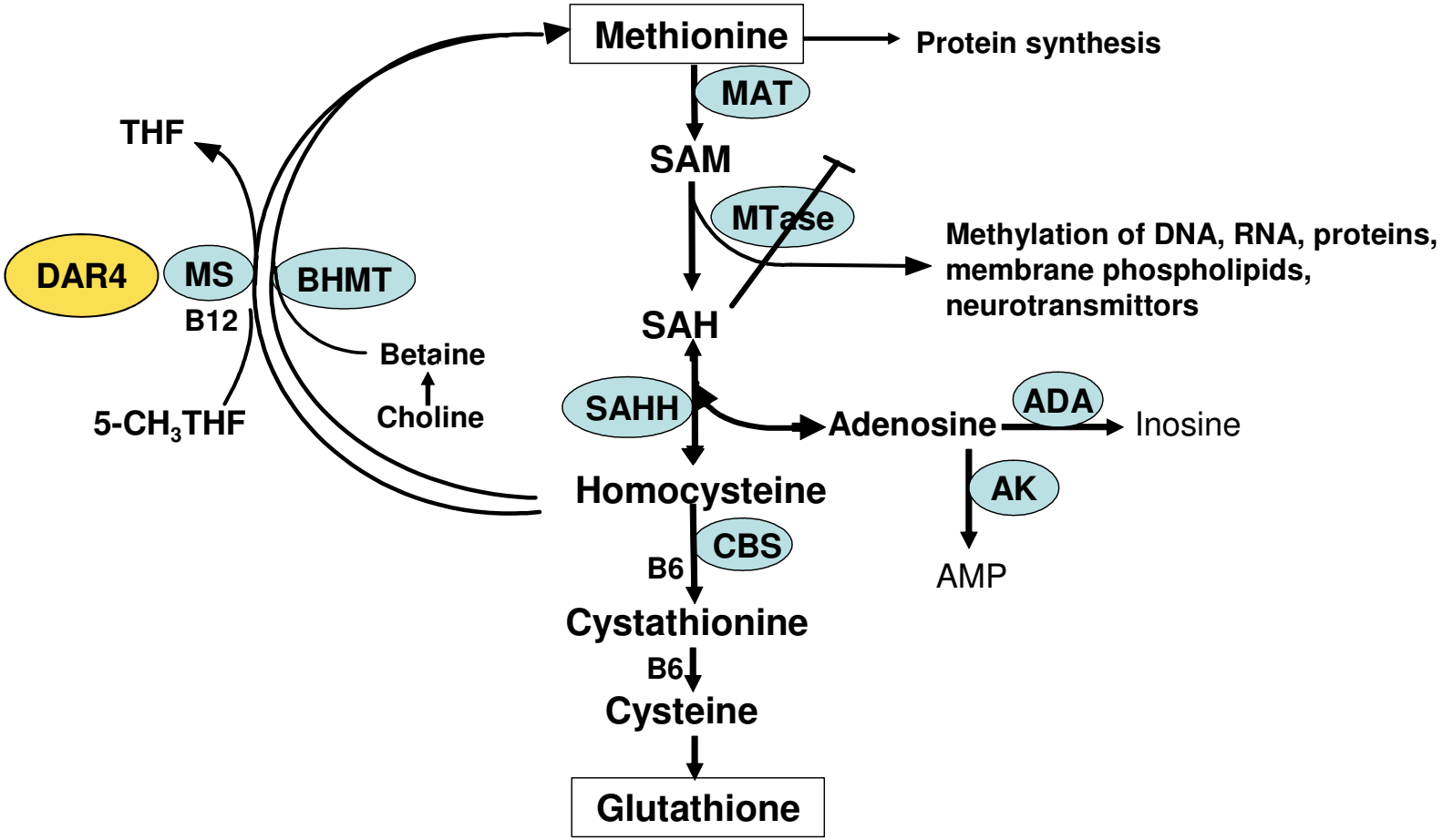
Ratios

	PATIENT DATA	EXPECTED RANGE
CA/MG	42.9	4- 15
CA/P	3.7	2.6- 6.1
MG/K	> 8	2.0- 4.5
NA/K	> 13	1.8- 4.5
ZN/CU	12.6	4- 12
ZN/CD	>999	>800

One more caveat

- We measure chemical concentrations in blood and urine.
- The relevant concentration is the concentration in the brain, or specifically in brain cells

One carbon metabolism-a central abnormality in autism



Autistic children have specific deficiencies in one-carbon cycle which resolve with therapy with TMG, folinic acid, and methyl B12

	Control Children (n=33)	Autistic Children (n=20) Baseline Levels	Autistic Children After Intervention
Methionine (µmol/L)	30.6 ± 6.5	19.3 ± 9.7	28.0 ± 7.2
SAM (nmol/L)	90.0 ± 16.2	75.8 ± 16.2	112.9± 21
SAH (nmol/L)	20.1 ± 4.3	26.1 ± 5.4	16.9 ± 86.5
Homocysteine	6.3 ± 1.2	5.4 ± 0.9	6.7 ± 0.7
Adenosine (µmol/L)	0.28 ± 0.16	0.39 ± 0.19	0.18 ±0.4
Cysteine (µmol/L)	210 ± 18.5	163 ± 14.6	180 ± 11
Total glutathione	7.9 ± 1.8	4.1 ± 0.5	5.7 ± 1.0
Oxidized Glutathione	0.30 ± 0.1	0.55 ± 0.2	0.38 ± 0.9
GSH/GSSG Ratio	25.5 ± 8.9	8.6 ± 3.5	24.8 ± 4.8

Paul Cutler, MD and Jill James, PhD (2004)

A few more caveats,

- This tells us about populations, not about individuals.
- These values are not easy to obtain, and the ranges in the normal and autistic populations overlap, meaning these measurements cannot be used to define the diagnosis of autism.

Nonetheless,

- This study guides one of the most common and apparently effective treatments we have:
  - Methylcobalamin
  - TMG
  - Folinic acid
  - Glutathione supplementation (I am not convinced it is absorbed? I prefer NAC)

Cerebral folate deficiency

- A substantial fraction of children with acquired brain dysfunction have low CSF folate.
- Clinical improvement is seen with supplemental folinic or 5-methylfolate.
- Anti-folic acid receptor antibodies elevated in milk protein allergy

Mitochondria

- Depending on criteria, about 30% of autistic children have mitochondrial “dysfunction”
- About 8% have mitochondrial “disease”
- This is associated with oxidative stress
- If nerve cells do not have sufficient energy they will not function.
- Mitochondrial cocktails available.

Immune dysregulation

- Increased TNF-α production by both intestinal and peripheral blood immune cells from autistic children in autistic children with cow's milk intolerance when cells are exposed to cow's milk protein. There are fewer IL-10 positive cells, and more IFN-γ cells.
- NO elevated in autistic children
- Elevated neopterin

Brain Inflammation

- Elevated TNF-α in CSF of autistic children
- Brain specific antiantibodies in 37% vs 13%
- Autopsy studies of children who suffered accidental death show marked microglial activation. Many differences in cytokine expression are seen between autistic and nonautistic populations, but there is a lot of variability.

How do we treat this inflammation?

- Heal the gut.
- HBOT
- Antibiotics
- Anti-inflammatory substances
  - Quercetin
  - Curcumin
  - Low Dose Naltrexone
  - Singulair
  - Pro- and Pre- biotics

Antioxidants

- “Supplemental”
  - Vitamin C, Vitamin E (mixed tocopherols), zinc, selenium, coenzyme Q10, taurine, glutathione, N-acetyl cysteine
- “Herbal”
  - Curcumin, pycnogenol, milk thistle, green tea
- “Whole foods”
  - Fruits and vegetables, Acai, mangosteen, red juices, JuicePlus

Other therapies I recommend

- Epsom salts
- Omega 3 fatty acids
- Vitamin A and D, High dose B vitamins
- Low Dose Naltrexone, curcumin
- Valtrex
- Carnosine, Taurine, GABA
- Chelation
- Hyperbaric oxygen therapy
- NAET
- Worms

First clean up the environment

- Cleaning supplies
- Water
- Plasticizers
- Pesticides in food
- Antibacterial handwashes
- Excess fluoride and chlorine
- Wireless

Epsom Salts

- Children with autism are sulfate deficient
- Epsom Salts are Magnesium sulfate
- This is an excellent laxative
- Soaking in Epsom salts allows the magnesium and sulfate to soak through the skin
- One can rub it on as a lotion

Omega 3 Fatty acids

- Fish or krill or algae oil is definitely superior to flax seed oil (ALA).
- Structural lipids for brain growth and function
- Precursors of anti inflamatory prostaglandins
- Borage or Evening primrose oil (GLA) are anti-inflammatory omega 6 fatty acids

Vitamin A and D

- Vitamin A seems to improve eye contact and activate the immune system. Carotenoids are a good source. Excess retinol can be toxic.
- Vitamin D is needed for calcium absorption and much more. It is anti-inflammatory and associated with lower risks of multiple sclerosis, BD, and cancer. It reduces respiratory illnesses in children. All children probably need more than 1000 IU per day. Some people need huge doses.

Low Dose Naltrexone

- Naltrexone is an opioid used to prevent narcotic abuse.
- In low doses, naltrexone appears to up regulate opioid receptors, down regulate cellular immunity, and reduce the impact of exposures to dietary opioids.

Valtrex

- Valtrex is an inhibitor of herpes virus replication.
- In autism, it seems to do something else, possibly through affecting one-carbon metabolism.
- About 1/3 of patients seem to respond to it.

Carnosine,Taurine, and GABA

- Carnosine is a peptide that has anti-inflammatory and anti oxidant properties, gut healing properties, and positive cognitive effects.
- Taurine is an amino acid that is a calming and focusing neurotransmitter, and is a precursor of bile salts.
- GABA is nature's Valium, it is very soothing for irritable children.

What is chelation?

- Chelation is the administration of chemicals that bind to heavy metals more firmly than the heavy metals bind to proteins.
- The chemicals used are DMSA, DMPS, and Ca EDTA.
- These can be given orally, rectally or IV.
- The patients need to be supplemented with minerals and followed for liver injury.

How effective is chelation?

- No one has any data – 20-30%
- Very hard to study
- Hard to distinguish from antioxidant effects
- Not necessarily benign – Don’t do a lot all at once.
- Perhaps one can do as well by healing the detox mechanisms – Infrared sauna?

Procognitive medications

- Often used for Alzheimers:
  - DMAE
  - Acetyl Carnitine
  - DMG, TMG
  - Aricept
  - Galantamine
  - Namenda
  - Nicotine

Doses of reality

- There are many paths to autism. There are probably many paths back to normal.
- There are no reliable tests that identify which of these therapies will be helpful for a given child.
- There is minimal published data about any of the therapies that we recommend, and few have been subjected to randomized trials.
- None of the doctors who care for these children have summarized their experiences.

More of my philosophy

- I am very skeptical of biomedical therapies, but I have seen simple interventions bring amazing improvements.
- My impression is that 1/3 get much better, 1/3 get somewhat better, 1/3 do not respond at all.
- The only way to know whether biomedical therapy is going to make a difference for a given child is to try it.
- When it works it is great.

- Even if the therapies do not cure the core symptoms of autism, they can often bring about significant improvements in quality of life.
- Biomedical therapies can be expensive and can require great effort.
- “What if” can be expensive too.
- So try something reasonable and if it helps, try something else.
- If you are doing a lot and not getting very far, change directions.
- The hardest part is knowing whether you have done enough or too much.

Implications for healthy children

- Many non-autistic children exhibit some of the same physiologic abnormalities seen in the autistic population, especially children with chronic allergic or inflammatory conditions and gastrointestinal dysfunction.
- ADHD and behavioral problems often respond to similar therapies.
- It is possible that other disorders might also respond.

Emerging Evidence Requires a New Paradigm

From →	To
Conventional view	Biomedical view
A rare tragic disorder	An alarmingly frequent disease
Clear, if complex, genetic causes	An environmental disease with genetic risk factors
Outcomes are inevitably determined in utero	Outcomes result from preventable events
A neurology problem	A multi disciplinary problem
The best and only treatment is behavioral therapy	Many opportunities for prevention, treatment, and recovery

The children are defective → The children are sick

Have we seen this paradigm before?

- Phenylketonuria is an inherited condition which uniformly causes autism and mental retardation.
- It is a defect in the detoxification of a phenylalanine.
- Complications are completely preventable by reducing the toxic load of protein from the diet.
- Why can’t some autism be the same?