4. Autism, Depression and Alzheimer's disease



Stephanie Seneff
Wise Traditions Workshop
Weston Price Foundation
Nov. 8, 2013



"Alzheimer's disease is at epidemic proportions, with 5.4 million Americans—including one in eight people aged 65 and over—living with the disease. In the next 20 years, it is projected that Alzheimer's will affect *one in four Americans*, rivaling the current prevalence of obesity and diabetes."

-- Dr. Mercola*

^{*}http://articles.mercola.com/sites/articles/archive/2013/09/29/dr-perlmutter-gluten.aspx

Outline

- Introduction
- Demographic Study of 50 States
- Pineal Gland and Sulfate
- Sulfated Sterols and Lipids
- Vaccines and Aluminum
- Summary

A Hypothesis

Many neurological diseases of the brain have a common origin:

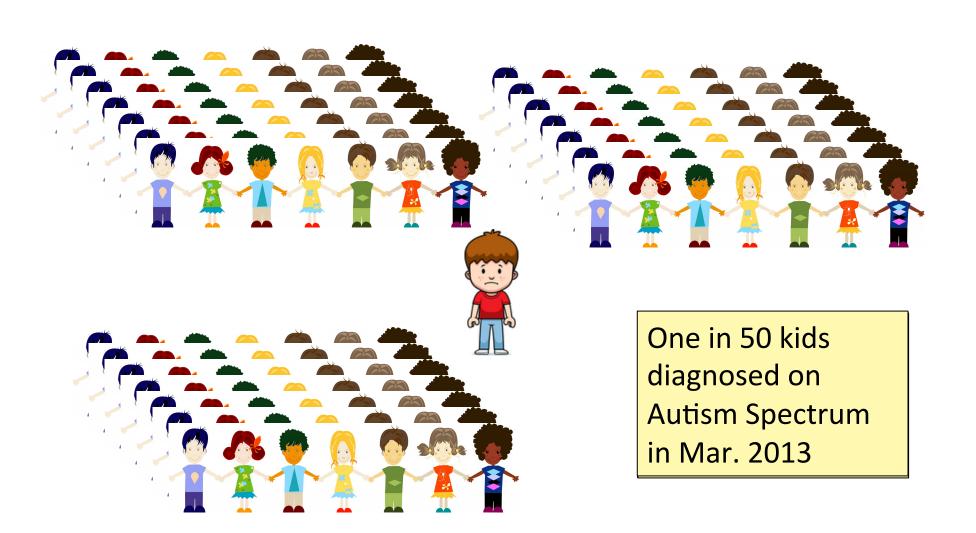
 Insufficient supply of cholesterol and sulfate to the brain (cholesterol sulfate deficiency)

Powerful additional burden of toxic metal exposure (e.g., aluminum, mercury)

due to impaired ability to detoxify and eliminate them

Toxic metals interfere with sulfate synthesis

The Autism Epidemic in the U.S.



One in Two in 2025?





ปเองเกรร์ใกเล.com

The rate was 1 in 10,000 in 1970

Comorbidities with Autism*

"chronic inflammation of gastrointestinal tract, dysbiosis, maldigestion, malabsorption, malnutrition, food intolerance, allergies, chronic viral, fungal and bacterial infections, impaired kidney function, impaired detoxification of endo- and exotoxins, disorders of metal ion transportation."

^{*} M. Cubala-Kucharska, Acta Neurobiol Exp (Wars). 2010;70 (2):141-6.

Factors We Have Identified to be Causative in Autism

- Insufficient sunlight exposure to the skin and eyes
- Excess exposure to environmental toxins, especially glyphosate, aluminum, nitrogen oxides and mercury
- Nutritional deficiencies, especially in sulfur

I have recently published 7 journal articles in the biomedical literature with various collaborators on factors influencing autism

Demographic Studies of 50 States

Demographic Studies on 50 States

- Public schools in U.S. keep track of # students enrolled in each grade and # students enrolled in programs specifically targeting autism
 - Ratio becomes a measure for autism rate in the state
- We can obtain statistics for many other factors
 - Weather-related, population density, industrial pollution, fluoride, vaccination rate, ...
- Pearson's correlation coefficient can be used to detect correlations (ranges from -1.0 to 1.0)
 - Correlation does not necessarily mean causation

Demographics of 50 States

Demographic	Pearson Rating	Explanation
Rank, population density	0.50	Car exhaust?
Rank, # clear days	-0.40	Sunlight exposure
Latitude	0.22	Sunlight exposure
Annual rainfall	0.16	Sunlight exposure
RMS (rainfall, latitude)	0.34	Sunlight exposure
Temperature	-0.16	Sunlight exposure
Elevation	-0.28	Sunlight exposure
% vaccinated	0.33	Aluminum, mercury
Per child funding	0.25	Funding constraints
Obesity rates	-0.28	Toxin Sequestering?
Industrial pollution	0.01	Not significant factor
% water fluoridation	03	Not significant factor

1. Lack of Sunlight

Demographics of 50 States

	Demographic	1//		Explanation
	Rank, population d		 0.50	Car exhaust?
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A Really Bad Idea!





"The two flavins in eNOS absorb light in the blue range (peaks at 443 and 475 nm) and emit light in the green range (~525 nm) when oxidized."

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Take Off the Sunglasses and Look at the Blue Sky!



World's oldest person dies at 116 in Japan*

- 116-year-old Jiroemon Kimura in Japan died on Wednesday, June 12, 2013
- He attributed his longevity to getting out in the sunlight:

"I am always looking up towards the sky. That is how I am."

2. Aluminum in Vaccines

Demographics of 50 States

Demographic Pearson Rating Explanation	Demographic	Pearson Rating	Explanation
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This correlation is detected despite the fact that the range is very narrow:

From 63% in the least vaccinated state to 80% in the most vaccinated state (Massachusetts!!)

remperature	0.10	Jamight exposure
Elevation	-0.28	Sunlight exposure
% vaccinated	0.33	Aluminum, mercury
Per child funding	0.25	Funding constraints
Obesity rates	-0.28	Toxin Sequestering?
Industrial pollution	0.01	Not significant factor
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"Our studies demonstrate that, in contrast to magnesium-, iron- and zinc-sulfate, aluminum-sulfate has an unusual and significant ability to induce ROS, NF-κB signaling, and ... down-regulating the important inflammation inhibitor CFH."*

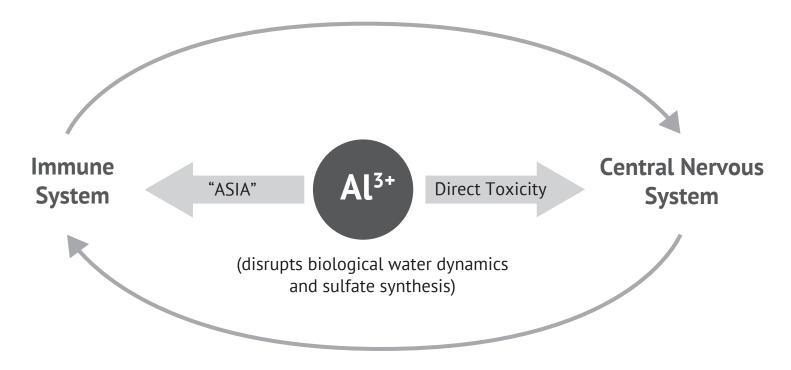
Aluminum induces inflammation

Recent Publication

C.A. Shaw, S.D. Kette, R.M. Davidson, and S. Seneff. Aluminum's role in CNS-immune system interactions leading to neurological disorders. Immunome Research, *To Appear*, 2013.

Figure from Our Paper

ASIA = Autoimmune Syndrome Induced by Adjuvants



Aluminum Exposure and Memory, Depression*

- 25 symptomatic workers from the same aluminum smelting plant
 - 22 (88%) reported frequent loss of balance
 - 21 (84%) reported memory loss
 - 21 (84%) showed physical signs of incoordination
- 19 were tested for depression on the Minnesota Multiphasic Personality Inventory
 - 17 (89%) tested positive for depression

^{*}White et al., Arch Intern Med. 152(7):1443-1448, 1992.

Our Studies with VAERS Database on Aluminum & Depression

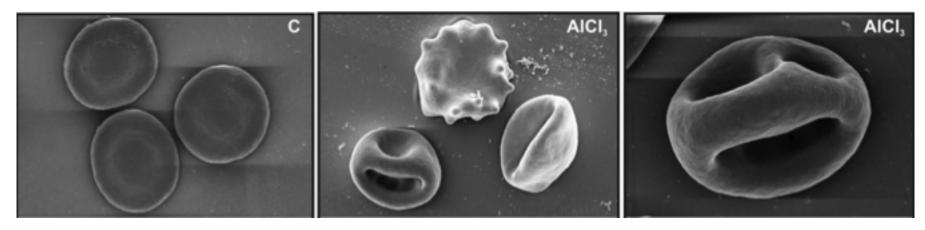
- VAERS: Vaccine Adverse Event Reporting System, maintained by CDC
- Tabulate word frequencies for mentions of "depression" in adverse reactions to aluminum-containing vaccines versus non-aluminum-containing vaccines.
 - 231 mentions in aluminum-containing vaccines versus 85 in age-matched controls
 - Highly significant result (p = 0.005)

Aluminum's effect on Red Blood Cells*

- Aluminum causes microcytic anemia
 - Induces severe morphological changes in RBCs
 - Leads to eryptosis cell dies
- N-acetyl cysteine (a source of sulfur) affords some protection

Normal

With Aluminum



* D.M. Vota et al., Journal of Cellular Biochemistry 113:1581–1589, 2012.

Aluminum's effect on Red Blood Cells*

Aluminum causes microcytic anemia

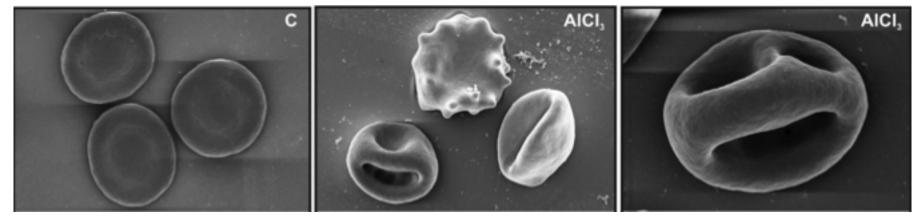
Induces covere marchalogical changes in DD CS

Anemia is an adverse reaction to aluminum-containing vaccines

rds

Normal

With Aluminum



^{*} D.M. Vota et al., Journal of Cellular Biochemistry 113:1581–1589, 2012.

3. Nitrogen Oxides in Pollution

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Residential Proximity to Freeways and Autism in the CHARGE Study*

- 259 normal children compared with 304 children with autism
- Children with autism were 1.86x more likely to live near a freeway



- Living near freeway during third trimester yielded
 2.22 fold increase in autism
- There was no correlation with living near other major roads

^{*} H.E. Volk et al., Environmental Health Perspectives 119(6), 2011, 873-877.

A Role for Nitrogen Oxides??*

- Oxides of nitrogen are a major contaminant in car exhaust
 - Autism is associated with excess serum nitric oxide/nitrate and insufficient serum sulfate
- Excess nitric oxide can lead to excess ammonia via metabolism of intermediary, GSNO
 - Excess ammonia in brain is implicated in autism

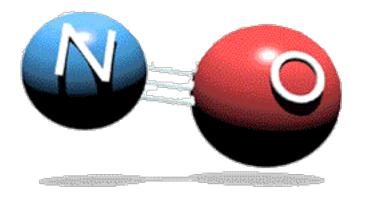
*S. Seneff, A. Lauritzen, R. Davidson, and L. Lentz-Marino. Is Encephalopathy a Mechanism to Renew Sulfate in Autism? *Entropy* 2013, 15, 372-406.

Nitric Oxide and Autophagy

- Autophagy is a natural mechanism by which cells clean up debris and dysfunctional organelles
- Excess nitric oxide inhibits autophagy
- Switchover to nitric oxide by eNOS leads to autophagy dysfunction and accumulation of garbage in the cell
- Long-term autophagy inhibition leads to cellular dysfunction and cell death

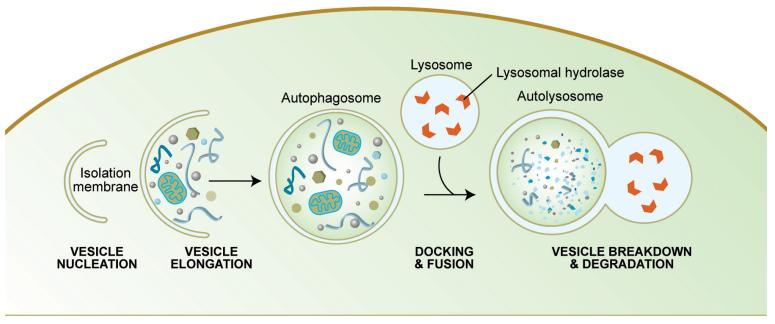
Some Effects of Excess NO on the Brain*

- Impairs autophagy
- Damages lipids in cell membranes
- Disrupts mitochondrial synthesis of ATP
- Interferes with reuptake of serotonin, dopamine, and epinephrine



*O. Akyol et al., In Vivo 18: 377-390, 2004

Autophagy



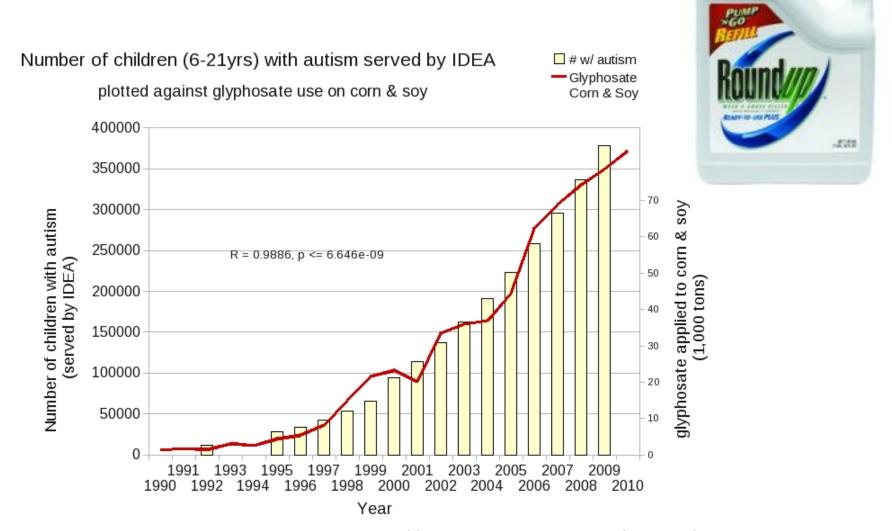
- Allows cell to recycle damaged goods
- Both damaged mitochondria and damaged endoplasmic reticulum are absorbed into the lysosome and broken down
- Autophagy depends on sulfates in HSPGs

4. Glyphosate!

Demographics of 50 States

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Rank, population density	0.50	Car exhaust?
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Glyphosate and Autism*



*http://www.examiner.com/article/data-show-correlations-between-increase-neurological-diseases-and-gmos

Rosemary Waring on Autism in 1990*

"These results indicate that there may be a fault either in manufacture of sulphate or that sulphate is being used up dramatically on an unknown toxic substance these children may be producing" (p. 198).

This was a very clairvoyant statement

*O'Reilly, B.A.; Waring, R.H. Enzyme and sulphur oxidation deficiencies in autistic children with known food/chemical intolerances. Xenobiotica. 1990, 20, 117–122.

Glyphosate*

- Glyphosate is the active ingredient in the weed killer, Roundup
- Glyphosate disrupts gut bacteria
 - Disrupted gut bacteria is a key feature of autism
- Glyphosate disrupts Cytochrome P450 enzymes
 - eNOS is a P450 enzyme disrupted sulfate synthesis
- Glyphosate impairs sulfate transport through competition (Jones-Ray effect)
 - Toxic phenols in gut needed to transport sulfate
- GMO crops
 much more glyphosate present in food sources



I'll have much more to say about glyphosate in the next section!

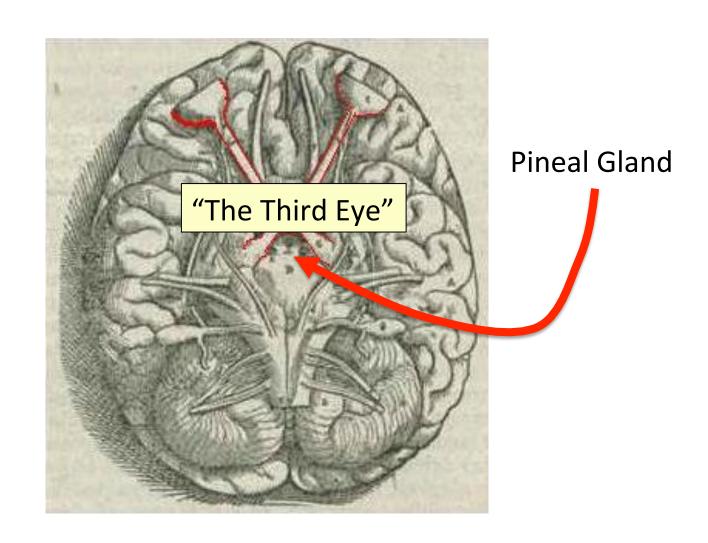
Recapitulation

Demographic studies on the 50 states suggest several factors related to autism:

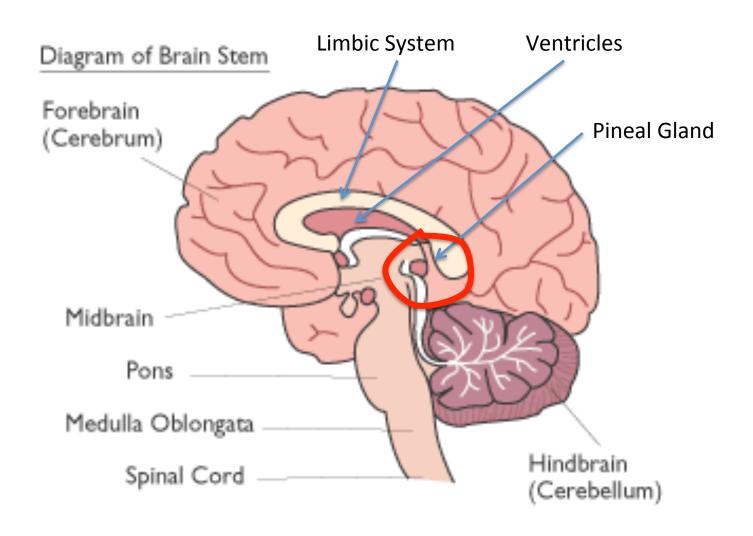
- Insufficient sunlight exposure to the skin and eyes
- Exposure to aluminum from vaccines and other sources
- Exposure to nitrogen oxides in air pollution from automobile exhaust
- Exposure to glyphosate (Roundup) and other chemical pesticides

Pineal Gland and Sulfate

Sunlight and the Pineal Gland

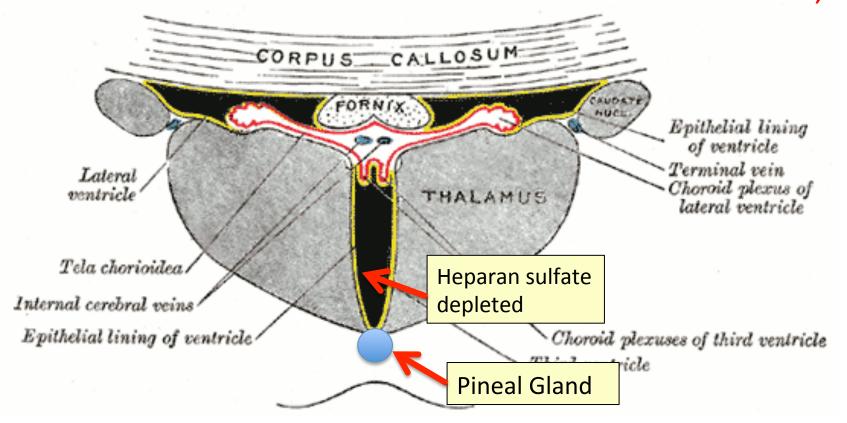


The Brain



Third Ventricle and Pineal Gland

- Pineal gland is attached to the third ventricle
- The third ventricle is depleted in heparan sulfate in association with autism in both humans and mice*,**



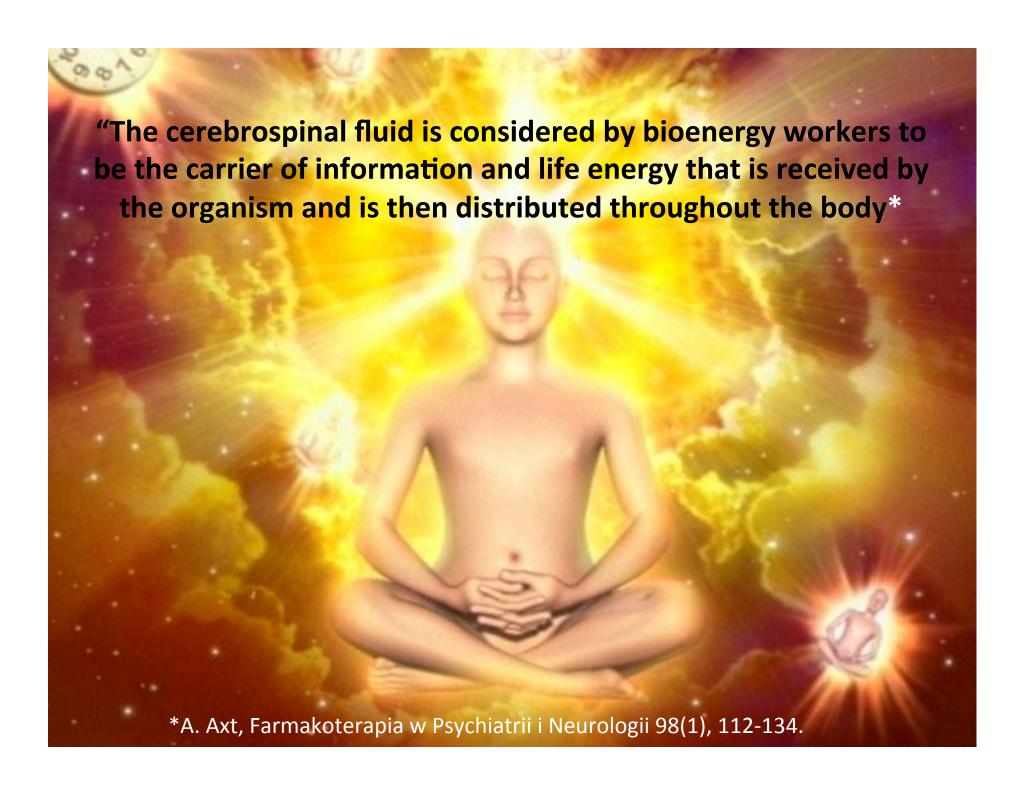
^{*}B.L. Pearson et al., Behav Brain Res. 2013 Apr 15;243:138-45.

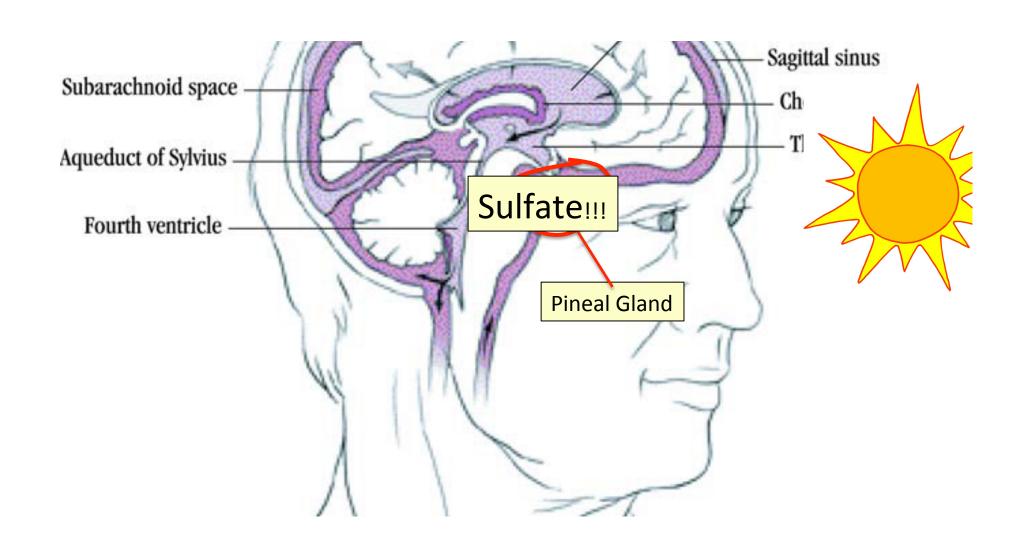
^{**}F Mercie et al., Neurosci Lett 506, 2012, 208-213.

"Melatonin Enters the Cerebrospinal Fluid through the Pineal Recess"*

- The tip of the third ventricle is encased in the pineal gland
- The pineal gland delivers melatonin to the third ventricle and it diffuses to all the cerebrospinal fluid
- I propose that a key purpose of melatonin is to deliver sulfate to the neurons at night.

^{*}H. Tricoire et al., Endocrinology 143(1):84–90





"Light-induced 3-O-Sulfotransferase Expression Alters Pineal Heparan Sulfate Fine Structure: A SURPRISING LINK TO CIRCADIAN RHYTHM"*

- Pineal gland builds up heparan sulfate supplies by day
- Melatonin is sulfated in transport at night
 - Highly lipophilic molecule needs sulfate to make it water-soluble
 - This allows it to move through the cerebrospinal fluid
- When melatonin is delivered, sulfate is released!

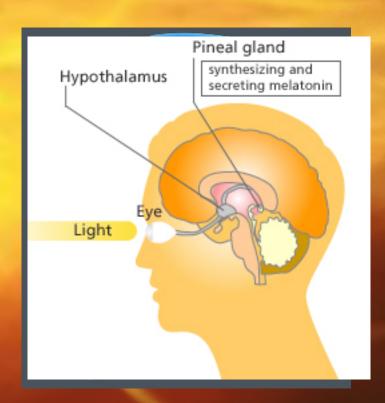
Melatonin is a sulfate-delivery system!!

*B. Kuberan et al., J. Biol. Chem. 2004, 279:5053-5054.

Pineal Gland: "Seat of the Soul"

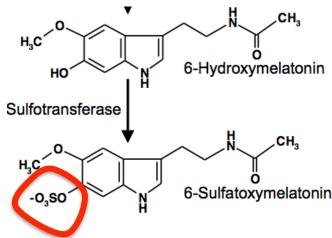
The pineal gland produces sulfate by day (responding to light) and stores it in heparan sulfate molecules

The pineal gland produces melatonin in the evening and transports it as melatonin sulfate to various parts of the brain



Pineal Gland: "Seat of the Soul"

- Pineal gland produces melatonin _{H,c} [∞]
 - Induces REM sleep
- Alzheimer's is associated with reduced REM sleep cycle
 AND calcified pineal gland*



- Pineal gland calcification correlates inversely with REM sleep**
- DHEA SULFATE but not DHEA injections increase melatonin production in rats***

*R. Mahlberg et al., Neurobiol Aging. 2008 Feb;29(2):203-9

**R. Mahlberg et al., Sleep Med. 2009 Apr;10(4):439-45.

***Y. Djeridane et al., Steroids. 2004 May;69(5):343-9.

Aluminum in the Pineal Gland*

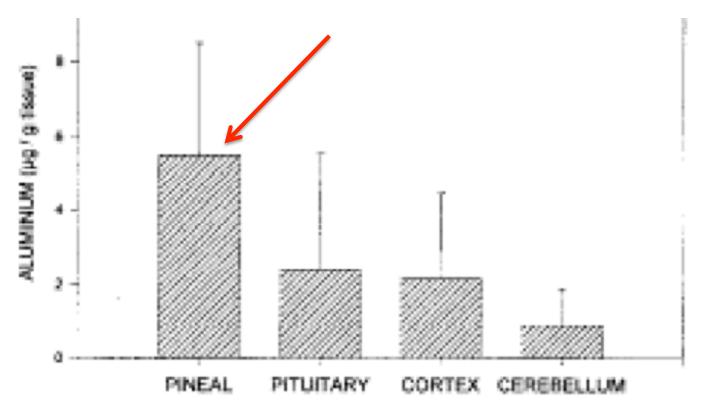
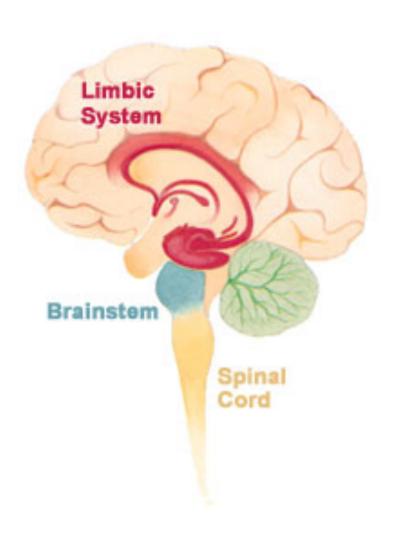


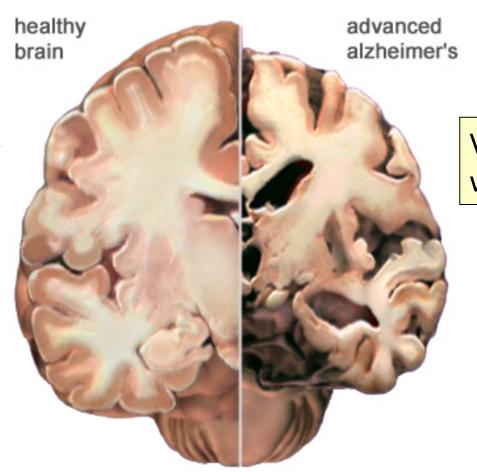
Fig. 6. Aluminum contents of brain tissues (mean \pm SD). The results are expressed per unit weight of dried tissues. Four samples of each tissue were examined.

Limbic System

- Includes hippocampus, olfactory bulbs, amygdala, thalamus, etc.
- Controls emotion, behavior, motivation, long-term memory, and olfaction
- Surrounds the ventricles



Changes Associated with Alzheimer's



Ventricles expand in size while brain tissues shrink

Habenula! Mission Control!

- Involved in pain processing, reproductive behavior, nutrition, sleep-wake cycles, stress responses, and learning.
- Divided into limbic and motor parts.
- Noradrenergic inputs from the locus ceruleus
- Ships acetylcholine to the pineal gland
- Sends control signals to midbrain nuclei that release *dopamine*, *norepinephrine*, *and serotonin*.

All of these neurotransmitters are sulfated in transit

Habenula! Mission Control!

 Involved in pain processing, reproductive behavior, nutrition, sleep-wake cycles, stress

Habenula is closely connected to the pineal gland

JS

- Ships acetylcholine to the pineal gland
- Sends control signals to midbrain nuclei that release dopamine, norepinephrine, and serotonin.

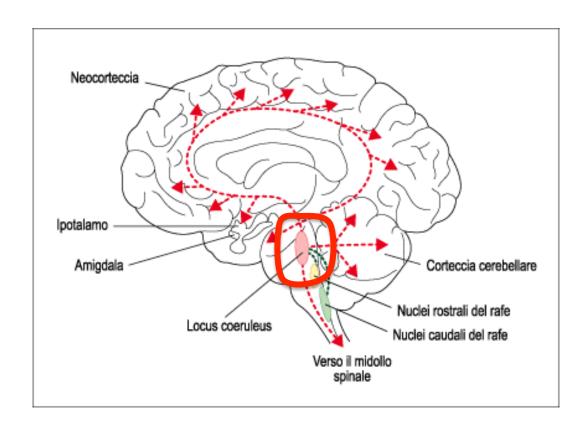
All of these neurotransmitters are sulfated in transit

Habenula and Depression*

- Habenula is tiny:
 It covers an area only about 1-2 mm across.
- Neurons in habenula are hyperactive in mouse-models of depression.
 - Inhibits dopamine and serotonin receptors downstream.
- Deep brain stimulation reversed the effect.

Locus coeruleus

- Supplies adrenalin throughout the nervous system
- Controls experience-dependent alterations in neural function and behavior
- Pathology associated with ADHD, sleep disorders, posttraumatic stress disorder



Novel role for Noradrenaline and Dopamine?

- Locus coerulius (source of noradrenaline)
 - Is colored blue due to neuromelanin formed by polymerization of noradrenaline
- Substantia nigra (source of dopamine)
 - is colored *black* due to dopamine-based neuromelanin
- Both of these may need the melanin to protect from UV exposure (melanin production causes suntan)

Recapitulation

- The pineal gland behind the eyes produces melatonin sulfate
 - Shipped via the cerebral spinal fluid to all parts of the brain
 - Regulates the wake/sleep cycle
 - Sulfate synthesis in pineal gland depends on sunlight
- The habenula is "mission control" for neurotransmitter regulation in the brain involved with pain management, wake/ sleep cycle, stress, learning and nutrition
 - Closely connected to the pineal gland
- The limbic system surrounds the pineal gland and produces neurotransmitters like serotonin, dopamine, and norepinephrine
 - These are also sulfated in transit

I hypothesize that an important role served by all of these molecules is maintenance of sulfate supplies to the brain

Sulfated Sterols and Lipids

Cholesterol Sulfate Deficiency Explains Autistic Correlates

- Autism is associated with several health issues:
 - Eczema, asthma, digestive problems (leaky gut)
 - Increased susceptibility to infection
- Cholesterol sulfate in skin stimulates filaggrin synthesis*
 - Filaggrin deficiency leads to eczema and asthma
- Sulfate protects cells in blood from bacteria
- Sulfate deficiency leads to leaky gut syndrome **

^{*} Nakae et al. The FASEB Journal 22:782.2, 2008

^{**} Waring and Klovrza, J Nutr & Environ Medicine 10, 25-32, 2000.

Recent Papers

"Might cholesterol sulfate deficiency contribute to the development of autistic spectrum disorder?" Stephanie Seneff, Robert Davidson, Luca Mascitelli Medical Hypotheses 2012, 78, 213–217

"Impaired Sulfate Metabolism and Epigenetics: Is There a Link in Autism?"

Samantha Hartzell and Stephanie Seneff Entropy 2012, 14, 1953-1977

Sulfate in Fetal Development*

- Fetus depends on mother for sulfate supply
- Sulfate is essential for transporting sterols (like estrogen and DHEA) and supplying extracellular matrix proteins everywhere with sufficient negative charge
- Sulfate detoxifies xenobiotics like acetaminophen (tylenol) and is essential for excreting toxins like aluminum and mercury
- Sulfate is severely deficient in autistic children (1/3 the normal level of free sulfate in blood stream)

^{*} Dawson, "Sulfate in Fetal Development," Semin Cell Dev Biol 2011

Heparan Sulfate Deficiency and Autism*

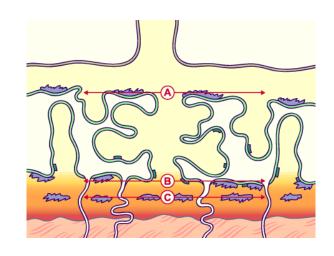
- Experiment with
 "designer" mice:
 impaired heparan
 sulfate synthesis in brain
- Mice exhibited all the classic features of autism – both cognitive and social



^{*} F. Irie et al., Autism-like socio-communicative deficits and stereotypies in mice lacking heparan sulfate. PNAS Mar. 27, 2012, 109(13), 5052-5056.

Cholesterol Sulfate in Placental Villi*

 Placental villi are highly enriched in cholesterol sulfate, especially in third trimester of pregnancy

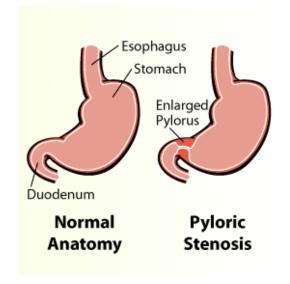


- Mother's serum cholesterol sulfate steadily rises through pregnancy
- In third trimester, villi contain 24 pmol/mg of cholesterol sulfate, compared to only 1.5 in blood serum of a non-pregnant woman

^{*} Lin et al., Journal of Chromatography B, 704 (1997) 99–104

Pyloric Stenosis and Autism

- Affects 2 out of 1000 births
 - Pyloric valve at base of stomach is enlarged, constricting flow
 - Severe projectile vomiting and dehydration, with electrolyte imbalance.
 - Corrective surgery is often required
- Pyloric stenosis is associated with low serum cholesterol*
- Autism is associated with increased risk to pyloric stenosis**



*Feenstra B, et al. JAMA 2013; 310(7): 714-721. **M.L. Wier et al., Med Child Neurol 2006;48(6):500-507.

Parkinson's and Low LDL

- Low serum levels of LDL (the "bad" blood lipid measure) are associated with increased risk to Parkinson's disease
- Men at the 80th percentile had less than half the incidence of Parkinson's compared to men at the 20th percentile

^{*}X Huang et al., Mov Disord. 2008 May 15;23(7):1013-8.

Mouse Experimental Model of Parkinson's Disease*

- Testosterone is produced from cholesterol in the testes
 - Statin drugs lower testosterone levels
 - Low testosterone is found in Parkinsonian men
- Castration in mice activated microglia and astrocytes in substantia nigra
 - leads to sharp increase in nitric oxide synthesis
 - Dopaminergic cells die
 - Produces Parkinson's-like symptoms

Hypothesis

- Testosterone sulfate normally supplies sulfate to the brain
- When testosterone is deficient, dopamine must replace testosterone for this role
- Dopamine induces nitric oxide synthesis by iNOS in glial cells*
 - Dopamine sulfate delivers sulfate to brain
 - Nitrate can compensate for sulfate to balance
 Hofmeister effects
- Neurons die from exposure to ONOO⁻

^{*}S.C. Cunningham et al., Eur J Neurosci. 2005 Apr;21(8):2199-208.

High Serum Cholesterol Beneficial in Elderly*

"In this study, we found marginally significant associations of a higher LDL-C level and a lower TG/HDL-C ratio with better memory function among community dwelling, functionally independent dementia-free older adults aged 80 years and older, even after controlling for demographic characteristics and use of lipid-lowering drugs."

Alzheimer's and Serum Glucose Levels*

- Analyzed 35,264 measures of glucose levels from 2067 participants
 - Mean age at baseline was 76 years old
 - Median follow-up of 6.8 years
- Dementia developed in 524 people (>25%)
 - Among participants with diabetes, higher levels of glucose correlated strongly with increased risk to dementia (P=0.002)
 - Dementia was also correlated with higher blood sugar levels in people without diabetes (P=0.01)

Alzheimer's and Serum Glucose Levels*

 Analyzed 35,264 measures of glucose levels from 2067 participants

Sulfate deficiency leads to impaired sugar metabolism

- Among participants with diabetes, higher levels of glucose correlated strongly with increased risk to
 - dementia (P=0.002)
 - Dementia was also correlated with higher blood sugar levels in people without diabetes (P=0.01)

*P.K. Crane et al., N Engl J Med 2013; 369:540-548

"Alzheimer's research breakthrough"*

 Researchers in New Zealand are synthesizing a form of heparan sulfate to be administered as a treatment for Alzheimer's disease

"may play a part in determining the type of cell a stem cell will form into, and producing stem cells that proliferate and do not show normal signs of ageing"

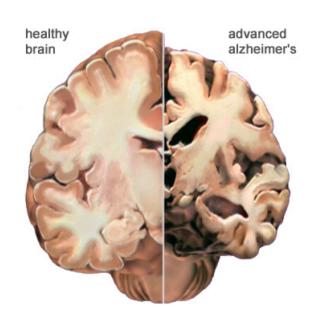
Quote from Dr. Richard Furneaux, manager of project

^{*}http://www.stuff.co.nz/national/health/9007969/Alzheimers-research-breakthrough

Sulfatide

Sulfatide Depleted in Alzheimer's Brain*

- Study of Alzheimer's brains postmortem
- Sulfatide was found depleted up to 93% in the gray matter.

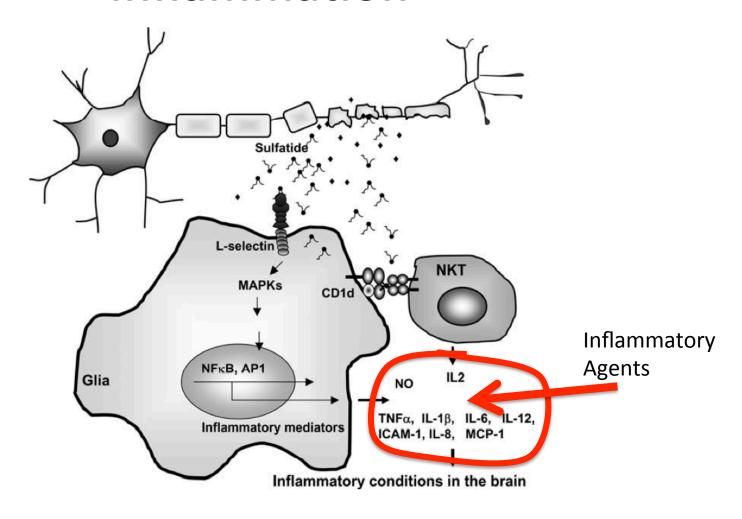


*X Han et al., J Neurochem 82(4): 809-18.

WIKI on Sulfatides*

• Sulfatides are a class of sulfated galactosylceramides. ... Sulfatides are thought to play a major role in myelin function and stability, as evidenced by the fact that mice lacking the enzyme ... have thinner myelin sheaths, and experience progressive hindlimb paralysis as a result of demyelination of their lower spinal cords.

Sulfatide Breakdown Induces Inflammation*



*S-B Jeon et al., The Journal of Immunology, 2008, 181: 8077–8087.

TNFα and Multiple Sclerosis*

"These studies illustrate that while TNF α accelerates the process of acute demyelination, its presence in the CNS may be necessary for remyelination to occur."

• TNF α induces both synthesis and degradation of the myelin sheath

I propose that sulfatide in myelin is a source of sulfate to supply the blood stream

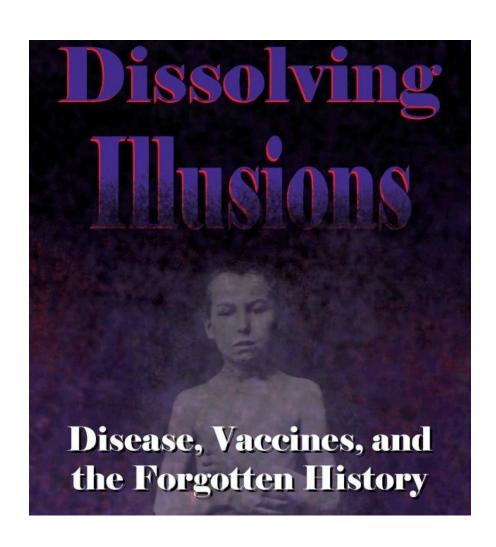
^{*}M.D. Magnano et al., Clin Exp Rheumatol 2004; 22 (Suppl. 35): S134-S140.

Recapitulation

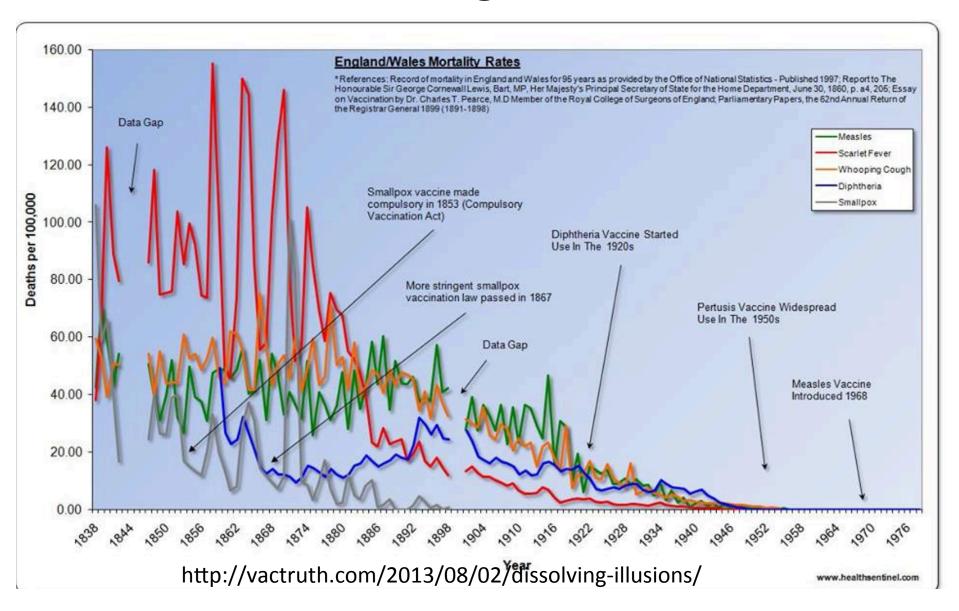
- Sulfate plays an essential role in fetal development
 - Heparan sulfate deficiency in the brain is linked to autism
- Parkinson's disease is associated with:
 - Low serum LDL
 - Testosterone deficiency
 - Statins cause reduced testosterone synthesis
- High LDL improves cognition in elderly
- High blood sugar is a risk factor for dementia
- Heparan sulfate is a new treatment for Alzheimer's
- Sulfatide breakdown causes neurological disease

Vaccines and Aluminum

Book by Suzanne Humphries, MD



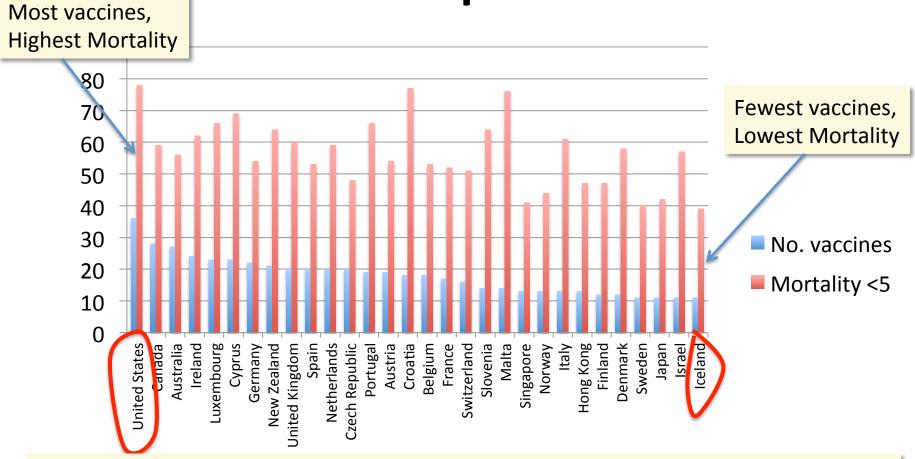
History of Death from Various Infectious Diseases in England/Wales



"The United States has the highest number of mandated vaccines for children under 5 in the world (36, double the Western world average of 150 the highest autism rate in the world (1 in children, 10 times or more the rate of some other Western countries), but only places 34th in the world for its children under Emertality rate. What's going 50th on?"*

^{*} Vaccine Schedules, Autism Rates, and Under 5 Mortality, Generation Rescue, Inc. 2009

Mortality under 5 Years Old vs. Number of Required Vaccines*

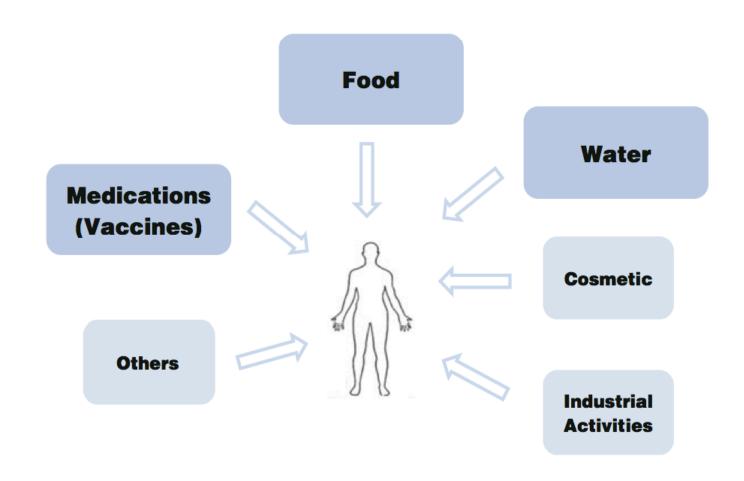


If vaccines are protecting our children from death due to infection, they're not doing a very good job!

"Aluminum is not perceived, I believe, by the public as a dangerous metal and, therefore, we are in a much more comfortable wicket in terms of defending its presence in vaccines"

-- Dr. John Clement, World Health Organization, San Juan, Puerto Rico, May 11th - 12th, 2000, p. 64

We live in the age of aluminum*



^{*}C.A. Shaw and L. Tomljenovic, Immunol. Res. Epub ahead of print, 2013

Recapitulation

- Disease incidence had already plummeted before vaccines were introduced
- Contrary to widely held beliefs, vaccines are not safe
 - Key problems are mercury and aluminum
 - US has highest infant mortality rate among developed nations along with highest vaccination rates
- Aluminum is also found in many other everyday items
- Aluminum is neurotoxic

Summary

- Autism rates have reached an alarming level of 1/50.
 - Related to Alzheimer's and depression, which are also highly on the rise
- Hypothesis: Autism is caused by a severe system-wide deficiency in sulfate supplies
- Pineal gland can synthesize sulfate stimulated by sunlight
 - This supplies sulfate to multiple neurotransmitters and hormones that deliver It to the neurons and muscle cells
- Aluminum and glyphosate are two pervasive environmental toxins contributing to our health problems