Long-Term Health Beyond Autism – Attending to Underlying Medical Risks in ASD

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Decades after the autism epidemic began, the battle over answers and responsibility still rages. Our nation's most valuable resource, our children, have become the victims in this war. Unlike a true war, where casualties receive care, parents of a child with autism often have to work to engage the medical community to have their child's injuries treated – and, in some instances, even recognized. This lack of medical treatment creates further health risks for the child.

In 2011, electronic health records were used to investigate future health risks for persons with ASD. This investigation led to the following statement:

> ***"Without intervention initiated in childhood and continued through adolescence and early adulthood, a cascade of health conditions, including diabetes, coronary heart disease, heart failure, osteoarthritis, and cancer will likely ensue."***
>
> [Reference 159]

As an example: for years, parents told their pediatricians that their ASD children suffered from gastrointestinal (GI) problems. Yet physicians and the medical insurance industry refused to recognize this as a problem deserving treatment. As a result, parents often sacrificed countless hours and financial resources in their fight to secure appropriate medical treatment for their children. Parents of autistic children often need to travel far from home searching for help, incurring significant costs in time, money and emotion.

Subsequently, medical literature documenting the collateral damage experienced by autistic individuals on the frontlines of this war has improved and should be useful in getting proper care. The following list of medical conditions co-occurring with autism helps provide a parent some insight into the current situation and can be useful in discussions with physicians and insurance companies:

TABLE 1 Associated Issues	References
1. Gastro-intestinal distress	[1-14]
2. Altered gut flora	[15-24]
3. Increased intestinal permeability	[4, 25-27]
4. Celiac disease or gluten sensitivity	[28-32]
5. Abnormalities in functioning of mitochondria	[33-42]
6. Chronic inflammation	[43-52]
7. Oxidative stress	[1, 53-71] [72]
8. Low levels of the glutathione (GSH) and/or altered ratios of GSH to Oxidized glutathione (GSSG) represented by GSH/GSSG	[37, 38, 53, 55, 58, 65, 67, 68, 72-82]
9. Differences in genes involved in GSH utilization	[57, 63]
10. An increased occurrence of seizures	[83-93]
11. Immune irregularities	[68, 82, 94-103]
12. Autoimmunity	[104-116]
13. A burden of toxic metals	[72, 117-125]
An assortment of nutritional deficiencies	
a. Zinc	[117-119, 126-129]
b. Zinc/copper ratio	[118, 130-133]
c. Folate	[134-137]

d. Central nervous system folate	[113, 138, 139]
e. Genetics involved in folate metabolism	[79, 140-146]
f. Magnesium	[117-119, 147, 148]
g. Selenium	[118, 119]
h. Iron	[118, 120, 149-152]
i. Vitamin D	[153-158]

The reader should take critical note of the many *modifiable* factors on the list which can be treated through easily implementable interventions. Correcting most of these factors doesn't require prescription drugs or pharmaceuticals; most are safe, low cost and will improve general health. Correcting these problems, like a metabolic deficiency, won't cure a child of autism. However, instead of leaving these issues unchecked, correcting them may prevent further deterioration and minimize the risk for health consequences and future investments of both time and money.

Below, we have highlighted two underlying metabolic issues that have a profound effect on the risk for many diseases. Correcting these should be a consideration for any parent of a person with ASD.

Oxidative stress

Understanding oxidative stress is key to following the concepts present in this paper. Oxidative stress results when a person's reactive oxygen/nitrogen species (ROS/RNS) exceed their neutralizing capacity. In short this means their **pro-**oxidants exceed their **anti-**oxidants.

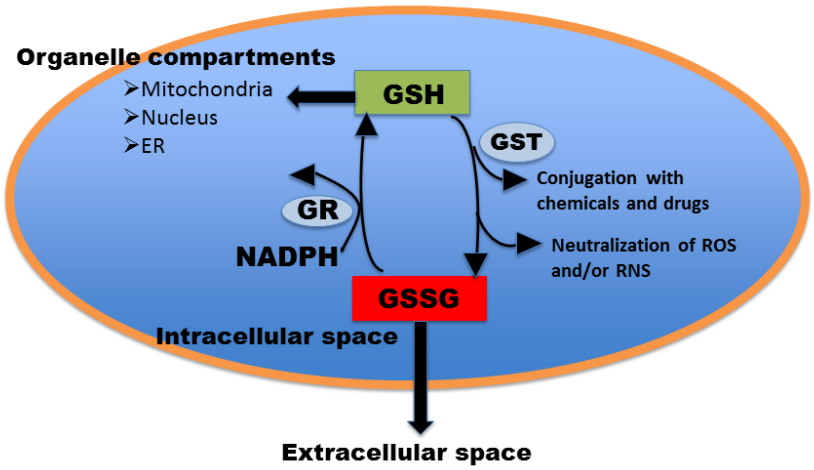
Such an imbalance may result from a number of factors such as:

- Low levels of dietary antioxidants (vitamins E, C, D, flavanoids, carotenoids, etc.)
- Low levels of the micronutrients (Zinc, selenium, copper, iron) needed for functioning of antioxidant enzymes (Cu/Zn SOD, glutathione peroxidase, catalase)
- Chronic activation of the antioxidant enzymes due to exposure to excessive environmental toxins and/or medications.
- Chronic inflammatory conditions (immune activation, obesity, poor gut flora, etc.)

Failure to address oxidative stress results in oxidative damage to cellular DNA, lipids and proteins. This damage has been widely documented in autistic individuals. Compelling evidence demonstrates many other serious diseases; including cancer, diabetes, autoimmunity, atherosclerosis, and neurodegenerative diseases like Alzheimer's and Parkinson's result from this same oxidative stress and damage. Because these outcomes generally result from long-term chronic damage, bringing anyone's oxidative stress under control *as soon as it is identified* results in healthier outcomes. One of the reasons cited for why clinical trials utilizing antioxidant supplementation failed to impact Alzheimer's disease progression has been the treatment's timing. Treatment described as surpassing *"a point of no return*" condemned the patient to a negative outcome because too much time elapsed between the initiation of damage and treatment .[160]

Limiting treatments when simultaneous multiple deficiencies are occurring further limits opportunities for recovery. As a result, one can conclude that failure to treat a known condition of oxidative stress and nutrient deficiencies found in children with autism may likewise put them past the "point of no return" and on their road to other negative health outcomes. This can prove to be incredibly costly for families on emotional, physical and/or financial levels.

Glutathione and GSH/GSSG imbalance

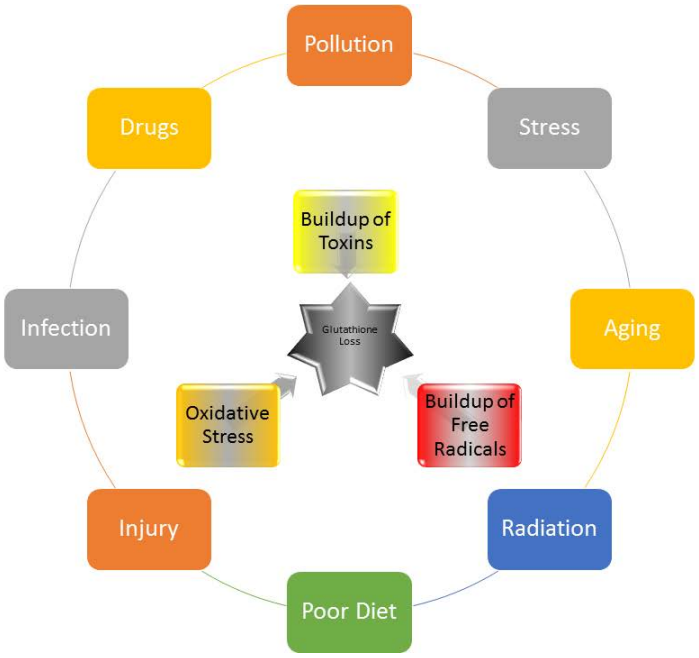


GSH - Reduced glutathione
GSSG – Oxidized glutathione
GR – Glutathione reductase
GST – Glutathione S-transferase
ER – Endoplasmic reticulum
ROS – Reactive Oxygen species
RNS – Reactive Nitrogen species

A common form of oxidative stress occurs as cells seek to optimize their glutathione molecules. Glutathione molecules exist in two forms – the reduced form (GSH) and the oxidized form (GSSG). In its reduced form, GSH serves as a major intracellular antioxidant, protecting the cell and its components from oxidative damage. The reduced form, GSH, represents the majority of glutathione present in healthy cells, with a much smaller portion present in the oxidized form, GSSG. Some environmental circumstances place demands on a cell that challenge the balance between its antioxidant defenses and its ability to cope with the onslaught of pro-oxidants. During such cellular challenges, levels of GSSG rise altering the ratio of GSH to GSSG. When GSH/GSSG ratios fall below a certain level, the result is oxidative stress. In an attempt to maintain balance, if GSSG levels get too high, the cell will release GSSG from the cell. Sustained releases from the cell result in less GSSG to recycle back into GSH (see diagram). In the face of continued demand without any outside intervention, the cell becomes vulnerable to oxidative damage from the loss of GSH. As noted in Table 1, individuals with autism often have chronic low levels of GSH and elevated levels of GSSG – classic oxidative stress and leaving them vulnerable to oxidative damage. These low levels of GSH and/or oxidative stress are also associated with autoimmunity. [109, 161-165] The exact mechanism behind the oxidative stress and autoimmunity association is now in the early stages of being elucidated (see explanation below). Fortunately, several studies have shown non-pharmacological treatments capable of raising GSH levels in autism. [53, 75, 77, 78]

Researchers have attempted to clarify how oxidative stress induces autoimmunity. A recent animal model of autoimmunity investigated one mechanism that likely explains much of this association [163]. Trichloroethene (TCE), a fairly ubiquitous industrial environmental pollutant, generates free radicals at relatively low exposures. Free radicals, highly reactive molecules, require quenching by antioxidants to prevent oxidative damage to cellular components. It is these free radicals and the resultant oxidative stress that was demonstrated to induce autoimmunity [165]. Using an autoimmune prone mouse model exposed to TCE, Wang et al., compared the results to a group of mice receiving both TCE and N-acetylcysteine (NAC)

[163]. NAC is a precursor to GSH shown to increase GSH, thereby providing protection against oxidative stress as well as modulating inflammatory response.



Biomarkers of oxidative damage have been correlated with autoimmune response. IL-17 (a potent pro-inflammatory molecule) is significant in the progression of autoimmune diseases. Researchers track IL-17mRNA and IL-17 release to follow this potential. As anticipated, TCE exposure increased the markers of oxidative damage, IL-17 release and IL-17 mRNA. These correlated with an increase in the autoimmune markers. Several important points with this study need to be highlighted:

"... NAC supplementation attenuated not only the TCE-induced oxidative stress, IL-17 release and its mRNA expression, but also the markers of autoimmune response, as evident from decreased levels of autoantibodies in the sera."

"More importantly, this study also provides evidence that increased formation of ROS- modified proteins could be averted by antioxidants, such as NAC supplementation."

In closing, the authors note, *"Our results clearly support the role of oxidative stress in TCE- induced autoimmune response. Attenuation of TCE-induced autoimmune response in mice by NAC could be important in developing preventive and/or therapeutic strategies" [163].*

What is the significance of these findings to children with autism? Research shows that children with autism suffer from oxidative stress making them more prone to autoimmune disorders (see table 1). The Wang study clearly demonstrates not only the role of oxidative stress in autoimmunity, but profiled a non-pharmacological treatment capable of attenuating the oxidative damage and ensuing autoimmunity.

Other human clinical trials aptly demonstrate the utility and safety of using NAC. [167-206]. Two trials of NAC use in autism[177, 180] show a decrease in irritability scores with NAC. However; **both** trials suffered from the methodological limitation of utilizing psychotropic drugs in conjunction with both the placebo and the NAC groups. In the autism/NAC study by Haradan[180] they acknowledged the current approval by Food and Drug Administration of psychotopic drugs, "*have a propensity to cause serious side effects (weight gain, metabolic abnormalities, and tardive dyskinesia), which have limited their use considerably."* Additionally, the autism/NAC study by Ghanizadeh stated, *"the concomitant use of risperidone may limit the*

efficacy of obtained results." Thus, it would be more informative to know the results of NAC alone compared to a **true** placebo group (ie.no psychotropic drug). Better yet, would be to simultaneously address all the deficiencies that an individual has, following the lead of the emerging field of "individualized medicine".

Another risk factor for autism is maternal autoimmunity. [28, 166] Testing and treating mothers with autoimmune disorders *prior* to conception could result in reduced risk. As a side note, it should be born in mind that the autoimmunity suffered by the mother may stem from her exposure to medications and/or chemicals that induce oxidative stress. This indicates further, the immense need to focus research dollars on environmental contributors to autism.

The hyperfocus on genetic research minimizes the role environmental toxins play in the development of autism. This overreliance on a genetic approach almost completely ignores the well-documented underlying metabolic factors in the autism population. The NAC trials along with other beneficial uses of nutritional/supplemental therapies [53, 75, 77, 78, 212-218] clearly demonstrate the need for

> *"The good news is that things that people can change – what we call modifiable risk factors – make a huge difference."*
>
> *Dr. Tom Freiden, Director at the Centers for Disease Control and Prevention*

individualized treatment with autistic children.

In closing, CBS news reported on May 2, 2014 that a new CDC study showed premature deaths can be prevented by changing aspects of one's lifestyle
http://www.cbsnews.com/news/thousands-of-premature-deaths-could-be-prevented-cdc-says/

Wide agreement exists with Dr. Frieden's announcement that changing modifiable risk factors can make a huge difference in health outcomes. Taken a step further, the serious health consequences stemming from failure to address these "modifiable risk factors" documented in autism demonstrate a form of medical and/or societal negligence – possibly resulting in condemning a child with autism to a future of poor health and premature death; an outcome not keeping with the CDC's program of prevention.

> *"Without intervention initiated in childhood and continued through adolescence and early childhood, a cascade of health conditions, including diabetes, coronary heart disease, heart failure, osteoarthritis, and cancer will likely ensue."* *[159]*

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