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Review

Is Cholesterol Sulfate Deficiency a Common Factor in Preeclampsia, Autism, and Pernicious Anemia?

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Abstract: In a recent paper, we proposed that a contributing factor in autism is a deficiency in cholesterol sulfate supply. In this paper, we investigate a link between preeclampsia and subsequent autism in the child, and we hypothesize that both conditions can be attributed to a severe depletion of cholesterol sulfate. Through studies on the Vaccine Adverse Event Reporting System (VAERS) database, we demonstrate a strong statistical relationship among the signs and symptoms associated with autism and those associated with preeclampsia, pernicious anemia, and serious adverse reactions to vaccines. We show that VAERS reports associated with symptoms typical of pernicious anemia produce both a set of symptoms that are highly correlated with preeclampsia and another set highly correlated with autism. We explain this observation via an argument that, in a severe reaction, the cascade of events subsequent to vaccination reflects a profuse production of nitric oxide (NO) and consequential destruction of both red blood cells (RBCs) and cobalamin. This may explain the diverse signs and symptoms associated with both preeclampsia and severe vaccine adverse reactions. We argue that excess NO synthesis, induced by the aluminum and antigen in vaccines, results in hemolysis of RBCs, which allows hemoglobin to scavenge the excess NO, converting it to nitrate. The NO is also scavenged by cobalamin, leading to its inactivation and contributing to subsequent pernicious anemia. Finally, we demonstrate that severe adverse reactions to vaccines can be associated with life-threatening conditions related to the heart and brain, as well as

stillbirth, when the vaccine is administered to a woman in the third-trimester of pregnancy, as demonstrated by statistical analysis of the Gardasil records.

Keywords: encephalitis; preeclampsia; autism; cobalamin; pernicious anemia; nitric oxide; cholesterol sulfate; aluminum; seizures

PACS Codes: 87.19.xm; 87.19.xt; 87.19.xw; 87.18.Vf; 87.18.Sn; 87.19.lk; 87.19.lv; 87.19.um; 87.19.uj

1. Introduction

Preeclampsia is a serious condition, life-threatening to both the mother and the fetus, which typically develops late in pregnancy, associated with hypertension and proteinuria [1,2]. It is estimated to affect 6–8% of pregnancies in the U.S. The etiology of preeclampsia remains poorly understood, but it is clear that an underlying pathology related to the coagulation cascade is involved, with vasoconstrictive factors as secondary effects. Excess free iron in the blood suggests that hemolysis is a contributing factor [3].

Preeclampsia diagnosed in the mother is highly correlated ($p < 0.0001$) with a future diagnosis of autism for the fetus [4]. We have previously argued [5], that autism may be due to a deficiency in the supply of cholesterol sulfate to the fetus, and, subsequently, to the infant postnatally. We further argue that it is caused by a deficiency in the supply of critical nutrients, namely cholesterol, zinc and sulfur, and in the amount of sunlight exposure to the skin, again, both for the mother and the child. Here, we argue further that cobalamin (vitamin B_{12}) deficiency is likely also present, as this nutrient is found naturally mainly in animal foods, and is especially enriched in foods containing cholesterol such as molluscs, clams, liver, and eggs, which are not likely to be major components of a modern diet. This will lead to a tendency towards anemia, which further increases vulnerability to factors that perturb blood stability.

Proteinuria, a strong risk factor for preeclampsia, comes about because the glomeruli of the kidney allow large blood proteins like albumin and globulin to pass through a defective filter. Such defective filtering in the kidneys has been shown to be a consequence of both a decreased production of heparan sulfate and an increased breakdown of heparan sulfate by both reactive oxygen species (ROS) and active enzymes like heparanase [6]. In preeclampsia, this is likely due to the pressures to deliver sulfate to the fetus. Preeclampsia is also associated with elevated serum levels of homocysteine [7–9], which is a precursor for sulfate synthesis. A deficiency in cobalamin is associated with elevated homocysteine levels [10] and with preeclampsia [9]. Cobalamin depletion is the key factor in pernicious anemia [11].

In this paper, we will present an argument that there is an intricate relationship among preeclampsia, pernicious anemia, autism and acute adverse reactions to vaccines, and, further, that all of these conditions are consequential to a preexisting severe deficiency in sulfate supply to the tissues and the vasculature. We are not claiming that vaccines cause autism, but rather that the appropriately predisposed child is especially vulnerable to an acute reaction to an aluminum-adjuvanted vaccine,

which could in rare cases lead to neuronal damage, mediated in part by exuberant production of nitric oxide. We support our arguments through a review of the research literature, as well as through a statistical study of word frequencies in various subsets of the VAERS database. We demonstrate a remarkable correspondence among symptoms in VAERS associated with autism, pernicious anemia, and preeclampsia, and we explain those symptoms as plausibly following from an acute reaction to blood instabilities brought on by an exuberant synthesis of nitric oxide by endothelial nitric oxide synthase (eNOS).

In the remainder of this paper, we will first briefly introduce our hypothesis concerning a role for cholesterol sulfate insufficiency in autism. The next section will argue for a common underlying pathology in preeclampsia and anaphylactic reactions to vaccines. Section 4 discusses the association of autism with abnormal gut bacteria, and argues that this can lead to chronic excess NO synthesis. Section 5 links autism with preeclampsia through the shared feature of NO-induced seizures. Section 6 discusses the potential role of mitochondrial DNA released by necrotic tissue in inducing an antigenic reaction. Section 7 proposes the hemolysis cascade that arises in certain contexts following provocation, which we believe is induced by instabilities in the blood coagulation system. Section 8 discusses our studies with VAERS, which use statistical analyses of word frequencies to demonstrate a strong link among autism, preeclampsia, and pernicious anemia. Following a discussion section where we recapitulate our major findings, we end with a conclusion summarizing the main points of the paper.

2. A Crucial Role for Cholesterol Sulfate and Endothelial Nitric Oxide Synthase

Cholesterol sulfate is a very interesting molecule whose many biological roles are poorly understood [12]. In the third trimester of pregnancy, the placental villi are normally highly enriched in cholesterol sulfate [13]. We have argued that this placental cholesterol sulfate plays an important role in providing the fetus with adequate sulfate to populate the glycosaminoglycans (GAGs) in the extracellular matrix proteins in diverse cells throughout the body [5]. This is especially crucial for maintaining the zeta potential of the vasculature, in order to stabilize the colloidal suspension of blood particles [14]. This then places a huge demand on the mother. If her cholesterol sulfate levels are insufficient, the sulfate levels in the artery walls will be depleted and the RBCs' and platelets' ability to maintain adequate cholesterol sulfate in their membranes will be impaired, leading to hemolysis. The red blood cells play an essential role in the disease process. Crucially, cholesterol sulfate has been shown to protect them from lysis due to osmotic stress or viral attack [15,12].

RBCs are among the small number of cell types known to produce significant amounts of cholesterol sulfate [16]. Other cell types that produce it are platelets [17] and fibroblasts and melanocytes in the epidermis [18]. Intriguingly, all of these cell types also produce endothelial nitric oxide synthase (eNOS). Furthermore, mast cells, which produce large amounts of heparin, the most highly sulfated molecule known to biology, also contain eNOS. It has been known since 1927 [19] that prior administration of heparin protects from anaphylactic shock, and this is likely due to additional buffering of sulfate supplies. We have argued previously [5] that all of these cell types use eNOS predominantly to synthesize sulfate rather than NO, and that sunlight exposure catalyzes the reaction and supplies energy.

It is well established that calmodulin and caveolin regulate the activity of eNOS, where caveolin is associated with the membrane-bound form of eNOS attached at caveolae: a configuration we believe is responsible for the synthesis of sulfate [20]. Calcium entry into a cell, through a signaling mechanism that involves calcium-calmodulin binding, causes eNOS to detach from caveolin and catalyzes the synthesis of NO, following phosphorylation. Such calcium entry is triggered by TNF-α during an immune reaction.

3. A Relationship between Disseminated Intravascular Coagulation and Vaccines?

In this section, we describe the underlying process in acute preeclampsia that can result in a life-threatening situation, developing as a consequence of insufficient sulfate buffering, and leading to serum colloidal instability and a complex reaction cascade involving profuse release of NO along with hemolysis of RBCs, ultimately developing into a profound crisis in the circulatory system and severe impairment in oxygen delivery. We argue that a similar process unfolds in an acute anaphylactic vaccine adverse reaction.

Hemoglobin is a major scavenger of NO. In an extremely fast, irreversible, reaction (< 4 seconds reaction time) [21], nitrate and methemoglobin are produced, and this impairs oxygen delivery to the tissues; *i.e.*, the effect is analogous to that of carbon monoxide [22]. Serum infusion of *free* hemoglobin solution results in hypertension. This is due to the reaction of NO with oxyhemoglobin in the blood circulation [23], which interferes with NO's normal role, via the guanylyl cyclase pathway, in producing vasodilation [24]. Oxyhemoglobin reduces the half-life of soluble guanylyl cyclase from 106 minutes to only 18 seconds [25]. Hemoglobin within red blood cells is 1,000-fold less reactive with nitric oxide than free hemoglobin, due in large part to the barrier of the RBC cell membrane. Under deoxygenated conditions this difference reduces to only 50-fold [26].

A case study of a patient who experienced a postpartum cascade leading ultimately to death illustrates the complex response associated with preeclampsia [27]. The patient presented with disseminated intravascular coagulopathy (DIC), resulting in a sudden rapid drop in platelet counts. The rapidly following consequences included blindness, severe abdominal pain, jaundice, and liver and kidney failure. Two seminal papers by Donald McKay describe the processes that ultimately lead to DIC [28,29], which are initiated by a precipitous destabilization of the blood colloidal system, followed by massive numbers of small clots formed from platelets in diverse organs, and with devastating consequences. It is triggered by a number of different agents, including bacterial endotoxins, particulate matter, proteolytic enzymes, anoxia, and hemolyzed RBCs.

In [29] a phenomenon, associated with DIC, is described in which the synthesis of a fibrin mesh by platelets causes RBCs to be sliced into fragments, releasing their contents into the vasculature. We propose that this phenomenon offers protection from potentially toxic build-up of NO, produced in reaction to exposure to appropriate triggering factors (Selye provocation). The released hemoglobin would neutralize the NO by the rapid, irreversible reaction leading to methemoglobin and nitrate. The nitrate would be disposed of through the kidneys and the gut, and the methemoglobin would be broken down by macrophages through the action of heme oxygenase [30,31], which also suppresses the induction of cytokines.

Protamine sulfate, an L-arginine enriched protein, is used medically to reverse the anticoagulant effects of heparin. However, it can cause systemic hypotension, anaphylactoid reactions, and catastrophic pulmonary vasoconstriction. In [32], it is proposed that these effects are mediated by the profuse production of NO by endothelial cells, using the L-arginine in protamine as substrate. The hypotension induces an emergency cascade reaction that leads to hemolysis in order to release hemoglobin to rapidly neutralize the effects of NO on hypotension, thus inducing vasoconstriction instead of the vasodilation normally induced by NO.

We consider an anaphylactic reaction to a vaccine to mimic in many respects the above cascade. In the case of a vaccine, the triggering factors are likely to include both endotoxin and aluminum. A reaction to an aluminum-containing vaccine could precipitate a crisis due to depletion of serum sulfate followed by excess build-up of NO. A study involving exposing mice to aluminum hydroxide and endotoxin demonstrated a significant and immediate synthesis of large amounts of NO in endothelial cells lining the artery walls [33], leading to anaphylactic shock. The authors were surprised to find that it was eNOS rather than iNOS (the inducible isoform) that was responsible for NO release.

We hypothesize that aluminum plays a critical role in this effect. Aluminum binds to calmodulin with an affinity that is an order of magnitude higher than that of calcium [32]. Thus, the presence of even minute amounts of aluminum in the endothelial cells and RBCs would cause them to switch from producing sulfate to producing NO, resulting in both further depletion of sulfate supply and toxic build-up of NO in the blood stream [34].

In addition to the effect of switching eNOS from sulfate production to NO production, aluminum binds strongly to sulfate, and both molecules are strong kosmotropes, which are well known in colloid chemistry to promote the "salting out" of proteins [35]. In fact, aluminum sulfate is used as a flocculating agent in the purification of drinking water [36], for this reason. Furthermore, antigens, such as the dead or weakened pathogens or LPS in vaccines, also trigger increased production of NO, mainly mediated via iNOS (the inducible form), thus compounding the problem [37]. NO synthesis via iNOS is a key factor in killing invasive pathogens, mediated by its reaction with superoxide to produce peroxynitrite [38].

4. NO Synthesis and Gut Bacteria in Autism

It has recently become apparent that the gut bacteria are a vast and diverse ecosystem [39], and abnormal gut biota have been proposed to play an important role in autism. [40,41]. All such bacteria are interactive and are known to affect the overall balance of the ecosystem in the gut. Autism is associated with gastrointestinal disturbances such as abdominal pain and bloating, as well as constipation and diarrhea [42,43], symptoms that are also commonly associated with pernicious anemia.

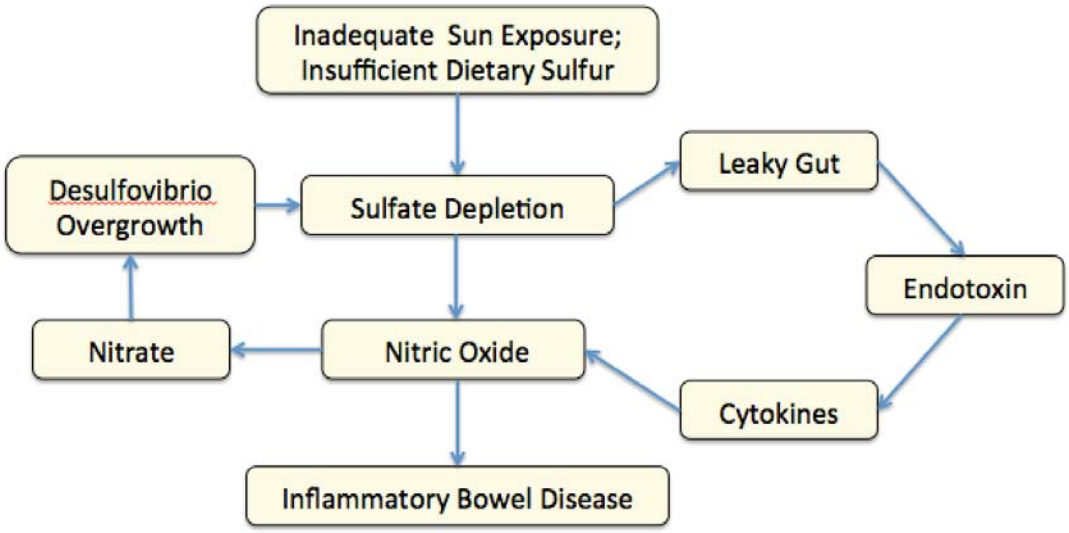
Others have specifically investigated the distributions of intestinal bacteria flora in autistic individuals compared to normal controls, and these efforts have borne fruit. Most significant is the unusually high content of a sulfate-reducing bacterium (SRB) called *Desulfovibrio*, found in 50% of autistics examined and in none of the controls [44]. Since this anaerobe is resistant to penicillin, it would likely gain an advantage following penicillin treatment. However, there are further reasons for it to flourish in the context of excess bioavailability of nitrates. *Desulfovibrio* can metabolize both sulfate and nitrate, whereas nitrate is toxic to many other intestinal flora, particularly the methanogenic

bacteria (MB). A direct quote from [45, p. 246] is highly relevant: "The relative insensitivity of SRB to the toxic effects of nitrate or its reduction product, nitrite, compared with MB, suggest that nitrate could potentially play a role in selecting for SRB in the large gut."

In an experiment where gut bacteria were grown in culture under controlled conditions, it was found that the addition of gastric mucin had profound effects on the distribution of the bacteria in culture, leading to a large increase in the number of sulfur-reducing bacteria, at the expense of the methanogenic bacteria [46]. The authors attributed the effect to the release of sulfate from the polysaccharides in the mucin. Thus, if the GAGs in the gut lining are broken down by inflammatory agents, significant sulfate supply from the degraded mucins would maintain the excess presence of Desulfovibrio in the gut biota.

Childhood inflammatory bowel disease is associated with an excess of nitrate and nitrite in both the stool and the serum [47], and inflammatory bowel disease is also associated with an overgrowth of *Desulfovibrio* [48]. Most significantly, excess plasma nitrate and nitrite are also found in association with autism [49–52]. It has been demonstrated that depletion of the sulfate in the intestinal GAGs is associated with both colitis and Crohn's disease [53]. The breakdown of sulfated GAGs in the gut by *Desulfovibrio* likely plays a role in depleting the gut lining of sulfate, further aggravating the problem by compromising the gut barrier function. This also results in an increased penetration of endotoxins generated by this gram-negative bacterium through the leaky gut, which would further stimulate the synthesis of nitric oxide in a positive feedback loop [54,55], as schematized in Figure 1. Indeed, serum endotoxin levels are significantly elevated in autism and are inversely correlated with socialization skills [56].

Figure 1. Feedback loop leading to excess production of nitric oxide and *Desulfovibrio* overgrowth in the gut in autism, resulting in inflammatory bowel disease.



How might nitric oxide synthesis be triggered in preeclampsia? In preeclampsia, the serum levels of corticotropin-releasing hormone (CRH) are elevated, and it has been shown that this has a direct effect on eNOS in the placental villi, leading to both upregulation of eNOS synthesis and increased production of nitric oxide by eNOS [57]. Furthermore, a key feature of the third trimester of pregnancy

is a sharp rise in the levels of progesterone in the blood stream. One of the well-known properties of progesterone is that it interferes with the storage of cholesterol in cells, and it therefore causes them to give up their cholesterol to the medium [58]. It could be argued that this feature is beneficial to the fetus because it frees up an additional supply of cholesterol for its use. However, cholesterol depletion from cells that are already deficient leads to ion leaks [59], which will eventually deplete ATP, as the cell has to consume a great deal of energy maintaining the ion gradients for sodium and potassium. A drop in ATP activates the ATP-sensitive potassium channels [60,61], which hyperpolarize the cell, leading to calcium entry [62]. This then stimulates eNOS to produce nitric oxide [20] via calmodulin-calcium binding. It has been demonstrated in in vitro experiments that progesterone activates eNOS by stimulating phosphorylation within 30 minutes of exposure, and that this effect is mediated by the PI3K/Akt pathway [63,64].

It has been observed that preeclampsia is associated with an increased presence of fetal erythrocytes as well as cell-free fetal DNA in the maternal blood stream [65]. In [66], it is proposed that the cell-free DNA is most likely of placental origin, and reflects damage to the placenta. The presence of such DNA in the blood stream could stimulate the mother's immune system, causing oxidative stress and damage to the endothelial wall [67,68], a subject to which we will return in Section 6. The resulting inflammatory cascade, triggered by TNF-α release, would induce a profuse synthesis of nitric oxide, mirroring the feedback effects observed in autism when endotoxin is released by *Desulfovibrio*. We suggest that the placental damage may be similar to the damage to the glomeruli of the kidneys observed in preeclampsia, as well as the damage to the lining of the digestive tract in autism, both of which are due to excess depletion of sulfated GAGs.

5. Autism, Nitric Oxide and Seizures

It has recently been demonstrated, through longitudinal studies spanning the ages from six months to 24 months, that autistic brains exhibit a pathology in the development of white matter, particularly the anterior thalamic radiation fibers connecting thalamic nuclei to the cerebral cortex [69]. In vitro studies have demonstrated that, when neurons, oligodendrocytes, and astrocytes are exposed to nitric oxide, the neurons are more susceptible to damage than the glial cells, and, furthermore, it is specifically the axons in the neurons (white matter) that suffer the most damage [70]. This suggests that excess NO exposure may be the source of damage to the white matter associated with autism. In vitro experiments with rat optic nerve have demonstrated that NO is highly toxic to axons, producing both degeneration and persistent swelling [71]. Such damage, which could explain the visual dysfunction associated with both preeclampsia and pernicious anemia, is irreversible, but is inhibited by the NO scavenger, oxyhemoglobin [70].

Given the hypothesis that autism is associated with excess nitric oxide synthesis, it thus becomes plausible that the white matter associated with the thalamus, which is situated in a region of the brain that is less protected than most other parts by the blood brain barrier, might be especially vulnerable to exposure to excess nitric oxide from the blood. It might also be the case that the endotoxins released into the blood across the leaky gut have gained access to this vulnerable part of the brain, triggering nitric oxide synthesis by nNOS in these cells as a consequence of a cytokine response to the endotoxin.

Preeclampsia can in rare cases evolve into eclampsia, with the key differentiating feature being the onset of seizures. Seizures are also associated with autism, particularly in early childhood [72]. During epileptic seizures, calcium-dependent activation of eNOS and nNOS results in an increase in NO formation [73,74]. In [75], it was argued that NO-dependent enhancement of synaptic transmission is a key promoting factor in seizure initiation. NO, in part through its conversion to peroxynitrite, also inhibits mitochondrial electron transport [76,77], which could contribute to the metabolic impairment seen in the hippocampus in association with epilepsy [78,79]. Metabolic impairment due to mitochondrial dysfunction is identified as a key factor in epileptic seizures [80] and has also been found in association with autism [81].

6. Necrosis and Autoimmune Reactions

Aluminum adjuvant (alum) plays an important role in vaccines by boosting adaptive immunity, and there are a number of hypotheses explaining probable mechanisms [82–85]. One explanation is the "depot effect" [82], whereby alum retains antigen at the injection site. A second explanation is that alum binds with antigen, producing insoluble alum-antigen aggregates that enhance immunogenicity [83]. A third idea, for which there is substantial evidence, is that it induces additional inflammatory agents, particularly nitric oxide, which cause cellular distress to the point of necrosis, mediated in part through the highly reactive peroxynitrite produced as a reaction product of NO with superoxide. Dying cells release uric acid as a catabolic product of purines in nucleotides [86], and uric acid is known to induce an immune response even in the absence of antigenic stimuli [87].

We predict that aluminum would induce excess nitric oxide, at the expense of sulfate, due to its strong ability to bind calmodulin and emulate the effect of calcium on NO synthesis by eNOS. Indeed, in [84], an exuberant production of both NO and uric acid was induced in mouse experiments, following injection of alum alone or alum plus antigen, measured at 4 days, 7 days, and 10 days post injection. Autism is associated with elevated levels of nitrate in the blood stream [49–52], and aluminum likely plays a role in the excess nitrate production. In the study on aluminum and uric acid mentioned previously [84], it was shown that, in addition to inducing uric acid synthesis, aluminum administered parenterally also led to a profusion of NO synthesis. Abnormally high levels of aluminum were recently found in hair analyses of over half of 34 autistic children analyzed [88].

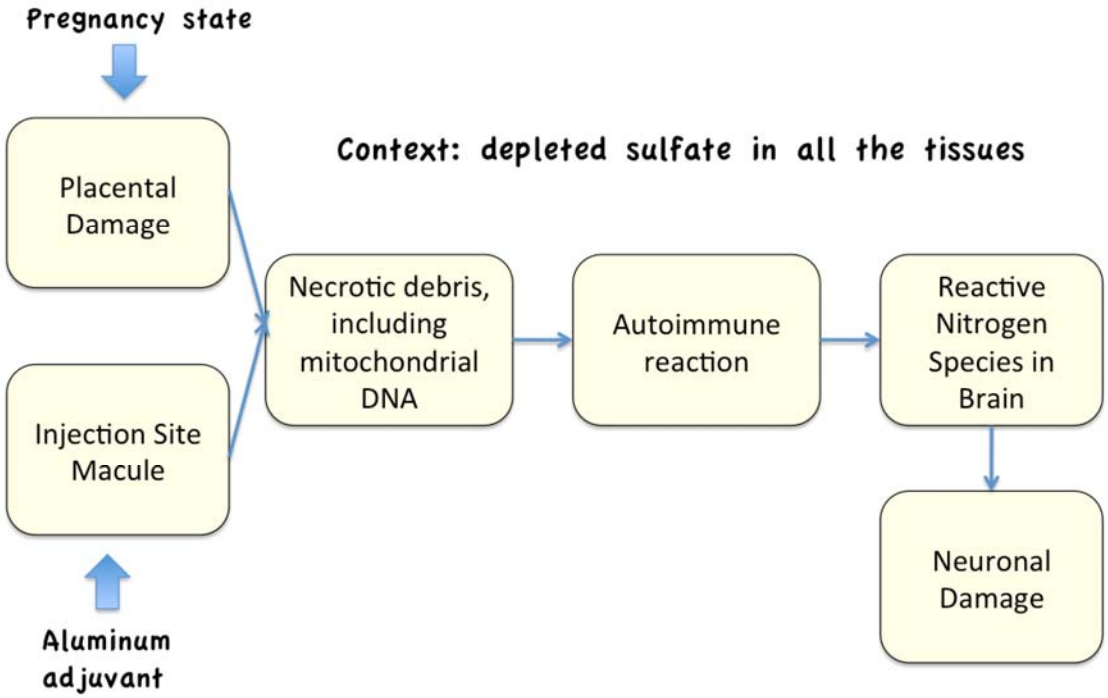
It is likely that the immune response triggered by necrotic cells is induced by mitochondrial DNA released into the surrounding tissues. Mitochondrial DNA resembles bacterial DNA due to evolutionarily conserved similarities between the two. An interesting hypothesis to explain preeclampsia [89] proposes that the observed elevated serum levels of mitochondrial DNA associated with preeclampsia may be due to excessive necrosis of trophoblast cells in the placenta, consequential to placental inflammation. This in turn stimulates TLR9 to mount an immune response, leading to vascular dysfunction and hypertension. These authors suggest that this effect may apply more generally to any circumstance associated with abnormal cell death, and thus it would fit well as a hypothesis for alum-mediated adverse reactions as well. TLR9 is known to be specifically responsive to bacterial DNA antigen [90]. Thus, the response to mitochondrial DNA may be due to strong homology with bacterial DNA. Children with inflammatory bowel disease may have been primed by prior exposure to bacterial DNA in the gut wall lining.

Recently, attention has been drawn to the aluminum in vaccines as a potential neurotoxin on par with mercury [91]. Aluminum has been identified as a factor in chronic fatigue syndrome [92], and it is known to have extensive negative impact on the brain [93–101], if it cannot be properly disposed of by the body. Patients with macrophagic myofasciitis often experience cognitive and memory deficits in addition to chronic fatigue. For these patients, vaccine-derived aluminum hydroxide can persist long-term in the brain in association with chronic cognitive dysfunction [95]. Recent experimental studies have confirmed that nanosized aluminum-containing particles are phagocytosed by macrophages and can be transported into the brain via the lymph nodes in a Trojan horse mechanism [97], and this mechanism was proposed to explain observed cognitive dysfunction in association with aluminum-induced macrophagic myofasciitis. In a mouse model, alum brain levels peak 2-3 days following injection of alum adjuvants [102].

Recently, an entire issue of the journal *Lupus* was devoted to the topic of Autoimmune Syndrome Induced by Adjuvants (ASIA) [96]. Aluminum adjuvant in vaccines was one of the key triggering factors considered to enhance symptoms of autoimmune diseases such as lupus, likely mediated by the effects describe above. It is well established that autism is associated with abnormal immune function [103], which we argue is initiated through dysbiosis in the gut consequential to sulfate depletion, but enhanced by aluminum adjuvants.

Figure 2 schematizes a proposed common mechanism mediated by either placental debris or debris from cells damaged by aluminum exposure at the injection site of a vaccine, leading to neuronal damage due to exuberant expression of nitric oxide, in the context of a prior severe deficiency in sulfate.

Figure 2. Schematic of the common pathway by which preeclampsia and an acute reaction to a vaccine may induce a similar outcome, in the context of severe sulfate deficiency.



7. The Hemolysis/Nitric Oxide Synthesis Cascade

RBCs play a critical role in the transport of oxygen and carbon dioxide: crucially, they shield the other elements in the blood from the strong oxidizing effects of oxyhemoglobin. When hemolysis occurs, hemoglobin enters the blood stream and the oxidizing potential of the exposed iron will further compromise the cell membranes of neighboring cells through the Fenton reaction, resulting in a dangerous cascade effect. Extreme vaccine adverse reactions exhibit a complex array of signs and symptoms which we argue can be explained by the cascade effect following upon the induction of hemolysis by aluminum, antigens, endotoxin, and nonionic surfactants such as Tween 80 and Triton 100. By "extreme adverse reaction," we mean outcomes such as death, life-threatening heart issues, loss of consciousness, seizures, narcolepsy, ischemic thrombohemorrhagic events, etc.

Hemolysis and nitric oxide synthesis can work together to produce nitrates in the blood stream, negatively charged ions that may partially compensate for the loss of sulfate in restoring zeta potential. This also constitutes a switch from kosmotropic to chaotropic anions, in an attempt to balance out the highly kosmotropic cation, aluminum [104]. However, the exuberant production of NO and release of oxyhemoglobin associated with a vaccine reaction is an out-of-control process with high risk of collateral damage.

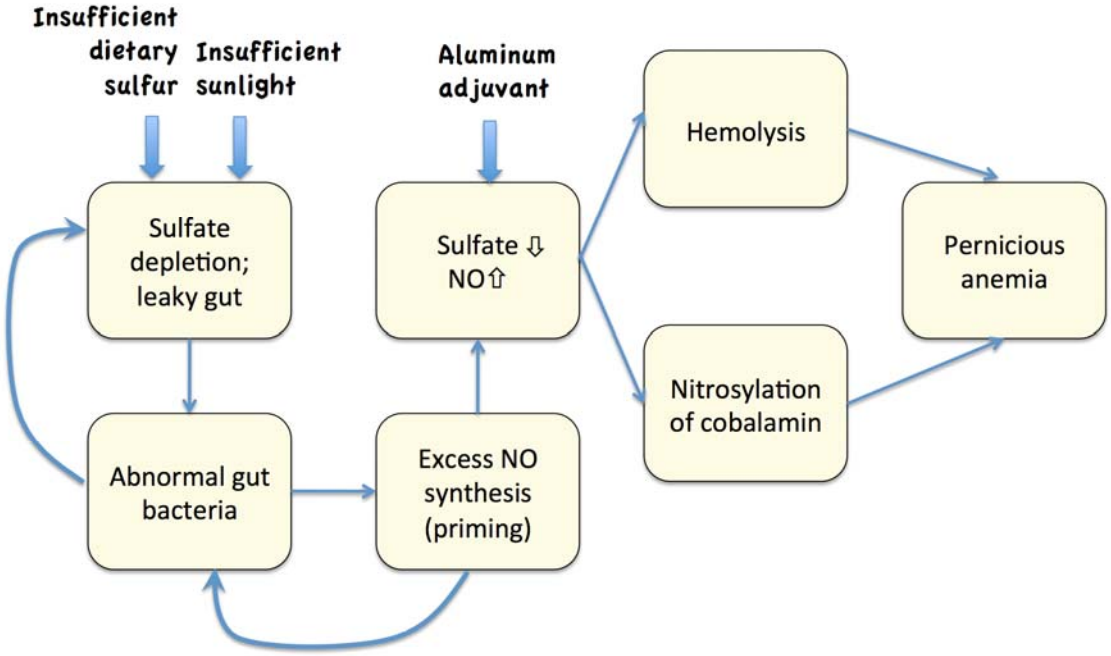
An excellent review of the clinical sequelae of hemolysis and excess synthesis of NO is provided in [105]. NO release will ultimately lead to a neutralization of the oxidizing potential of the free hemoglobin, through its conversion to methemoglobin. The reaction rate is enhanced 1,000-fold in free hemoglobin compared to hemoglobin sequestered inside RBCs [26]. Widespread hemolysis of RBCs ultimately results in a severely impaired ability to deliver oxygen to the tissues, and this can have life-threatening consequences. Macrophages come into play to ingest the accumulating neutralized methemoglobin and break it down via heme oxygenase 1 (HO1), producing carbon monoxide, free iron, and bilirubin from the oxyhemoglobin [30]. Endotoxin further enhances the production of heme oxygenase by macrophages.

There is a known association between excess bilirubin manifested as jaundice and autism. In a study conducted in Denmark, where sunlight availability in the winter months is scarce, infants with postnatal hyperbilirubinemia had nearly a four-fold increased risk to autism [106], and this effect was most pronounced for infants born in the winter months [107]. Treatment for jaundice involves sunlight or UV light therapy, which would lead to an increased production of cholesterol sulfate in the skin, thus ameliorating the deficit.

Another way in which the NO is likely to be neutralized is through reaction with cobalamin, leading to the formation of nitrosylcobalamin. In experiments with mice, it was demonstrated that mice overproducing NO as a result of exposure to endotoxin eliminated nitrosylcobalamin via the urine [108]. The authors concluded that cobalamin can bind NO and quench its effect. But this will result in a severe depletion of serum cobalamin, leading directly to pernicious anemia. Furthermore, cobalamin deficiency itself seems to provoke hemolysis, further compounding the problem [109]. NO's reaction product with superoxide, peroxynitrite, also reacts with cobalamin [110].

The reaction cascade is schematized in Figure 3. Importantly, our model predicts that a precondition associated with sulfate deficiency and chronic over-production of NO by eNOS leads to a disruption of gut bacteria and a heightened susceptibility to an anaphylactic reaction to an aluminum-adjuvanted vaccine.

Figure 3. Schematic of the reaction cascade associated with aluminum adjuvant exposure following a preexisting sulfate deficiency and gut dysbiosis, leading to pernicious anemia.



8. Experiments with VAERS

The Vaccine Adverse Event Reporting System (VAERS) is an on-line database, freely accessible, maintained by the CDC, where doctors and patients can report any notable adverse reactions to vaccinations. Data have been accumulating since 1990, and, to date, there are over 340,000 recorded events. This database is a valuable resource for researchers interested in finding associations among diverse signs and symptoms, which can then be compared against the research literature to identify probable biological explanations for the observed symptom complex. Many of the records also contain a detailed account of the temporal sequence of the development of individual symptoms; e.g., that pallor was followed by loss of consciousness, and nausea appeared ten minutes later. Many of the VAERS reports also include diagnostic lab-analyses reports and medical expert diagnoses.

We have previously developed a strategy for identifying salient symptoms in selected subsets of a drug side effect database, based on a tabulation of word and phrase frequencies. The methods, detailed in [111,112], utilize log likelihood ratios to compute the likelihood that a given distribution of a word would have occurred by chance, and to provide a *p*-value for the confidence level of the observed skewed distribution. Given a pre-defined ontology of features, we analyze which features are strongly associated with a certain data set, using a standard computer science methodology, the log-likelihood ratio algorithm [112]. In statistics, a likelihood ratio test is used to compare the fit of two models, one of which (the null model) is a special case of the other (the alternative model). The test is based on the likelihood ratio, which expresses how many times more likely the data are under one model than the other. This likelihood ratio, or equivalently its logarithm, can then be used to compute a *p*-value to decide whether to reject the null model in favor of the alternative model. The results are normally considered as statistically significant when the *p*-value is less than 0.05. All of the results reported in this paper show *p*-values less than 0.05, and most are substantially below that number.

Our methods first involve selection of a targeted set that contains a specified set of words or phrases, and then producing a comparison set sampled from the remainder of the records (those not containing these words or phrases). The sampling is done with a sample bias that preserves the age distribution of the target set. Both sets then contain equal numbers of records, distributed the same way by age, but with all instances of the targeted words or phrases occurring in the targeted set. A process is then used to assign groups of words or phrases to specific symptom classes in order to gain statistical power. For example, "abdominal pain," "abdominal discomfort," "abdominal distention" and "abdominal tenderness" formed a common class representing abdominal pain. Importantly, each record only records a "0" or "1" count of each event class. Thus, if multiple references to abdominal pain occur under various fields in a given record, a count of "1" is added to the tally. A record with no mentions of words in a particular class gets a "0" count.

In what follows, we will discuss results for three distinct targeted sets. The first set simply contains all records where the words "autism" or "autistic" are mentioned in any of the "symptoms" fields or under "lab data" or "history." This set allows us to detect reactions and conditions that are associated with autism. The second set was selected on the basis of a number of words and phrases known to express symptoms associated with anemia. The set of words and phrases we searched on are shown in Table 1. We also identified a set of symptoms associated with preeclampsia from PubMed Health [113], and examined the degree to which these symptoms were also over-represented in our anemia data set. The third set distinguishes between aluminum-containing and non-aluminum-containing vaccines, and we use it to determine whether aluminum enhances injection site reactions. Please note that we recognize that "symptom" is not quite the right terminology as an umbrella term for all the words we are studying. However, for brevity and convenience, we will adopt this word, consistent with its usage in VAERS.

Table 1. Words and phrases selected as representative of signs and symptoms of pernicious anemia.

Class	Alternates
diarrhoea	diarrhea
constipation	
fatigue	lethargy; lack of energy
light-headed	light headed; faint
appetite loss	loss of appetite; reduced appetite
pallor	pale skin
dyspnoea	dyspnea; hypoventilation; shortness of breath
swollen tongue	
depression	
loss of balance	gait disturbance
numbness	tingling; paresthesia; prickling

8.1. Common Symptoms Found in Association with Autism, Preeclampsia, and Anemia

The relationships among anaphylaxis, preeclampsia, anemia, hemolysis, and vaccine toxicity are neither immediately obvious nor intuitive. However, when viewed under the theory presented here, and with the statistical methodology described here to ferret out the relationship, an almost self-evident pattern can be discerned.

Results from our analyses, illustrated in Tables 2, 3 and 4, are quite illuminating. First of all, it is satisfying that anemia itself comes out with extremely high bias towards the anemia data set (p = 0.00074) even though it was not one of the search terms we indexed on. Table 2 shows all the words and phrases that were present in the autism dataset with a p-value less than 0.05. The corresponding p-value for these words and phrases in the anemia dataset are aligned on the right hand side of the table. It is striking that the anemia profile predicts autism itself with a p-value of 0.00066. It also strongly predicts all the autism-related words: anxiety, infection, eczema, asthma, premature, and pneumonia. In [5] we discussed how these conditions can all be explained by a deficiency in the supply of cholesterol sulfate.

Table 2. Signs and symptoms with a p-value < 0.05 in the autism data set, and the associated counts and p-values for the anemia data set (note: here and in subsequent tables, we use the word "symptom" as an umbrella term representing signs, symptoms, and conditions, consistent with the VAERS database usage of the term.).

Symptom	count: autism	count: control	p-value	count: anemia	count: control	p-value
anxiety	49	2	0.01	1720	728	6.78E-06
infection	54	6	0.01	1015	354	2.20E-05
autism	-	-	-	206	28	0.00066
ear infection	32	3	0.03	117	24	0.0053
eczema	18	0	0.04	134	44	0.0096
asthma	24	3	0.05	682	307	0.00054
premature	20	1	0.05	75	24	0.024
pneumonia	19	1	0.05	613	350	0.0035

Table 3 shows count distributions between the anemia data set and its control set for a set of signs, symptoms and conditions that are associated with preeclampsia according to PubMed. Once again, all of these symptoms are strongly prevalent in the anemia data set. For example, several symptoms related to eye problems—vision blurred, visual impairment, eye irritation, and sensitivity to light—are significantly more common in the anemia data set than in the comparison set.

Table 3. Signs and symptoms that occur with enhanced frequency in the anemia data set, compared with the control set, which are also known to be highly common in preeclampsia.

Symptoms	count: anemia	count: control	p-value
nausea	8817	3088	4.20E-14
headache	4495	1839	9.50E-10
abdominal pain	945	146	8.30E-07
anxiety	1720	728	6.70E-06
pulmonary	453	113	0.00016
vision blurred	420	129	0.00042
visual impairment	258	54	0.00069
facial swelling	288	162	0.015
eye irritation	119	50	0.022
sensitivity to light	70	11	0.011

The PubMed description of symptoms related to vision problems associated with preeclampsia states: "temporary loss of vision, sensations of flashing lights, auras, light sensitivity, spots, and blurry vision," which corresponds well with our detected symptoms related to the eyes. It has been reported that nitric oxide may be a key contributor to damage in glaucoma, resulting in neurodestruction of the optic nerve due to the generation of peroxynitrite as a product of the reaction of NO with superoxide [114,115]. Thus, excess NO synthesis may also be the key contributor to the vision symptoms associated with preeclampsia and anaphylaxis.

Finally, Table 4 shows a variety of other signs and symptoms that showed up with high significance in the anemia subset. We grouped these symptoms into five categories—brain and nervous system problems, heart problems, muscle problems, life-threatening events, and "other." Severe reactions like seizure, heart failure, heart rate irregularity, myalgia, dysphagia, paralysis, loss of consciousness and death are all significantly represented in the anemia data set.

Table 4. Other signs and symptoms that were identified as highly significantly over-represented in the anemia data set, besides those specifically associated with autism or preeclampsia.

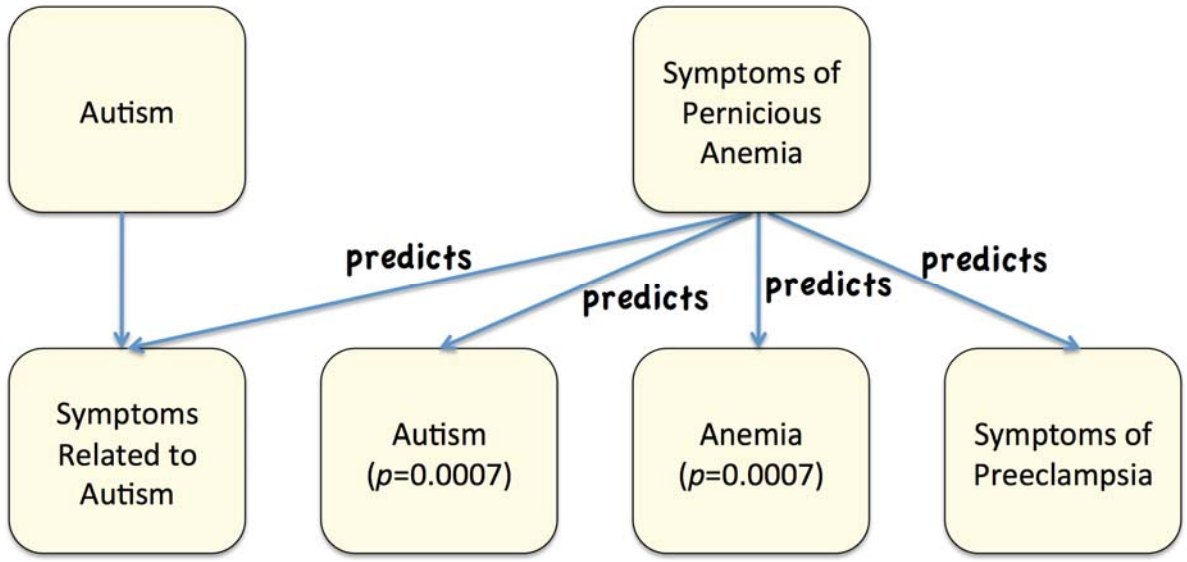
Symptom	**count: anemia**	**count: control**	***p*-value**
Brain and Nervous System Problems			
sleep disorder	534	140	0.000097
seizure	1144	632	0.00047
nerve injury	69	0	0.0042
disorientation	112	32	0.01
Heart Problems			
Symptom	**count: anemia**	**count: control**	***p*-value**
chest pain	1366	278	2.00E-07
heart rate irregular	963	279	1.00E-05
heart failure	64	8	0.011
Muscle Problems			
Symptom	**count: anemia**	**count: control**	***p*-value**
myalgia	981	416	0.000096
paralysis	384	71	0.00013
dysphagia	353	96	0.0005
Life Threatening Conditions			
Symptom	**count: anemia**	**count: control**	***p*-value**
loss of consciousness	832	447	0.001
death	180	74	0.01
Other			
Symptom	**count: anemia**	**count: control**	***p*-value**
swollen tongue	1116	322	0.0000044
pulmonary	453	113	0.00016
red blood cell	361	109	0.00065
drooling/foam	123	32	0.007
lymph node pain	219	107	0.013

Due to their high oxygen demand, the skeletal muscles and nervous system are especially susceptible to damage from anoxia, which is a direct consequence of the cascade triggered by overabundant synthesis of nitric oxide and excess hemolysis of RBCs. Responses such as loss of consciousness and paralysis are likely a direct consequence of a signaling cascade that shuts down oxygen supply, for example through pulmonary hypertension, in order to prevent further damage to lipids in cell membranes from exposure to oxidized iron and peroxynitrite. NO plays an essential role as a mediator of neuronal death during anoxia [116].

We believe that the effects of the cascade launched by a switch from sulfate to NO synthesis by eNOS is especially damaging to newborns and infants. Infants are especially susceptible to cyanosis due to exposure to nitrates and nitrites in well water [117], which are not however damaging to older children. Furthermore, administration of ethyl nitrite to infants has been demonstrated to induce acute methemoglobinemia and anoxia, resulting in sudden death [118], thus suggesting that the NO synthesized in the acute response of a severe adverse reaction to vaccines can be fatal.

The results of our studies are summarized in Figure 4. The alignments among symptom sets uncovered automatically through these statistical analyses are remarkable. Additional symptoms derived from a database subset obtained by filtering on the symptom set associated with anemia predict not only anemia itself, but also autism, a symptom set intersecting with the set produced from the autism dataset, and a symptom set that well describes preeclampsia, including many of the unusual effects on vision.

Figure 4. Schematic of discoveries arising from our studies of selected subsets of the VAERS database.



8.2. Effects of Aluminum in Vaccines

Table 5 quantifies the effects of aluminum in vaccines, independent of other factors such as antigen and LPS, in association with symptoms of anemia. To produce this table, we separated the anemia data set into two subsets: one representing vaccines known to contain aluminum and the other representing those known *not* to contain aluminum. We discarded records associated with the vaccines, HiB-titer,

Anthrax, and Rabies, because the literature is ambiguous regarding their aluminum content. The table shows only those symptoms with a p-value < 0.02. "Sleep disorder", "fatigue", "joint pain", "depression", "pain", "infection" and "seizure" all had a significant count bias towards the aluminum-containing subset. We feel that this result is highly intriguing, particularly the relationship with seizures. Due to its enhanced binding to calmodulin, we would expect aluminum to further promote nitric oxide exposure in the brain, and subsequent seizures. Future work will involve research to better explain the association of aluminum with these symptoms, many of which suggest involvement of muscles and neurons.

Table 5. Signs and symptoms that were highly over-represented in the reports involving aluminum-containing vaccines (p-value < 0.02) compared to the non-aluminum containing vaccines, obtained by partitioning the anemia data set into two distinct subsets.

Symptom	count: aluminum	count: not aluminum	p-value
sleep disorder	224	86	0.0051
fatigue	2262	1817	0.006
joint pain	495	291	0.0066
depression	319	175	0.011
pain	2008	1658	0.013
infection	329	192	0.014
seizure	536	369	0.018

In order to determine whether aluminum might induce an increased reaction at the injection site, we collected two age-matched datasets drawn from the entire VAERS database, each containing nearly 150,000 records, where one set concerned only non-aluminum containing vaccines and the other concerned only aluminum-containing vaccines. The two sets were matched for age distribution. We selected a set of phrases representing redness or discoloration at the injection site, such as "injection site macule" or "vaccination site erythema" and a set of phrases representing "injection site reaction" such as "local swelling" or "vaccination site inflammation". These two classes were over-represented in the aluminum-containing set with p-values of 0.00000023 and 0.000017 respectively. This aligns with the hypothesis that aluminum achieves its adjuvant effects in part by stimulating a stronger immune reaction at the injection site, either by retaining the antigen complex in the site, by inducing profuse NO synthesis by eNOS, or by causing an enhanced immune response due to necrosis of localized tissues. This therefore also supports the idea that cell necrosis following aluminum exposure could lead to an autoimmune reaction due to mimicry of bacterial DNA by mitochondrial DNA, as previously discussed.

No vaccine has been specifically approved by the FDA for use during pregnancy in the United States, yet vaccines are being given to pregnant women. Gardasil, in particular, is of grave concern, as it is given specifically to women in their reproductive years, and it contains aluminum hydroxide [119,120]. It has been demonstrated that even ultra-low doses of endotoxin infused into pregnant rats mimics the predominant features of preeclampsia [121]. Since preeclampsia can lead to stillbirths, we investigated, using our log likelihood tools, the relative risk to spontaneous abortion in Gardasil records from the VAERS database compared to age-matched controls. Our analysis showed 200 spontaneous abortions

or stillbirths for Gardasil as against only 18 for the sampled age-matched control database ($p = 0.00044$). Even if 18 is doubled to account for the gender bias, this is still a highly significant result.

9. Discussion

In this paper, we have developed an argument supporting a link among preeclampsia, autism, pernicious anemia, and anaphylactic shock, and have proposed that all of these conditions arise due to a deficiency in the supply of cholesterol sulfate to stabilize the colloidal suspension system of the blood. In a hypothesis put forth in a previous paper [5], we argued that the cholesterol sulfate supply is normally maintained by eNOS, acting in the epidermis, the endothelium, and the suspended blood cells, and that it requires the substrates cholesterol and sulfur, as well as sunlight, to provide the necessary activation energy for the reaction. Because cholesterol sulfate is the major source of both cholesterol and sulfate to a fetus, a pregnant woman can develop a major deficiency towards the end of the pregnancy. The association of preeclampsia with proteinuria reflects a raid on the sulfate in the GAGs in the glomeruli of the kidneys, to supply the fetus.

Through careful study of the literature on autism, we have developed the hypothesis that excess synthesis of NO by the endothelium characterizes this condition, and explains the damage to axons in the brain associated with impaired cognitive abilities. We propose a feedback mechanism by which an overgrowth of *Desulfovibrio* in the gut leads to a destruction of the gut barrier through sulfate depletion. This in turn allows the endotoxins released by *Desulfovibrio* to enter the bloodstream, triggering an immune reaction and subsequent increase in NO synthesis, completing the feedback cycle. The excess NO synthesis by eNOS is necessarily associated with an impoverished synthesis of sulfate, as eNOS, according to our hypothesis, is a dual-purpose enzyme, which switches between nitric oxide and sulfate depending on the environment. Aluminum-containing vaccines are problematic, not only because aluminum causes eNOS to switch from sulfate to nitric oxide production, but also because aluminum can induce necrosis of tissues at the vaccination site, emulating the process of tissue damage to the placenta in preeclampsia. In both cases, the release of mitochondrial DNA into the blood stream may trigger an acute autoimmune reaction.

This paper focuses on the sequence of events following an anaphylactic-shock-like reaction to vaccination, and shows how these symptoms share a common basis with symptoms of preeclampsia, autism, and pernicious anemia. The aluminum, present in many vaccines, such as hepatitis A and B, DTaP, and Gardasil, is a major contributor to the crisis, through its ability to bind and inactivate available sulfate. It also induces a switch from sulfate to nitric oxide synthesis on the part of eNOS, acting as a potent analog to calcium. Aluminum damage to cells at the reaction site can induce necrosis, resulting in the release of uric acid and mitochondrial DNA into the vasculature, paralleling the autoimmune reaction to a damaged placenta.

The pathological response is initiated in the vascular system. An abundant and near instantaneous synthesis of NO results in an immediate precipitous drop in blood pressure. A reaction cascade triggers the release of coagulation factors, resulting in the widespread release of a fibrin matrix, which slices open trapped RBCs, liberating their contents into the blood serum. Eventually the released oxyhemoglobin will quench the excess NO, forming, irreversibly, methemoglobin and nitrate. Cobalamin also quenches NO, while simultaneously disabling cobalamin's ability to function in its

catalytic roles. This leads to a severe cobalamin deficiency and the resulting symptoms of pernicious anemia [122].

Our studies of the signs and symptoms associated with anemia in the VAERS database revealed a concomitant symptom complex that is well explained by the above cascade of events. Furthermore, the data set associated with the symptoms of pernicious anemia also yielded a strong signal for all of the symptoms that are associated with autism, as well as autism itself. This link between anemia and autism is not intuitive—it is established based on statistical analyses of the symptoms found in the US CDC VAERS database, notwithstanding its flaws—underreporting and selection bias.

In a previous paper [5], we explained how several signs and symptoms found in association with autism—eczema, asthma, premature birth, and digestive disorders—could all be attributed to a deficiency in the supply of cholesterol sulfate. Thus, the increased susceptibility to a serious vaccine reaction associated with autism in the VAERS database is likely tied to increased vulnerability to a crisis in colloidal stability in the blood induced by the additional load of the vaccine-supplied toxins to an already vulnerable blood system.

Aluminum-containing vaccines, compared to non-aluminum-containing vaccines, show an increased incidence of sleep disorder, depression, and seizures, in association with the anemia symptom complex. These are all potential indicators of penetration of the aluminum into the brain, as a direct consequence of an inability to properly dispose of the aluminum due to the sulfate deficiency. Aluminum's negative impact on brain function is well established [93–101].

Finally, we argue that preeclampsia, itself a strong predictor of future autism in the fetus, is a manifestation of the same reaction cascade associated with an extreme adverse reaction to vaccines. The cholesterol sulfate depletion, in this case, is a direct consequence of the enhanced needs for this critical nutrient by the developing fetus, in the context of an existing nutritional deficiency in the mother. An aluminum-containing vaccine, administered late in pregnancy to a woman already predisposed to preeclampsia, will likely precipitate an acute event, leading to miscarriage or stillbirth, a concept that is supported by an analysis of spontaneous abortion rates for Gardasil in the VAERS database.

10. Conclusions

We have proposed in this paper a novel hypothesis for the underlying pathology that links preeclampsia, autism, pernicious anemia and extreme adverse reactions to vaccines. In all cases, we suggest that a deficiency in the supply of cholesterol sulfate to the tissues creates a vulnerability to environmental toxins, which precipitates the pathological response. Excess NO synthesis by nitric oxide synthases provokes a cascade response with devastating consequences. Severe cobalamin depletion due to its reaction with NO and NO metabolites, along with extensive hemolysis of red blood cells, manifests as symptoms of classic pernicious anemia, and the sequelae can lead to death. We have used statistical analysis of the VAERS database to support our hypothesis. Further research will be needed to either confirm or disprove our hypothesis. If it is valid, then we propose that an effective prevention program for this pathology might simply require enhanced dietary intake of sulfur-containing amino acids and greater sun exposure to the skin. We would also recommend the elimination of aluminum as an adjuvant in vaccines.

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