Endoplasmic Reticulum Hyperstress from Aluminum and Mercury Exposures Drives Autoimmune Diseases of Unknown Origin with a Genetic Risk and Food Allergies

James Lyons-Weiler

Institute for Pure and Applied Knowledge
Pittsburgh, PA

Abstract

Aluminum and mercury both cause Endoplasmic Reticulum Stress (ER Stress). When combined with genetic variations that lead to protein folding issues in the ER, these metals contribute to ER Hyperstress, including ER Overload and apoptosis. The basic mechanistic exposure of otherwise cryptic potential self-antigens via ER Hyperstress induced cell death leads to immunologic exposure to unusual post-translationally modified proteins. Interrupted protein production means partial (incomplete) acetylation, lipidation, citrullination, and glycosylation. This mode of production of near-self antigen sources is now recognized as crucial for specific autoantibody recognition in autoimmune diseases. Prototypical autoimmune disorders (ADs) like rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) have a genetic risk, exhibit female predominance, presence of autoantibodies and response to T-cell or B-cell-targeted therapies. Mechanistic evidence exists that shows that they also, without fail, involve pathophysiological outcomes of the Unfolded Protein Response (UPR). Animal models routinely employ injections of aluminum hydroxide as the environmental causal factor to reproduce the symptoms of a surprising number of ADs seen in humans. Human studies have linked aluminum exposures to the onset of ADs, and ER Stress and the Unfolded Protein Response (UPR) both are observed across many ADs in humans. The assumption that low doses of aluminum are not toxic now appears to be incorrect. The literature of autoimmune disorder pathophysiology strongly supports the ER Hyperstress model of autoimmunity, in which generic, otherwise harmless mutations that evoke the UPR, usually to a non-pathophysiological conclusion, contribute to ER Stress that is severely compounded by exposures to metals, including aluminum and mercury. Food allergies also involve ER Hyperstress and are inducible in animals with aluminum hydroxide injections. In a comparison of the protein intrinsic disorder (PID) of proteins known to carry mutations that confer genetic risk of autoimmune disorders to general proteins in the human proteome, the PID of autoimmune-related proteins was significantly lower than that of general proteins (average PID AID vs. PID null 8.58 vs. 16.165, $p=0.0003$). This result suggests that proteins involved in ADs cannot tolerate non-synonymous substitutions that change folding energies – and it suggests that genetic risk of autoimmunity aided by immune activation will have a cryptic component in which proteins unrelated to the functional aspects of proteins elicit an autoimmune attack. It is predicted that, due to ER Hyperstress and the direct cellular toxicity of metals, autoimmune disorders will also have a component of acquired cellular detoxification deficiency disorder (ACDD), consistent with the oft-reported comorbidity between autoimmune/autoinflammatory disorders and multiple chemical sensitivity. ACDD is a disorder that makes causality assessment challenging but that can be alleviated by aluminum chelation, pointing to ER stress as a shared root cause leading to toxin accumulation. Direct genetic risk exists due to variation in genes involved in detoxification (e.g., HLA and CYP genes), but more generic risk likely exists due to conformational differences in proteins that challenge the unfolded protein response. These realizations point to the importance of mutations in proteins associated with autoimmune disorders cognizant of (upweighting) low protein intrinsic disorder as potential biomarkers of the likely occurrence of autoimmunity following environmental exposures that can trigger ER stress and the UPR. If done well, such mutations may be useful in predicting the specific type of autoimmunity that could occur if exposed to aluminum and mercury containing vaccines and other compounds known to elicit ER stress, such as glyphosate. Overwhelming, convincing evidence supports a genetic susceptibility to aluminum and mercury exposures exist in humans. It must be accepted that some percentage of the population cannot tolerate aluminum exposures as well as others and exposure to aluminum and mercury will caused them to fall into a

cascade of events caused by ER Hyperstress. Medicine must shift away from a culture that turns a blind eye to the evidence in support of the fact that AD, NDs and food allergies are caused, in part, by aluminum exposures. Phased biomarker development studies will help Identify the genetic minorities at increased risk of autoimmunity from aluminum and mercury exposure that lead to ER Hyperstress. All future studies of the association of vaccines with autoimmune disorders should focus on the prevalence of autoimmune disorders in vaccinated individuals with known high-risk genotypes compared to individuals without high-risk genotypes, no evidence of familial risk of autoimmunity, and no mutations in the AD-related genes. The entirety of the evidence in the literature supports the clinical existence of ASIA, and ER Hyperstress is a plausible biological mechanism by which genetic variation and injected forms of metals interact to cause autoimmune/autoinflammatory condition in some people.

Introduction

The primary shared characteristics of autoimmune disorders are infiltration of eosinophils, neutrophils, macrophages, activated mast cells, and T helper cell type 1 (Th1) cells, Th17 increase, bias in and release of a diversity of cytokines, intracellular protein aggregates and inclusion bodies, autophagy, and poor understanding of pathogenic mechanisms of the disease. Autoimmune disorders are variably IgE-mediated or IgG and complement-mediated, and delayed-onset T cell-mediated systemic reaction are seen, with differences both within and among autoimmune conditions. Alterations in Th1/Th2 cytokine levels accompany serious adverse events from vaccines[1] (Rock et al., 2004). Th17 cells are pro-inflammatory subset whereas Treg cells reflect reductions in inflammation (Noack and Miossec, 2014)[2]. The Th17/Treg balance has importance in the control of immunity mediated by Th17 cells. Autoimmunity also involves shifts in the T17/Treg balance (Naock and Miossec et al., 2014)[2]. A study of pro-inflammatory Th17 cells found that the cytokine IL10 is reduced in multiple sclerosis (Hu et al., 2017)[3]. Hashimoto (2017)[4] reported that in rheumatoid arthritis, inflammation prevents T cells from regulating T17 cells. T-cell imbalances favoring Th1, Th2 and Th17 cells was found in Hashimoto's Thyroiditis (Safdari et al., 2017)[5]. Adjuvant-induced arthritis in mice is attenuated by Ras signaling inhibitors (Zayoud et al., 2017)[6] including farnesylthiosalicylic acid (Aizman et al., 2014)[7]. A role of aluminum adjuvants in impairing regulatory T cell function is suspected, and genetic mechanisms have been explored (Terhune and Deth, 2014)[8]. The effect of immunomodulatory treatments varies with each patient's immunogenic profile, and multiple contributors to the onset and exacerbation of autoimmunity are known.

Various specific mechanisms of autoimmunity are now widely recognized, and can involve pathogen proteins either during infection or from vaccination:

Molecular Mimicry. A patient is exposed to an antigen from a pathogen or nonpathogen (such as the yeast in come vaccines) which carries elements that are similar enough in amino acid sequence or structure to self-antigen that the alloantigen acts as a self-'mimic'. In molecular mimicry, T or B cells activated in response to the pathogen also happen to be cross-reactive to self proteins. This can lead to direct autoimmune damage and false-positive "friendly-fire" activation of the immune system (via, for example, cytokine signaling due to the release of cytokines as result of autoimmune attacks on self proteins, cells, and tissues).

Epitope Spreading. Antigens from pathogens can also cause autoimmune disease via epitope spreading. In epitope spreading, damage to self-tissue occurs due either to the immune response to tissue infected by a persisting pathogen, or direct lysis of healthy cells by the pathogen. Antigen-presenting cells (APCs) take up antigens released from damaged tissue, initiating a self-specific immune response.

Bystander Activation. In this model, an indirect or non-specific activation of autoimmune cells is caused by the generally inflammatory environment that results from infection. The non-specific activation of one part of the immune system leads to the activation of other parts.

Cryptic Antigens. Foreign antigens can lead to autoimmunity via the activation of immunity to antigens that are not usually dominant – they are instead normally invisible to the immune system. It is generally described as an

increase in “subdominant” antigens, and is usually attributed, like bystander activation, to the inflammatory environment that arises after infection. The involvement of cryptic antigens is considered likely when one observes increased protease production, and differential processing of released self-epitopes by APCs.

Of these mechanisms, the most discussed is molecular mimicry. Cross-reactive antibodies between foreign (e.g., viral, bacterial) epitopes and human proteins can occur either via infection (e.g., Guillan Barre Syndrome, or GBS from C. jejuni;[9] Nachamkin et al., 1998), or artificial immunization (e.g., narcolepsy due to similarity between human orexin protein and epitopes in the H1N1 swine flu vaccine; Ahmed et al., 2015[10]). The evidence of autoimmunity due to vaccination is quickly gaining increasing support. In 2017, The National Vaccine Compensation Program added GBS to the list of injuries recognized by the National Vaccine Compensation Program (HHS, 2017)[11]. The syndrome was first noted after the universal vaccination program against swine flu in 1976 (Schonberger et al., 1979)[12].

A general syndrome called ASIA (Schoenfeld et al. 2013)[13] now has mounting evidence as a contributor to autoimmunity/autoinflammatory conditions in some patients, and has been described as encompassing numerous autoimmune disorders of otherwise mysterious origin, including systemic lupus erythematosus (Bragazzi et al., 2017[14]; undifferentiated connective tissue disease (Perricone and Schoenfeld, 2013)[15], Hashimoto's thyroiditis and/or subacute thyroiditis (Watad et al., 2017)[16]; antiphospholipid syndrome (APS; (Watad et al., 2017)[16]; Sjögren’s Syndrome (Colafrancesco et al., 2014; 2016)[17,18]; Postural Orthostatic Tachycardia with chronic fatique (Tomljenovic et al., 2014)[19], and primary ovarian failure following HPV vaccination (Colafrancesco et al., 2013)[20]. Within the specific diagnosed autoimmune conditions, arthralgia, myalgia, and chronic fatigue symptoms predominate (Watad et al., 2018)[21].

The clinical recognition of ASIA is expanding (Cheng et al., 2016[22-25]; Anaya et al., 2016; Morris et al., 2017; Vadalà et al., 2017) and a registry has been established (Watad et al., 2018[21]). There is overwhelming evidence from animal and human studies that - for some individuals - vaccine-level exposures to injected forms of aluminum is unsafe (see Segal et al., 2017[26] for a recent review). Understanding autoimmunity in humans from adjuvants is impossible without due consideration of the role of genetic susceptibility, because not all humans develop autoimmune disorders and many who are vaccinated do not.

It was recently shown that the amount of aluminum in vaccines is not based on relevant safety data from dose escalation studies of vaccine-type aluminum into rat or mice pups, and that the doses used in vaccines are well beyond acute toxicity levels at certain points in the CDC’s recommended pediatric schedule (Lyons-Weiler and Ricketson, 2018 [27]; Masson et al. 2018[28]; Miller, 2016[29]). Infants acutely receive more biologically available aluminum from vaccines during the schedule than from dietary sources, and that the basis of our understanding of tissue fates, clearance, and accumulation is fundamentally flawed (Lyons-Weiler and Ricketson, 2018 [27]). Numerous calls have been made for consideration of alternative adjuvants (Masson et al., 2017[28]; Crépeaux et al., 2017[36]; Lyons-Weiler and Ricketson, 2018 [27-29]) and for the cessation or reduction of the use of aluminum salts in vaccines (Morris et al., 2017[24]).

While the general idea that aluminum adjuvants, or other adjuvants may induce autoimmunity conditions, the mechanism of autoimmune action have been broadly elucidated, a precise description of why risk is higher in some individual than others – that is, the manifestation of a genetic x environment interaction – has not been provided. Here, I review the evidence that aluminum hydroxide from vaccines (and thimerosal in some flu vaccines), and, by implication from published evidence aluminum from other sources as well - may be root causes contributing to the epidemic of diseases of mysterious origin in humans. As in ASD (Lyons-Weiler, 2018[30]), the literature very strongly supports ER Hyperstress as an important direct root causal mechanism for autoimmunity syndrome induced by adjuvants leading to other manifestations of autoimmunity. The main conclusion of this review is that the evidence of neuroimmune toxicity of aluminum-types found in vaccines is overwhelming, and that the specific

genetic x environmental interaction needed to explain why only some individuals appear hypersensitive to aluminum – and other toxins – is found in the ER Hyperstress model[30].

Aluminum Adjuvanticity and Toxicity

The cellular effects of aluminum are myriad and diverse. At high doses, aluminum can inhibit the formation of α-ketoglutarate and can cause toxic levels of ammonia in tissues. Aluminum can also bond to phosphorylated bases on DNA, disrupting protein synthesis and catabolism. It has long been known that brain cells, including neurons and glial cells, are susceptible to long-term accumulation of aluminum. When aluminum bonds to phosphate, it can inhibit normal catabolism of neuronal filaments in the central nervous system (Kawahara et al., 2011[31]). Among the most important of these effects include disturbance of normal protein folding, and initiation of the Unfolded Protein Response due to aluminum-induced ER stress (Aremu et al., 2011; Rizvi et al., 2016; Rizvi et al., 2016[32-34]).

Aluminum adjuvants induce immune responses that vary with type, and location of administration. When aluminum overstresses the ER, cell contents are released from dying cells, including dsDNAs, partially folded proteins, cytokines, and in tissues of the central nervous system, excitotoxins such as glutamate. The cell contents usually initiate a T helper type 2 (Th2) responses, IgE isotype switching and peripheral effector responses, through Irf3-dependent mechanisms (Marichal et al., 2011[35]). Exposure locations, dosage amounts, and specific forms injected determine the degree of localized vs. systemic short-term exposure. Intramuscular injections lead to the formation of granulomas, with slow the release of aluminum over time. Surprisingly, chronic exposures to low doses of aluminum appear to induce higher short-term toxicity by escaping tissue sequestration responses (Crépeaux et al. 2017[36]).

A systematic review of the dosing of aluminum hydroxide in animal studies that routinely and reliably induce the symptoms of autoimmune conditions reveals that the dosing used ranges from 5 to 10,000 times that typically used in vaccines (Table 1). Many of the studies used protocols with repeated injections over a period of weeks. Not all studies reported sufficient detail to be included. Notable, studies that employed mouse models with genetic risk used the lowest amount of aluminum (Table 1). For reference, in the CDC schedule, infants receive seven doses of aluminum-containing vaccines by the second month, totaling 1445 mcg aluminum injected, and sixteen doses for a total of 4925 mcg aluminum injected by 18 months of age.

Table 1. Dosing of aluminum hydroxide used to induce autoimmune symptoms in animal models for pharmacological treatment studies relative to human dosing in vaccines (last column)

Citation (et al.)	Condition	Animal	bw (g)*	bw (kg)	AL dose (mcg)	AL dose (mg)	mcg/kg	mg/kg	human max exposure** (mcg/kg)	x human max exposure
Zhu[37]	Atherosclerosis	apoE null C57BL/6 mice	20	0.02	25	0.025	1250	1.25	230	5
Zhu[37]	Atherosclerosis	LDLR null C57BL/6 mice	20	0.02	25	0.025	1250	1.25	230	5
Kelly-Scumpia [38]	Lupus	C57bl/6 mice	20	0.02	50	0.05	2500	2.50	230	11
Yasar[39]	Allergic rhinitis	rats	250	0.25	1000	1	4000	4.00	230	17
Elsakkar[40]	Asthma	CD1 mice (male)	25	0.025	292	0.292	11680	11.68	230	51
Elsakkar[40]	Asthma	CD1 mice (male)	20	0.02	292	0.292	14600	14.60	230	63
Qi[41]	CP/CPPS	Wistar rats	250	0.25	6250	1.25	25000	5.00	230	109
Brandt[42]	GI allergy, asthma	BALB/c	20	0.02	1000	1	50000	50.00	230	217
Qi[41]	CP/CPPS	Wistar rats	250	0.25	12500	2.5	50000	10.00	230	217
Agmon-Levin[43]	Lupus	NZBWF1 mice (female)	38	0.038	2000	40	52631	1052.63	230	229
Yang[44]	Rhinitis	SD rats	400	0.4	30000	30	75000	75.00	230	326
Xi[45]	Rhinitis	BALB/c mice (female)	24	0.024	5000	5	208333	208.33	230	906
Xi[45]	Rhinitis	BALB/c mice (female)	17	0.017	5000	5	294117	294.12	230	1279
Sagawa[46]	Arthritis	BALB/c mice (female)	20	0.02	40000	40	2000000	2000.00	230	8696
Sagawa[46]	Arthritis	DBA/1 mice (male)	18	0.018	40000	40	2222222	2222.22	230	9662

** estimated at 1225 mcg AL/5.326 kg (median body weight @ 2 mos). Meant to be typical.

ER Hyperstress: How Metals and Genetic Variations Collide

Unfortunately, the safety of pediatric dosing of aluminum in vaccines and in the CDC pediatric vaccine schedule is not well-founded (Lyons-Weiler and Ricketson, 2018 [27]; Masson et al. 2018[28]). Aluminum causes ER stress (Aremu et al., 2011; Rizvi et al., 2016; Rizvi et al., 2016[32-34]), which introduces problems with resolving challenges in protein folding protein and maintaining cellular homeostasis, and it also directly causes mitopathies (Han et al., 2013; [47]). The combined effects make cellular detoxification challenging. This likely explains why some individuals tend to accumulate toxins, including aluminum, faster than others, and may explain genetic susceptibility to aluminum toxicity in specific tissues. Part of this susceptibility is the role of non-synonymous substitutions that cause problems with ER-mediated protein folding, leading to genetically induced UPR, which generally resolves the issue without incident. When the ER stress caused by these proteins is compounded by metal-induced ER stress, this is called ER Hyperstress (Lyons-Weiler, 2018[30]), and it appears to represent an exact genetic X environment interaction point that explains why some individuals are more susceptible to serious adverse events from vaccines, and why the genetic variation related to that risk may not appear to be functionally related to the specific condition thought to be caused by vaccination.

The Unfolded Protein Response

The unfolded protein response (UPR) is a highly conserved, adaptive signaling pathway activated by accumulation of misfolded proteins within the endoplasmic reticulum (ER). The ER is mainly responsible for the translational biosynthesis, cellular trafficking, and posttranslational modification of proteins. These processes in the ER ensure timely and proper delivery and release of folded proteins via secretory pathways. Improperly or folded or modified proteins are degraded via ER-associated degradation (ERAD), or autophagy. Three transmembrane ER stress sensor proteins monitor and signal upon ER stress: inositol-requiring protein 1α (IRE1α), protein kinase RNA-like endoplasmic reticulum kinase (PERK) and activating transcription factor 6α (ATF6α). When unfolded proteins build up due to ER stress, the UPR either resolves the issue via a slowdown in transcription via ATF6α expression, or translational control via PERK and IRE1 α. When these fail, cellular apoptosis is initiated, and cellular contents are dumped into the extracellular matrix, initiating the cascade of signals due to cellular injury[Sano and Reed, 2013;48].

Proteins with high intrinsic disorder require assistance in folding within the lumen of the ER (Tovo-Rodrigues et al., 2016[49]). When mutations lead to abnormally folded proteins, they can accumulate in the ER, resulting in the induction of the unfolded protein response (UPR). The issue can be resolved via a rate reduction in protein production. For serious problems, proper degradation by the proteasome, or chaperoning out of the cell is usually possible. However, the exposure of cells to environmental toxins that induce ER stress can combine with the ER stress induced by unfolded proteins, leading to severe endoplasmic reticulum stress, and to cell death by apoptosis. These factors and ER Hyperstress have been implicated in ASD, specifically evidenced by the role of mutation that lead to generic non-synonymous substitutions contributing to ER Stress, compounded by ER Stress from environmental toxins. Injected and ingested doses of aluminum and synergistic toxicity with mercury from thimerosal are likely root-cause culprits for susceptible individuals (Rose et al., 2015[50]).

Eupedia[51] is a searchable online resource that stores information on genes and mutations associated with autoimmune diseases, and it includes entries for various autoimmune disorders, including allergies, Ankylosing Spondylitis, Celiac disease, Crohn's disease, Grave's disease, Intestinal Bowel Disorder, Psoriasis, Rheumatoid Arthritis, Sjögren's syndrome, SLE, Type I Diabetes, Type II Diabetes, and Ulcerative colitis (https://www.eupedia.com/genetics/autoimmune_diseases_snp.shtml). As a test of the potential contribution of diffuse genetic risk due to non-synonymous changes in proteins that are already intrinsically disordered, the protein intrinsic disorder (PID) of proteins encoded by genes known to carry mutations that confer genetic risk of autoimmune disorders to randomly selected general proteins in the human proteome was compared to the PID of

general proteins (N=200). PID values were retrieved from Mobidb (http://mobidb.bio.unipd.it/search). The average PID of AID-associated proteins vs. PID null was 8.58 vs. 16.165, p=0.0003).

This opportunistic result suggests that proteins involved in autoimmune disorders cannot tolerate non-synonymous substitutions that change folding energies. It also suggests that family-specific genetic risk of autoimmunity aided or exacerbated by immune activation from infections or vaccination will have a cryptic component in which proteins unrelated to the functional aspects of proteins can elicit an autoimmune attack.

When these toxins are metals like aluminum and mercury, the metals that are released upon cell death can be taken up by other, nearby cells. Double-stranded DNA (dsDNA) is also released upon apoptosis, activating cyclic GMP-AMP synthase, contributing to lethal autoimmunity in a SLE mouse model (Gao et al., 2015[52]). In conditions in which ER Hyperstress is sublethal to the cell, environmental toxins such as aluminum and mercury (and others) can also contribute to direct damage to mitochondria and the Golgi system, impairment of cellular detoxification, and a run-away accumulation of additional neotoxins in a vicious cycle of causality. By directly interfering with phosphate and ATP metabolism, aluminum can further impair cellular energy transfer processes.

The UPR and ER Stress are now widely known to be involved in the pathophysiology of numerous autoimmune diseases “of unknown origin”. The UPR is now recognized as a central process in neurodegenerative diseases including Alzheimer’s disease (Cornejo and Hetz, 2013[53]) and Parkinson’s disease (Varma and Sen, 2015[54]), metabolic diseases (e.g., type II diabetes; Back and Kaufman 2012[55]), inflammatory diseases (type I diabetes (Lee and Ozcan, 2014[56]) and inflammatory bowel disease), and autoimmune diseases (e.g., Systemic Lupus Erythematosus; Garaud et al., 2011[57]).

Here I systematically compile the evidence that symptoms consistent with those of autoimmune disorders in humans are reliably and consistently reproduced in animal models; studies of autoimmune disorders following vaccination in humans. I also review examples of studies that demonstrate the central causal role of ER Stress and the UPR in human studies of autoimmune disorders. I review the literature of the role of metals in vaccines in the UPR and ER Stress in autoimmune disorders focused on the ER Hyperstress model, and then point to evidence that, as in ASD, mutations that lead to ER protein folding problems interact with the ER Stress caused by vaccine doses of aluminum and mercury. An underappreciated result of the fatal outcome of UPR for cells is the sudden release of strangely folded proteins, and autoinflammation and autoimmunity resulting from this release of improperly processed, aberrantly folded proteins, which are a rich source of neoantigens for transient and persistent autoimmunity. Ethyl mercury induces mutations in mitochondria in astrocytes, and aluminum impairs astrocytic cytoskeletal dynamics (Lemire et al., 2009;[58]).

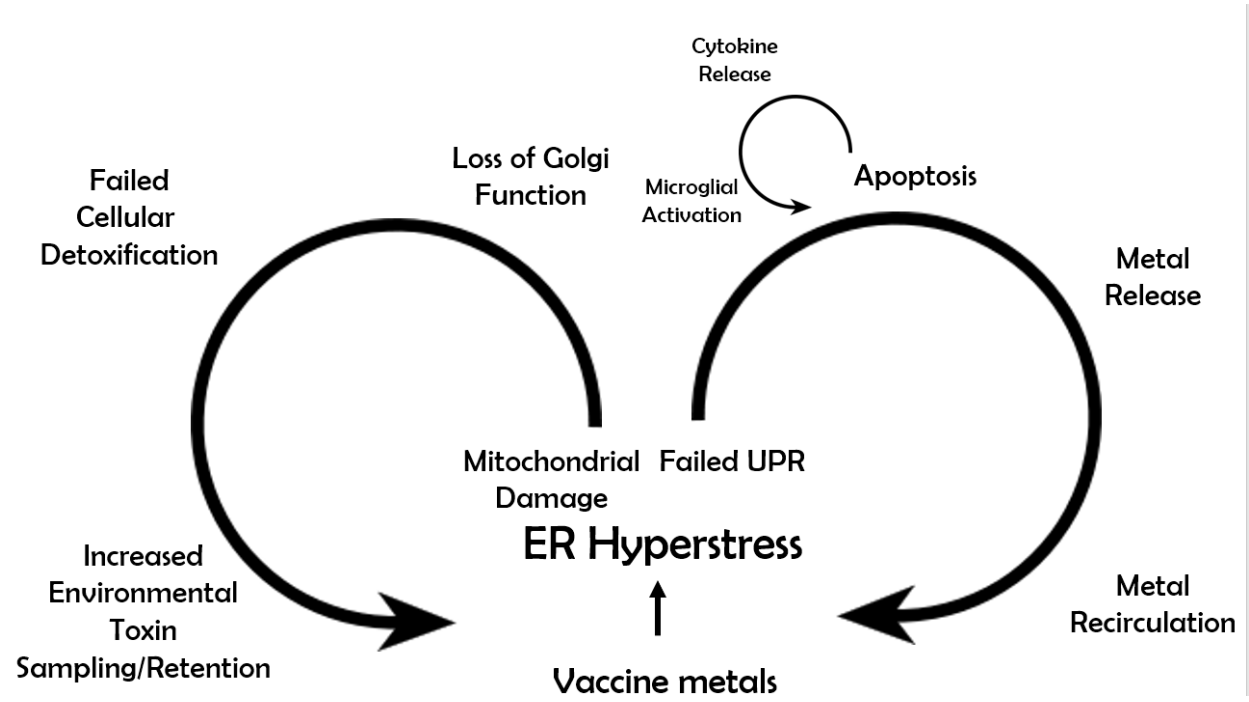

Figure 1. The ER Hyperstress model focuses on the interaction and combined effects of early-life exposure to aluminum and ethyl mercury and specific mutations that also cause ER stress. The combined effect is called ER Hyperstress (Lyons-Weiler, 2018).

ER Hyperstress Model of Neuroimmune Dysfunction

Additional aspects of ER Hyperstress include acquired cellular detoxification deficiency via mitochondrial and Golgi damage. When these cellular systems are impaired, individuals begin to take up parochial industrial and agricultural neotoxins from their environment. Thus, individuals with ER Hyperstress induced AD's, DD's and ND's likely will be found to have a constellation of toxins, including organic pollutants and other metals, making causality assessment within individuals and at the population level difficult. The rates of food allergy have skyrocketed since the expansion of the use of aluminum adjuvants in vaccines (Gupta et al. 2011[59]; Hoyt et al., 2016[60]), and a pilot study (Mawson et al., 2017[61]) found higher rates of allergies in children compared to unvaccinated children.

Asthma/Allergic Rhinitis

Individuals with a diagnosis of asthma usually have concurrent or prior atopy (Anderson et al., 1992[62]), or a family history of atopy. It has long been known that familial history of atopy reduces the capacity of infants to produce the TH1 cytokine interferon (IFN)-γ compared with infants from nonatopic families (Wright, 2004[63]). A large proportion of patients with asthma have increased CD4+ T cells, weak Th1 responses, strong Th2 immune responses, with Th2 based cytokine profiles including interleukin (IL)-4, IL-5, IL-9, and IL-13, which promote eosinophilic inflammation and immunoglobulin E (IgE) production in B cells. IL-5 drives eosinophil differentiation in the bone marrow, and IL-9 causes the differentiation of mast cells.

Children are exposed to large numbers of allergens throughout childhood, and simultaneous exposure to Th2- and IgE-enhancing adjuvants presents the opportunity to develop numerous triggers. The occurrence of anaphylaxis after immunization points to a pathogen's antigens as potential allergens. The role of airborne environmental triggers of asthma are well known (Kim et al., 2005[64]), but it is important to distinguish between

antigen/allergen source and root cause of autoimmunity. McDonald et al. (2008[65]) found that delay in the DTP vaccine was associated with a significant reduction in the risk of asthma.

Some animal studies have shown it is possible to develop allergic rhinitis and asthma without special exposure to airborne antigen sources. The drug development literature is replete with animal studies that routinely induce allergic rhinitis using aluminum hydroxide and ovalbumin, mainly for the purpose of testing drugs and other treatments for allergies. For example, Xi et al. (2014[45]) found that dosage of aluminum hydroxide determined the strength of the autoimmune reaction in a BALB/c mice model of allergic rhinitis. They found eosinophils in the nasal mucosa of mice who were injected with the aluminum hydroxide powder in solvent, but none resulting from the injection of the hydrogel form. No behavioral or neurological outcomes were studied. They used common "doses" of 5 mg per type of aluminum mixed with ovalbumin and provide a good example of the difficulties of comparing the biological equivalence of the same dose levels of different forms of aluminum. They found that high doses were immunosuppressive and lead to granulomas that could potentially lead to ascites (blockages) in organs.

Li and Geng (2015[66]) studied the effects of budesonide on the symptoms of allergic rhinitis induced by aluminum hydroxide and ovalbumin. They used 0.5 mL aluminum hydroxide gel in their induction model. Brandt et al., (2006[42]) developed a model of gastrointestinal allergy following asthma with TH2-associated humoral and cellular responses involving intestinal eosinophilia, mastocytosis and diarrhea by injecting 50 μg of ovalbulmin in the presence of 1 mg of the aluminum potassium sulfate adjuvant (alum).

Many other similar studies exist; some examples are Kovacova-Hanuskova et al. (2015[69]), Yasar et al. (2016[39]), and Yang et al. (2016[44]). Each of these conducted similar studies of treatments of allergic rhinitis caused by the administration of aluminum hydroxide and ovalbumin. Similarly, aluminum hydroxide is routinely used to create bronchial asthma in animals with high reliability. To study the efficacy of fruits of the *Vitis vinifera* plant, Arora et al. (2016[68]) sensitized rats to ovalbumin with 2 mg of aluminum hydroxide. Arora et al. (2017[69]) later used the same method to study the efficacy of Kanakasava in alleviating bronchial asthma. Zeng et al., (2014[70]) induced bronchial asthma using ovalbumin and aluminum hydroxide in Sprague-Dawley rats.

In humans, both Th1/Th2 and Th17/Treg imbalances can be found in patients with asthma (Shi et al., 2011[71]). This effect was produced using aluminum hydroxide and ovalbumin in mice (Liu et al., 2015[72]) who found that pingchuan formula, a traditional Chinese treatment, could restore Th17/Treg balance. T-regulatory cells modulate both Th1 and Th2 type responses (Shi et al., 2011[71]). Workers in aluminum production plants have increased risk of asthma (Taiwo et al., 2006[73]) involving granulomatous bodies in the lungs. The presence of aluminum within the granulomas differentiates "aluminum lung" from sarcoidosis and beryllium disease. Pulmonary fibrosis and pulmonary alveolar proteinosis and desquamative interstitial pneumonia, which involves the accumulation of macrophages in response to aluminum in the alveola all represent interstitial lung diseases that can result from chronic exposures to aluminum by workers in aluminum production (Taiwo, 2014[74]).

The improvement of aluminum-hydroxide induced asthma symptoms observed by Bibi et al. (2014[75]) after chelation aimed at sequestration of aluminum is evidence of reversibility, a key component of causal inference. The fact that volatile organic compounds can trigger asthmatic episodes, and individuals with asthma can accumulate persistent organic pollutants (Gascon et al., 2014[76]), point to cellular detoxification deficiency. A study of the cord blood of 2,050 infants found levels of pesticides in blood were associated with allergies and eczema (Karmaus et al., 2001[77]); children with increased levels of pesticides in their blood were at increased risk of asthma (Hernandez et al. (2013[78]). Both pesticides and IgE levels (marker for allergic response); pesticides were associated with higher IgE levels in the infants whose mothers had used pesticides during pregnancy (Hernandez et al., 2013[79]). The accumulation of pesticides was correlated with familial risk as reflected in the

presence of IgE in the cord blood of mothers with prior atopy only. This provides evidence of environmental toxin sampling and cellular detoxification deficiency. Known and suspected causal agents of asthma such as exposure to aluminum-or mercury containing vaccines were not included as factors in the study.

While the doses used in animal studies tends to be higher (per body weight) than used in vaccines, there are three good reasons to suspect that they are indeed highly relevant to the development of autoimmune disorders in humans. First, aluminum used in vaccines has a non-linear selective toxicity, and small doses may fly "under the radar" and fail to elicit tissue protective granuloma responses (Crépeaux et al., 2017[36]). Second, many autoimmune disorders involve genetic predisposition, a component not necessary for effecting autoimmunity in animal models.

Antiphospholipid syndrome (APS)/Immune System Activation of Coagulation (ISAC)
Antiphospholipid syndrome is an autoimmune condition in which the immune system mistakenly attacks phospholipids in cell membranes, causing vascular leakage and hypercoagulation. APS is diagnosed by the occurrence of antiphospholipid antibodies (aPL) and can provoke blood clots (thrombosis) arteries and veins, and can cause pregnancy-related complications such as stillbirth, miscarriage, short gestation, and severe preeclampsia. A moderate thrombocytopenia is usually involved. APS has been induced in mice using alhydrogel (Zivković et al., 2013[80]) and aluminum hydroxide combined with tetanus toxoid resulting in hyperimmunization (Zivkovic et al., 2011[81]). In one of the earliest studies, Pierangeli and Harris (1993[82]) successfully induced antiphospholipid antibodies (APAs) using aluminum hydroxide and either human beta 2 glycoprotein 1 or anticardiolipin antibodies.

Cross-reactive antibodies have been found following Hepatitis B vaccination in patients who developed thrombocytopenia. Cross-reactivity to platelet antigens has been detected in about 80% of cases. In thrombocytopenia occurring post- measles-mumps-rubella (MMR) vaccination, the presence of anti-rubella and anti- measles IgG antibodies that cross-react with platelet antigens has been consistently detected. D'alò et al., (2017[83]) reviewed the evidence determined that the role of vaccines as a pathophysiological mechanism in thrombocytopenia is "certain".

Given that antiphospholipid antibodies have been found in patients with persistent macrophagic myofasciitis (Rigolet et al., 2014[84]), and APS patients often experience a decline in kidney function (Martinez-Florez et al., 2016[85]), doses of aluminum in APS patients should be kept below the 4-5 mcg/kg/day limit required by the CFR/FDA (FDA/CFR 21CFR201.323, 2017) [86]. No specific limit is provided by FDA for injected aluminum exposures from vaccines. To date, no studies of the efficacy of aluminum-focused chelation therapy have been conducted on patients with APS.

Arthritis
Injections of either ovalbumin or collagen in the presence of aluminum hydroxide produced lymphocyte proliferation and interferon gamma production in mice (Sagawa et al., 2005[46]). The study found that arthritis in mice induced by aluminum hydroxide and these allergens could be alleviated by angiotension II receptor blockers. Xiao et al. (2008[87]) used aluminum potassium sulfate and ovalbumin to induce collagen-induced arthritis. Vaccination with OSPA and aluminum hydroxide caused severe destructive Lyme arthritis in hamsters upon infection with Borrelia burgdorferi (Croke et al., 2000[88]). Lyme arthritis sufferers often have lower frequencies of Treg cells, and higher expression of activation coreceptors that augment Teff cell function (Vudattu et al., 2013[89]).

Chelation with EDTA has been effective in reducing the severity of rheumatoid arthritis in a patient with aluminum, cadmium and lead intoxication (Bamonti et al., 2011[90]). Like other types of autoimmunity, co-morbidity of various types of arthritis with multiple chemical sensitivity (Bell and Baldwin, 2013[91]), points to involvement of

acquired cellular detoxification deficiency in arthritis. Evidence that RA pathogenesis involves the ER chaperone GRP78 is reviewed by Park et al. (2014[92]), including the release of pro-inflammatory cytokines.

One of the two studies conducted by Ray et al., 2011[93] to test the hypothesis of association of RA with vaccines found a significant association – yet the authors favored the interpretation of no association. The HLA-DR class II genetic component of RA risk in some families is well known; studies such as Mitchell et al. (1998[94]) that are more appropriately designed (via genetic stratification) report much higher odds ratios of association with vaccines. It is accepted that the MMR vaccine can cause arthralgia and arthritis in a significant number of women with no preexisting MMR vaccine exposure (10-25%). The contribution of vaccines to chronic arthralgia or arthritis has not been fully studied. This conclusion is based on an assessment in 2012 by the Institute of Medicine (2012[94]), who cited numerous studies reporting transient arthritis after vaccination. The IOM concluded they were unable to find sufficient evidence to conclude that vaccines do, or do not cause chronic arthralgia or arthritis; however, they did reference a variety of poorly conducted studies that failed to detect positive associations. For example, the study cited that reported no association between a recombinant DNA Hepatitis B vaccine and arthritis only had 44 patients with RA, and a control group of only 22 patients. The lack of studies of sufficient quality stymied the IOM's ability to determine (either way) whether vaccines contribute to chronic arthritis. Some studies did report a statistically significant association between influenza and HPV vaccines and arthralgia, but one cannot determine whether the negative results were due to low power or other problems with design of analysis, which is common in retrospective ecological correlation studies. One study of a vero-cell culture-derived trivalent influenza vaccine found a relative risk of arthralgia of 2.0 (95% CI: 1.6-2.5), and another study of an AS04-adjuvanted HPV-16/18 vaccine (Cervarix) among women in Korea (Kim et al., 2011[96]) found an odds ratio of grade 3 arthralgias of 2.68 (95% CI: 1.29-5.59) with vaccination use.

The reliance on weak retrospective studies, often underpowered, hinders causal inferences based on association only because correlation studies fall short of sufficiently critical test of causality (Lyons-Weiler, 2018[30]). They are almost always not designed to test the hypothesis of association in a genetically susceptible subgroup, which contributes to the inability to detect associations. Even in randomized clinical trials, inclusion criteria often exclude persons with known comorbid conditions – potentially excluding people from the study who carry the genetic risk of the autoimmune disorder(s) of concern. The study of Jackson et al. (2010[97]) is such an example, where patients with new medical conditions are excluded – as were patients with kidney issues. Such exclusions may remove those who are genetically susceptible – and the exclusions are not carried over into clinical practice as contraindications, and thus true associations are weakened. Thus, negative results should be reported as "failing to detect an association (or effect)" instead of "finding no evidence". Further, because correlations are not sufficiently critical tests of causality, finding of "no evidence" in epidemiological correlation studies should never be confused with proof of no causal relationship. Inconsistencies between strong evidence of vaccine-induced autoimmunity at the individual level and negative results at the population level are likely explicable due to the application of inappropriate epidemiological study designs that do not consider genetic and familial risk.

Atherosclerosis

ER stress plays an important role in atherosclerosis and other macrovascular complications (Chistiakov et al. 2014; Zhou and Tabas, 2013[98-99]). Numerous types of ER stress contributors have been identified, but many of these are manifestations of ongoing processes, not root causes. These include insulin resistance, hyperhomocysteinuria, oxidation and stress (Tabas, 2010[100]). Once ER stress is manifest, multiple additional processes lead to the recruitment of macrophages to the site of lesions where "foam cells" provide structure within which pro-inflammatory cytokines recruit localized immune responses. While experimental animal models such as APOE deficient mice fed a special diet can induce sufficient ER stress to cause atherosclerosis, Nishizono et al. (1999[101]) were able to induce atherosclerosis via injection of ovalbumin combined with aluminum hydroxide. It is interesting to note that inclusion of AGE-LDL in the injection led to reduction in atherosclerosis compared to aluminum hydroxide alone in diabetic ApoE and LDLR null mice (Zhu et al., 2014[37]). Incidental data suggest that

heavy metal chelation, including types aimed at aluminum, seem to improve outcomes of people with atherosclerosis-induced myocardial infarction (Lamas and Ergui, 2016[102]). Patients with end-stage renal disease also show signs of calcifications in blood vessels and atherosclerosis (Querfeld, 2002; Jablonski and Chonchol, 2013) [103-104]), correlated with serum levels of phosphate-binding medicines in the serum. Since aluminum-containing drugs are dangerous to neonates, and the toxicity of aluminum is dosage and body-weight dependent (Lyons-Weiler and Ricketson, 2018 [27]), it is prudent to avoid injections of aluminum in the NICU to avoid adding to renal and cardiovascular toxicity.

Oddly, while aluminum tends to increase Th2 immunity, atherosclerosis typically involves Th1 cytokines, and aluminum (alone) could be protective against atherosclerosis in such cases (see Jan et al., 2010 for a review[105]). In the presence of unsafe foreign epitopes (i.e., epitopes that are immunogenic but that are similar to human proteins), however, the shifting in the immunity profile could have multiple effects that vary over time, or with genetic background. The UPR is involved in AS lesion development at every stage in APOE deficient mice (Zhou et al., 2005[106]).

Systemic Lupus Erythematosus

Katz-Agranov and Zandman-Goddard (1985[107]) reported that SLE has been observed after "HBV vaccines, human papillomavirus (HPV) vaccine, influenza vaccines, diphtheria, pertussis, tetanus (dTP) vaccines, bacillus Calmette-Guérin (BCG) vaccines, measles, mumps, and rubella (MMR) vaccines, pneumococcal vaccines, vaccine adjuvants, autoimmune/inflammatory syndrome induced by adjuvants (ASIA) and other adjuvants such as oil adjuvants and metal adjuvants". A systematic review and meta-analysis of 16 studies conducted by Wang et al (2017[108]) concluded that both SLE and RA are associated with vaccination. Kelly-Scumpia et al. (2007[[38]) used aluminum hydroxide to induce a lupus-associated autoantigen and DC maturation, B and T cell activation/proliferation in mice. While renal iron accumulation can occur in SLE (KlackI et al., 2012[109]), patients are also at risk of anemia (Marks et al., 2017[110]). Agmon-Levin (2014[43]) found the aluminum hydroxide induced kidney tissue damage, decreased RBCs, caused memory deficits and measurable brain gliosis in mice. Paradoxically, certain aspects of SLE are treatable by oral aluminum hydroxide, specifically soft tissue calcifications that can be problematic can be softened and better removed by surgery (Mandelbrot et al., 2008[111]). Post-apoptotic ER stress is observed in bone marrow mesenchymal stem cells in patients with SLE (Guo et al., 2015[112]).

Sjögren's syndrome

Bagavant et al. (2014[113]) duplicated sialoadenitis (inflammation and malfunction of the salivary gland) in mice using aluminum hydroxide. Amyloid is partly aluminum, and amyloidosis of the parotid gland is not uncommon (see review in Jeong et al., 2015[114]). Numerous studies have found association of myriad environmental toxins and Sjögren's syndrome, which is consistent both with in-line causality and parallel effect of detoxification deficiency. Multiple chemical sensitivity has been suspected to share a root cause with Sjögren's syndrome since 2006 (Migliore et al., 2006[115]), pointing to a loss of cellular detoxification capacity. Sicca syndrome, which is similar to and sometimes comorbid with Sjögren's syndrome, responds to metal chelation (Ebert et al., 2012[116]).

Food allergies

Exposure of BALB mice to high aluminum-containing anti-acid powder in a diet of codfish causes IgE seroresponses to subsequent codfish exposure, establishing a causal link between aluminum and food allergies (Pali-Schöll er al., 2010[117]). In a study of the efficacy of quercetin for treating life-threatening anaphylactic reactions to foods, Shishehbor et al (2010[118]) were able to reliably induce immunoglobulin-E mediated peanut allergy in Wistar rats using crude peanut extract, Cholera toxin and injected aluminum hydroxide. Ahrens et al. (2014[119]) found that they could reproducibly induce allergy to ovalbumin, apple, soy, peanut, and pea allergens by sensitizing Brown Norway rats with specific protein extracts, ingested aluminum hydroxide, and Bordetella pertussis. Development of increased IgE levels and food allergies have been reported (Hoyt et al., 2015[120]).

Tong et al. (2017[121]) found that iron-focused chelation (the removal of iron from the allergen) reduced the allergenicity of ovotransferrin in the BALB/c mouse model. No studies of the potential utility of aluminum-focused chelation and the reduction of the severity of food allergies have been found. The concurrent massive increase in food allergy and in multiple chemical sensitivity disorders since the expansion of the use of aluminum-containing vaccines has been noted (Genuis et al., 2010[122]). The high prevalence of gluten allergies in ASD is noted, as is the finding that mothers of children with ASD have higher rates of MCS (Heilbrun et al., 2015[123]).

Glomerulonephritis

Glomerulonephritis is a serious condition that can occur as a frequent condition comorbid with many of these autoimmune conditions. It is a leading cause of death in SLE and can be induced reliably in animals using aluminum hydroxide (Bassi et al., 2012[124]). It has long been known that acute exposure to high doses of aluminum can cause kidney damage, and that detoxification with deferoxamine prevents and reduces kidney damage and glomerulonephritis (e.g. Hood et al., 1984[125]). Pathological deposition of aluminum in the bones accompanies glomerulonephritis and can lead to improper bone development and brittle bone disease. If genetic intolerance of aluminum in vaccine types and doses of aluminum and mercury in vaccine exists such that individuals tend to accumulate larger doses in their tissues, kidney damage could be a serious risk due to cumulative exposures. Naturally, impaired kidney function can also contribute to the accumulation of other chemicals – especially in the presences of accumulating adjuvants. Metals can themselves be antigenic, making any tissues within which vaccine metals are deposited targets of adaptive immunological attack (Levy et al., 1998[126]).

Table 2. Autoimmune Diseases Produced by Aluminum Hydroxide in Animal Studies

AA Disease	Aluminum Type	Symptom Manifestations	Citation
allergic asthma	Al(OH)3	asthma	Elsakkar et al., 2016 [40]
	Al(OH)3		Bibi et al., 2014 [75]
allergic rhinitis	Al(OH)3	allergic rhinitis immune suppression	Xi et al., 2014 [45]
	Al(OH)3	allergic rhinitis	Li and Geng, 2015 [66]
	Al(OH)3	allergic rhinitis	Yasar et al., 2016[39]
	Al(OH)3	allergic rhinitis	Yang et al., 2016[44]
bronchial asthma	Al(OH)3	bronchial asthma	
antiphospholipid syndrome	alhydrogel	APS antibodies	Zivković et al., 2013[80]
	Al(OH)3		Zivkovic et al., 2011[81]
arthritis	Al(OH)3	collagen-induced arthritis	Sagawa et al., 2005[46]
	Al(OH)3	severe destructive Lyme arthritis	Croke et al., 2000 [88]
atherosclerosis	Al(OH)3	OVA-specific IgG/ chymase increase	Nishizono et al. 1999 [101]
	Al(OH)3	atherosclerotic lesions	Zhu et al. 2014[37]
chronic prostatitis/ chronic pelvic pain syndrome	Al(OH)3	increased TNF-α and IgG prostatitis	Qi et al., 2012

gastrointestinal allergy preceding asthma	aluminum potassium sulfate	pulmonary inflammation	Brandt et al., 2006 [42]
systemic lupus erythematosus	Al(OH)3	kidney tissue damage decreased RBCs memory deficits brain gliosis	Agmon-Levin et al., 2014 [43]
	Al(OH)3	DC and lymphocyte activation and Sm/RNP autoantigen	Kelly-Scumpia et al., 2007 [38]
	Al(OH)3	accelerate proteinuria weight loss	Favoino et al., 2014 [223]
motor neuron disease	Al(OH)3	motor deficits motor neuron degeneration	Shaw & Petrik, 2009 [224]
Sjögren's Syndrome	Al(OH)3	salivary gland dysfunction	Bagavant et al., 2014 [113]
food allergy	Al(OH)3	IG-E peanut allergy	Shishehbor et al., 2010 [118]
	Al(OH)3	soy, peanut, pea, apple, ovalbumin	Ahrens et al., 2014 [119]
	multiple vaccines	peanut and egg allergies	Hoyt et al., 2015 [120]

The majority of these studies used ovalbumin in combination with aluminum hydroxide. Ovalbumin, which is found in many vaccines, and the pattern of use in animal models, suggests some cases of vaccine-induced autoimmunity unrelated to egg allergy. These studies typically employ intraperitoneal injection, using doses that range from 10x the amount used in vaccines (e.g., Hepatitis B 250 μg/2kg infant) to much larger doses. In these animal studies, the doses are often acute doses, given once, or twice, with short-term follow-up and do not represent the chronic exposure to low doses reflecting the CDC pediatric schedule.

The high doses, however, may mimic the toxicity of human patients with increased genetic susceptibility due to myriad effects of ER Hyperstress, including cellular detoxification deficiency, who appear to accumulate systemic aluminum at a faster rate than others. Cruz-Tapias et al., (2013[127]) noted the widespread use of aluminum hydroxide in animal studies of autoimmune rheumatoid arthritis-like disease, for systemic lupus erythematosus-like disease, autoimmune thyroid disease-like disease, antiphospholipid syndrome, myocarditis and others. To date animal studies have not focused specifically on whether acquired detoxification deficiency accompanies repeated acute aluminum intoxication in dose schedules and administration mimicking vaccine exposures. It can be expected that in a subset of patients with autoimmune disorders, multiple chemical sensitivity is a likely result due to failed cellular detoxification.

Aluminum Dose Toxicity – Non-Linear Due to Aluminum Biochemistry and Volumetric Development

Recently, Ameratunga et al. (2018[128]) called for a moratorium on animal studies examining health effects of vaccine-scaled doses in animals, claiming that there was insufficient basis for the ASIA syndrome in humans. Claiming to have applied Bradford's Criteria for causality, and that the use of larger doses of aluminum in

subcutaneous immune therapy (SIT) demonstrate safety of aluminum in vaccines, they make a number of errors. They ignore some available science that demonstrates reversibility of the effects of aluminum in mice (e.g., Kivity et al., 2017[129]). The mistakes in their assessments (Ameratunga et al., 2017; Ameratunga et al., 2018[128,130]) include an assumption of linear dose toxicity, which is an incorrect assumption, given the results of Crépeaux et al. (2017[36]). We also simply cannot afford to and should no longer ignore the role of genetic susceptibility, as this would represent a reversal of the norm of translational research.

The use of SIT began with treatment of allergies, but the history of the application of SIT in autoimmune disorder has not been straightforward; there have been many failures due to adverse events (Sabatos-Peyton et al., 2010[131]). Mechanisms of action of aluminum hydroxide efficacy in the treatment of autoimmune conditions have not been well characterized, and actual long-term health outcomes of the use of aluminum hydroxide in cases of autoimmune conditions have not been sufficiently studied. It is notable that failed treatment with aluminum hydroxide could be medically confounded with exacerbation: the practice is terminated in patients who do not respond well. Long-term adverse health outcomes of SIT interventions that use aluminum have not been systematically studied, such as risk of Alzheimer's disease, or risk of developing secondary autoimmunity (Turkcapar et al., 2005[132]; Linneberg et al., 2012[133]). The single long-term study found no difference in de novo autoimmunity between autoimmune patients receiving SIT and a non-allergic control group (Bozek et al., 2015[134]), but found an increase in autoimmune disorders in the control group over time. The study was short (3 years), and rare autoantibodies were not assayed. SIT is applied in the exact manner in which many believe vaccines should be administered – with patient monitoring for adverse events on an individual basis, and cessation of the application of the medical procedure upon evidence that the patient has developed an adverse event – both in the treatment autoimmune and allergic diseases (Sabator-Peyton et al., 2010[135]; Turkalj et al. 2017[136]).

The toxicity of any substance is only partly determined by the dose. The body weight of an individual, the duration and repeated exposure, and individual genetics all determine toxicity. Since body weight during development itself is non-linear, and whole-body burden toxicity is due to whole-body metabolism, it is reasonable to expect that the dose-toxicity of any adjuvant in vaccines will also be non-linear. Aluminum, however, has been shown to have an insidious escape of tissue response (sequestration) at very low doses (Crépeaux et al., 2017[36]). Not every patient forms a granuloma after injection of aluminum-containing vaccines, but when they do, the aluminum is released slowly, over time. With repeated doses in the vaccine schedule, accumulation and clearance dynamics are not well characterized. However, Flarend et al. (1997[137]) reported only 5.6% of aluminum hydroxide is excreted after 28 days – which means the available pharmacodynamic modeling that used serum-clearance rates is overly optimistic in a grand way. Individuals with impaired body and cellular detoxification likely accumulate retained fractions of aluminum at a greater rate than others, and aluminum toxicity includes renal dysfunction. We have a long way to go before we can say we truly understand aluminum clearance and accumulation rates; carefully conducted dose escalation studies reflecting vaccine schedule amounts have not been conducted.

ER Stress and The Unfolded Protein Response in Human Studies of Autoimmunity

Garaud et al. (2011[57]) found that some systemic lupus erythematosus patients had a unique and strong gene expression signature implicating the Unfolded Protein Response regulated by BLIMP1 and concluded that the group of patients likely experienced a different pathophysiological journey to their diagnosis. SLE, like other autoimmune disorders, can have multiple causes – and different primary causes in different patients. In a recent study, Vieira et al (2018[138]) discovered that a genetic mouse model of SLE involved the unusual occurrence of the translocation of one enteric microbe to the liver through the lining of the gut. In their study design, the mouse model (C57BL/6), was depleted of all enteric bacteria. The absence of commensal gut flora prevented the proper healing of the gut lining; they then colonized the gnotobiotic gut with *E. gallinarum*, which could be detected in the lymph system and the livers of the mice. Th17 expression was increased in the epithelial lining of the gut after re-colonization with *E. gallinarum*. The study used the absence of a healthy flora to induce leaky gut symptoms.

Numerous factors can contribute to leaky gut syndrome, contributing to increased risk of autoimmune disorders, including diet and stress (Mu et al. 2017[139]). Dietary aluminum has been shown to cause leaky gut in mice (Pineton de Chambrun et al., 2014[140]).

The mice used in Vieira et al (2018[138]) study have been used extensively in the study of other autoimmune conditions under exposure to aluminum hydroxide, including SLE with a bm12 transfer design (Klarquist and Janssen, 2015[141]). Morokata et al. (1999[142]) found that local autoimmune responses are more important than systemic responses due to aluminum hydroxide ovalbumin - induced autoimmunity using these mice. Reddy et al. (2012[143]) described a protocol for the induction of asthma in the C57BL/6 mice. Inbar et al. (2017[144]) found behavior anomalies in these mice when aluminum adjuvants or the HPV vaccine Gardasil, which contains an aluminum adjuvant, were injected. Dimitrijević et al. (2012[145]) induced antiphospholipid syndrome in these mice with tetanus vaccine (tetanus toxoid + aluminum hydroxide). The autoantibodies they found were not specific for the linear TLRVYK sequence present in TTd, but instead recognized the shape of the TTd conformation, which is similar to that of b2GPI. The supplier, Jackson Laboratories, warns that the C57BL/6 can have high genetic variability.

Human Studies Fail to Detect Association Due to Mis-design

The role of cross-reactive autoantibodies in autoimmune disease has been known for some time, beginning with risk of cardiac autoimmunity following Streptococcus infection (e.g., Kaplan and Svec, 1964 [150]). The first expressions of concern over cross-reactivity with pathogen proteins in vaccines occurred in the early 1980's with evidence of cross-reactivity leading to cardiac autoimmunity from Streptococcus vaccine experiments in rabbits (Hughes et al., 1980[151]). Clearly, not every person that receives vaccines or suffers an infection of agents with proteins that have similarity to human proteins develops autoimmunity; this points to a significant role of genetic variation by which those susceptible have higher structural similarity in self-antigens and antigens found in pathogens.

All of the studies that have demonstrated specific roles of aluminum and mercury in pathophysiological mechanisms of autoimmunity provide the strongest levels of evidence possible. An immense amount of direct causal evidence for the involvement of AL in a wide diversity of autoimmune conditions exists. Yet retrospective whole population association studies consistently fail to find an association at the population level. In autism, epidemiologic studies have failed to detect association of autoimmune disorders due to the use of incorrect study designs that are appropriate for population-wide effects. In the case of atopic disease (AD), an association has successfully been detected between AD and Hib vaccination – in a prospective cohort study.

Epidemiological vaccine safety studies often suffer flawed design by excluding genetic subgroups with comorbid autoimmune conditions such as RA, which represents a serious mistake in design. RA has a very well known HLA-DR class II genetic component in some families; studies such as Mitchell et al. (1998[94]) that are more appropriately designed (via genetic stratification) report much higher odds ratios of association with vaccines.

In the case of autoimmunity, as in ASD, genetic susceptibility to aluminum and mercury-induced ER stress would require studies that are informed by genetic risk. Increased susceptibility caused by mutations in proteins directly involved in pathways involved in each autoimmune disorder would tend to favor dominant patterns of inheritance.

However, more complex inheritance patterns are expected for risk that is due to proteins that confer risk expressed as ER Hyperstress. In ER Hyperstress, the proteins encoded by genes that confer small increases in risk are made more intrinsically disordered and more likely to require special handling by ER processes during folding. Two sources of ER stress – protein variation that leads to initiation of the UPR program and vaccine metals – leads to ER Hyperstress. In the case of ASD, cell death, release of cytokines[146], and the re-release of intracellular

metals – explains chronic brain inflammation, multi-organ involvement, and disruption of cellular detoxification leading to the accumulation of other toxins from the environment at a greater rate than seen in neurotypical individuals. ASD individuals also have a plethora of malformed proteins in their serum – pointing to a potential biomarker for diagnosis (Anwar et al., 2018[147]).

Numerous examples exist in which the Unfolded Protein Response and ER Stress play a central role in autoimmune disorders (Table 3). The question of whether autoimmune disorders are likely due to the expression of misfolded proteins is an important one. First, individuals who are heterozygous for misfolded proteins, which are likely to appear to be neoantigens to the mammalian immune system – expressing both copies will have proteins in tissues made of the properly folded protein with regular expression of the malformed proteins. In some individuals, the recurring cell death will yield a constant supply of malformed proteins. Progressive tissue loss will accompany inflammation. In other individuals, the autoimmunity will target both maternally and paternally inherited proteins when the antigenicity is not sufficiently specific to the malformed proteins.

Table 3. Examples of Unfolded Protein Response/ER Stress in Autoimmune and Autoinflammatory Disorders

Condition	Evidence	Detail	Reference
Amyotrophic Lateral Sclerosis	Review	ER morphology	Jaronen et al, 2014 [148]
		SOD1 accumulation	Doyle et al., 2011 [149]
Gullain-Barre Syndrome	Viral hijack	stress granule protein	Hou et al., 2017 [152]
Rheumatoid Arthritis	anti-citrullinated protein antibodies	GADD34 increased UPR signal	Clavarino et al. 2016 [153]
	haploinsufficiency	GRP78 chaperone	Park et al. 2014 [95]
	immunohistochemistry	GRP78 increased	Dong et al. 2009 [154]
Lupus	gene expression	BLIMP1 UPR	Garaud et al. 2011 [57]

Spondyloarthritis – The Exception that Proves the ER Hyperstress Rule?

In contrast to prototypical autoimmune diseases like rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), which fit the ER Hyperstress model, spondyloarthritis (SpA), a chronic immune-mediated inflammatory disease of unknown origin does not share genetic risk factors. It also does not share the presence of auto-antibodies and SpA patients do not respond to T-cell or B-cell-targeted therapies. For these reasons, Ambarus et al. (2012[158]) concluded that SpA was likely autoinflammatory, rather than of autoimmune origin.

Intrinsic Protein Disorder and Autoimmunity – Intolerance of Shape-Shifting Mutations

The protein folding and modification processes that occur in the unstressed ER include N-linked glycosylation, disulfide bond formation and proline cis–trans isomerization (Grootjans et al., 2017[156]). Mutations that change any of these protein folding dynamics could lead to ER Hyperstress in any cell in which the altered protein is expressed if that cell is already ER-stressed due to metal intoxication. Antigen folding requires proper execution of the unfolded protein response (Osorio et al., 2018[157]).

If individuals who are at risk of autoimmune disorders following vaccination carry mutations that cause changes to protein intrinsic disorder that manifests the genetic component to ER Hyperstress, the intrinsic disorder of the

proteins involved should be lower than that of most proteins in the human proteome. To determine if specific mutations involved in autoimmunity tend to increase disorder, proteins known to be encoded by genes that are screened for risk of ADs were studied. The ADs covered included those summarized in the Eupedia[52] Autoimmune Diseases SNP entries, and included: allergies (general), Ankylosing Spondylitis, Celiac Disease, Crohn's Disease, Grave's Disease, Inflammatory Bowel Disease, psoriasis, Multiple Sclerosis, Rheumatoid Arthritis, Sjögren's Syndrome, systemic lupus erythematosus, Type 1 Diabetes, Type 2 Diabetes, and ulcerative colitis. A total of 109 protein-AD associations were analyzed. Protein intrinsic disorder was determined for this list of proteins and compared to that of 200 randomly selected proteins from the human proteome with entries in the MobiDb, a curated database of intrinsic disorder, conformational diversity, and interactions in proteins (Piovesan et al., 2018[158]).

A great number of case reports exist that outline the clinical progression of a patient without autoimmune disorder who presented with AD after vaccination. Population-level studies that ignore the feasibility of mechanisms of autoimmunity from vaccines also tend to ignore the rates of autoimmune disorders in their study design. Clearly, if vaccines induce autoimmunity, they do in a subset of individuals. The hypothesis that the subset has higher specific risk of autoimmunity from vaccination is not well-tested by study designs that are better suited to test the hypothesis as if the risk was shared across the entire population. The use of whole-population correlational studies in the case of genetic susceptibility will dilute the strength of the association. In that setting, cohort studies and afflicted vs. not can be more powerful. However, the most appropriate study would focus on the rates of AD in individuals with genetic susceptibility who vaccinate compared to those who do not vaccinate. A small sampling of studies of various types that report ADs post-vaccination are presented in Table 4.

Examples from Human Studies

Molecular mimicry can occur between pathogen proteins and human proteins regardless of whether the source is infection or injection. Autoimmunity from vaccines has been reported for numerous conditions, including immune thrombocytopenic purpura and the MMR vaccine (Demicheli et al., 2012[159]). Hepatitis B vaccine 1991–1997 and multiple sclerosis (Hernán et al., 2004[160]); Narcolepsy and H1N1 influenza vaccine (Ahmed et al., 2017[161]); undifferentiated connective tissue disease and Hepatitis B vaccine (Bruzzese et al., 2013; Perricone et al., 2013[162-163]), ovarian failure, Lupus and human papilloma virus (Gatto et al., 2013[164]). Of these, the HPV vaccine and the current HepB vaccine contain distinct forms of aluminum. Many other studies have reported autoimmunity after aluminum-containing vaccines (Table 4).

Table 4. Autoimmune and other conditions reported after vaccination

Condition	**Adjuvant**	**Vaccine**	**Reference**
cognitive dysfunction	Al(OH)3	various	Couette et al., 2009[165]
glomerulonephritis	Al(OH)3	multiple	Levart, 2013[166]
	Al(OH)3	vaccines	Bassi et al., 2012[131]
Guillain-Barré Syndrome	Al(OH)3	HepB	Bogdanos et al., 2005[167]
		H1N1	Ahmed et al., 2015[10,164]
Hypoinsulinism (Tissue Scurvy)	Various		Innis, 2013[166]
Rheumatoid arthritis (genetic predisposition)	N/A	H1N1	Basra et al., 2012[169]
			Ray et al., 2011 (cohort study)[96]

Narcolepsy	N/A	H1N1	Ahmed et al., 2015[10] Verstraeten et al., 2016[170]
vaccine induced immune thrombocytopenic purpura (VI-ITP)	Al(OH)3 n/a	HepB MMR	Meyboom et al., 1995[171] Cecinati et al., 2013[172] O'Leary et al., 2012[173]
vasculitis, death	AAHS	HPV	Tomljenovic and Shaw, 2012[174]
vasculitis	AAHS	HPV	Gomes et al, 2013[175]
thrombocytopenic purpura	AAHS	HPV	Souayah et al. 2011[176] Pugnet et al., 2009[177]
demyelinating disease	AAHS	HPV	Alvarez-Soria et al., 2011[178]
systemic lupus erythematosus	AAHS	HPV	Gatto et al., 2013[164]
premature ovarian failure	AAHS	HPV	Gatto et al., 2013[164]
increased brain AL	AL(OH)3	adjuvant	Redhead et al., 1992[179]
undifferentiated connective	AL(OH)3	Hepatitis B	Bruzzese et al., 2013[180]
tissue disease	AL(OH)3	Hepatitis B	Perricone et al., 2013[163]

Additional examples are reviewed by Tomljenovic and Shaw (2012[174]) and include vasculitides, arthritis/ arthralgia, immune thrombocytopenic purpura and multisystem atrophy.

Guillain-Barré Syndrome and Hepatitis B Vaccination

One of the most important and convincing studies in this area (Bogdanos et al., 2005[167]) was conducted to study common peptide sequences between the small HBV surface antigen (SHBsAg) contained in the HepB vaccine to peptides in known MS (myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG). The study not only found numerous peptide sequences common between SHBsAg and MBP/MOG; they also found that 60% of patients with MS had autoantibodies to both SHBsAg and MOHG. The rate of double reactivity was 2% in the control group.

Ahmed and Steinman (2017[161]) similarly found cross-reactive antibodies against the orexin (hypocretin) receptor and the Pandremix H1N1 vaccine peptide, thereby interfering with the orexin production and resulting in narcolepsy. The cross-reactive antibodies were detected in the blood sera of Pandemrix-vaccinated individuals with narcolepsy than individuals without narcolepsy. Notably, individuals in Finland who developed narcolepsy had the (HLA) DQB1*0602 genotype (Schoenfeld, 2013[13]), supporting increased susceptibility to vaccine-induced autoimmunity due to genetic variation.

Aluminum Hydroxide and Ethyl Mercury from Thimerosal Both Activate ER Stress and Activate the UPR

The activity of aluminum as an adjuvant is one of its effects on ER stress. Specifically, aluminum leads to activation of the NLRP3 inflammasome, one route in the UPR to ER stress (Franchi and Núñez, 2008[181]). Li et al (2008[184]) found that the adjuvanticity of aluminum is dependent on activation of the NLRP3 inflammasome, meaning that ER stress and the UPR are involved with dose. Aluminum also wreaks havoc on neuronal and hepatic cells as an intracellular ROS generator (Han et al., 2013[47]) and causes mitochondrial damage and cytoskeletal dysfunction (Lemire et al., 2009[59]). The route to apoptosis via aluminum ER stress activation of the UPR can occur independent of the p53 pathway (Rizvi et al., 2014[34]). Cellular apoptosis is an unwanted side effect of aluminum hydroxide that leads to the release of incompletely or incorrectly ER-processed proteins. Further,

aluminum hydroxide induction of Interleukin-1B (IL-1B) may explain observations of its upregulation in autism, as reported by Goines and Ashwood (2013[185]).

This review has focused on the ER Hyperstress mechanism of cellular injury from aluminum adjuvants as a critically important pathophysiological mechanism that can bring about autoimmunity after vaccination. The ER Hyperstress process is the precise manifestation of the G x E interaction between genetics (risk of susceptibility) and environment (exposure to aluminum, mercury and other specific environmental sources of ER stress). ER Hyperstress explains why some individuals are more susceptible to vaccine induced autoimmunity than others; it explains chronic, low-grade inflammation in autoimmune disorders. It is perfectly complementary to and adds a critical step to explain how individuals could develop autoimmunity via widely-recognized downstream immunological outcomes such as molecular mimicry-induced autoimmunity (Pahari et al., 2017[184]; Vadalà et al., 2017[25]; Augustyniak et al., 2017[186]; D'alò et al., 2017[83]; Segal and Shoenfeld, 2018[187]).

Aluminum in Demylinating Disorders

A variety of demyelinating conditions with heterogeneous manifestation are autoimmune in nature that may be attributed to exposures to vaccines with adjuvants via mechanisms including molecular mimicry and ER Hyperstress. These include multiple sclerosis (adult and pediatric), Optic neuritis (ON), Transverse myelitis (TM), Clinically isolated syndrome (CIS), Neuromyelitis Optics (NMO), and Acute Disseminated Encephalomyelitis (ADEM). Fulgenzi et al. (2014[189]) found that aluminum was implicated in 44.8% of cases neurodegenerative cases studied; high levels of iron and aluminum have been found in the urine of patients with MS (Exley et al., 2006[190]). Numerous case studies have reported efficacy of chelation of aluminum in reducing symptoms of multiple sclerosis (Zanella and di Sarsina, 2013[191]); Alzheimer's disease (e.g., chelation with deferoxamine and ascorbic acid, Di Lorenzo and Di Lorenzo, 2013[192]); rheumatoid arthritis (EDTA chelation; Bamonti et al., 2011[90]). Special care must be taken to avoid sudden toxicity due to chelation of metals – autoimmunity can result (e.g., Fulgenzi et al, 2012[193]).

Therapeutic Effect of Aluminum in Autoimmune Diseases: Numbing Immunity?

The paradoxical use of aluminum in treatments for some symptoms of autoimmune disorders is understandable when a strong skew toward Th1 immunity exists. The boosting of Th2-type immunity in those cases would favor a less inflammatory response (Berger, 2000[188]). However, balance, not imbalance is sought, and follow-up medical exposures to aluminum hydroxide could lead to exacerbation, or to new autoimmunity. Repeated exposure to high doses of the suspected allergen can tip the immune system toward the infection-like Th1 level; repeated exposure again to the adjuvant (in the form of vaccines) would then amplify Th2. Long-term health outcome studies of patients with autoimmune disorders treated by allergen alone vs. allergen with adjuvant are needed.

Conclusions

Animal studies and human studies alike point to ER Hyperstress as a likely manifestation of genetic x environment interactions in autoimmune disorders. Together, the studies reviewed here provide strong support for the role of aluminum as a contributor to autoimmunity in individuals for whom "small" doses may represent larger effective doses, or for whom exposures to other sources of ER stress are present. In addition to molecular mimicry, which contributes to autoimmunity from vaccines, as is evidenced by the discovery of cross-reactive antibodies, the ER Hyperstress mechanism unleashes a number of additional mechanisms of autoimmunity. The release of semi-processed human proteins due to cell death resolution of the unfolded protein response is one of the most logical sources of problematic self-antigens. The toxicity of aluminum adjuvanted vaccines is seriously underestimated for an unknown percentage of persons and families in the population. Rather than identifying patients who are most susceptible via the induction of myriad conditions of mysterious or unknown origin, screening individuals for risk, using more broadly defined risk factors and specific biomarkers would seem more humane. The use of adjuvants

that do not involve mechanisms of action that include ER Stress would leave the unfolded protein response intact, prevent ER Hyperstress, and reduce the global burden of disease from autoimmunity induced by adjuvants.

There are limitations to using animal models to determine general risk of autoimmune disorders. In particular, the chronic doses, while injected, are typically much higher than used in aluminum-containing vaccines, but in some studies the doses are delivered in a saline vehicle. Low doses of aluminum can be more, not less toxic due to failure to initiate a protective response, such as granulomas (Crépeaux et al., 2017[36]). Also, intraperitoneal injection is not used in the administration of vaccines; instead, either intramuscular or subdermal injections are used. Further, the various forms of aluminum used in animal models of autoimmunity are variously represented as dissolved powders, often in non-specified liquid with non-specified volumes. Also, the timing of injections is often planned to reflect experimental convenience and have not been replications of the CDC's current recommendations, including regular influenza vaccines, some of which contain thimerosal.

Nevertheless, it is noteworthy that the vast majority of animal studies that employ aluminum hydroxide succeed in creating autoimmune disorders in part by including ovalbumin. The evidence that aluminum hydroxide is involved in autoimmunity at vaccine dose levels in some individuals is overwhelming. The ASIA syndrome has been, by happenstance, replicated in commercial sheep (Luján et al., 2013[194]). While the inclusion of alloantigens is central to the strategy of artificial immunity, the option of excluding peptides that match human proteins to avoid molecular mimicry also appears to be have been completely overlooked in spite of the extensive work of by Kanduc and colleagues (Trost et al., 2010[195]). Discussions of the complexity of autoimmunity must – and does – overtly include a role for vaccines (Gershwin et al. 2018[196]).

The localization of the aluminum from vaccines to the brain has been empirically demonstrated – as has its long-term persistence (Khan et al., 2013[197]). Neurodegenerative diseases such as Alzheimer's disease are not usually seen as autoimmune disorders, but evidence of intrinsic immune reactions initiated by aluminum is overwhelming. Correlation of elevated Al with degenerative dementia and Alzheimer's disease has been well documented (e.g., Di Lorenzo and Di Lorenzo, 2013[192]). Excessive dietary AL can also form insoluble aluminum phosphates in the gastrointestinal tract and may lead to hypophosphataemia. Although the role of ER stress has been recognized in Parkinson's disease (Varma and Sen, 2015([54]), the importance of metals (including aluminum) is only now coming to light (Bjørklund et al., 2017[198]). The disease burden of and cost of industrial and medical uses of aluminum is likely so large as to be immeasurable.

The multifactorial causality of autoimmunity cannot exclude vaccine adjuvants including aluminum based on high doses typically used in animal models. While it is reasonable to conclude from these studies that not all and perhaps most humans will develop intermittent or chronic autoimmunity given that doses of aluminum (mg/kg) in vaccines are so low compared to experimental levels used in non-genetic risk animal models, the low dose non-linear response cannot be ignored. Additionally, the actual CDC pediatric schedule involves repeated vaccinations, separated by months, combined with vaccination of non-aluminum-containing vaccines, repeated over nearly two decades. None of the studies focused on autoimmune disorders were dose escalation studies, or synchronicity studies of multiple antigens/vaccine formulations, and none specifically tested whether ER stress from unfolded proteins combined with stress from aluminum or thimerosal administration, and few employed genetic models of mice based on observed human genetic variants associated with autoimmunity. Exceptions exist. Zhu et al. (2014[37]) successfully induced atherosclerotic lesions using vaccine-representative doses in genetic (apoE null and LDLR null C57BL/6 mice) in an environmental (dietary) background conducive to atherosclerosis.

Studies of autoimmunity that point to infectious pathogens cannot easily dismiss a role of vaccine adjuvants as causal co-factors to infections. Retrospective studies that are designed to test the hypothesis of "association" fall short of testing causality, and are ill-posed to test the ER Hyperstress hypothesis, or any other model that involves a genetically susceptible subgroup.

Nevertheless, grave concerns over the lack of empirically informed aluminum clearance rates, accurate clearance models, and tissue fates have been expressed (Masson et al., 2018[28]; Miller, 2016[29], Lyons-Weiler and Ricketson, 2018 [27]). One of the most important studies focused on injected aluminum pharmacokinetics using rabbits (Flarend et al. 1997[137]) reported very slow body clearance, often misrepresented, because 94% of the labeled, injected aluminum had not passed in urine after 28 days. The study investigators misplaced or destroyed brains and bones of some of rabbits, and body clearance and tissue compartment modeling by Mitkus et al. (2011[199) were not sufficiently informed by empirical measurements.

A greater question, however, is whether exposure to many doses of injected aluminum has led to impairments that will manifest as a pandemic in countries that use them. The increased rates of ASD, ADHD and autoimmune/autoinflammatory conditions may be the tip the iceberg. Redhead et al. (1992[178]) simulated vaccination-level exposures to aluminum hydroxide in mice and found elevated levels of aluminum in the brain 2-3 days after injection. Other animal studies focused on neurological, cognitive and behavioral effects (Yang et al., 2016[200]; Sheth et al., 2017[201]; Petrik et al., 2007[202]) have consistently reported evidence of neurological and cognitive impairment at vaccine-scaled doses of aluminum adjuvants. In individuals for which cellular detoxification is impaired, either via environmental exposures that impair ER protein folding (like aluminum (Rivzi et al., 2014[34]) and thimerosal (Stamogiannos et al., 2016[203]), genetics, or to the combined effects of both with genetic risk leading to ER Hyperstress (Lyons-Weiler, 2018), the small vaccine doses (compared to animal models) may represent unsafe doses for some individuals, families or ethnic groups.

The literature also supports the careful use of aluminum-focused chelation therapies to ease the symptoms of neuroimmune effects of aluminum exposures with added benefits of removal of other metals accumulated as a result of acquired cellular detoxification deficiency (ACDD) caused by ER Hyperstress. Responsible application of chelation techniques requires consideration of limitations (Smith et al., 2013[204]). Reduction of tissue aluminum has been reported due to consumption of high-silicic acid mineral waters (Buffoli et al., 2013[205]).

Treatments that May Ameliorate Autoimmune Effects

There is a large body of literature on drugs, supplements and treatments that can help reduce inflammation in the human body. Candidates include Vitamin D (reduces inflammation in idiopathic urticaria, astrogaloside in renal failure patients undergoing treatment (Sun et al., (2018)[206]). Jones et al., (2017[207]) measured a significant increase in the excretion of aluminum in patients who drank silicic acid-rich mineral water. Treatment of patients affected by Al burden with ten EDTA chelation therapies (EDTA intravenous administration once a week) was able to significantly reduce Al intoxication (Bamonti et al., 2011[90]).

New findings show that pediatric dosing of aluminum in vaccines, acutely high doses (mg/kg/day) in low birthweight and low body weight infants can occur (Lyons-Weiler and Ricketson, 2018 [27]). Depending on variation in clearance rates, and tissue fates, which are also inadequately characterized for the population as a whole, the repeated chronic exposures likely lead to greater rates of accumulation of aluminum in some individuals. In proper translational research, the dosage toxicity of substances – including carrier molecules in drugs – are subjected to demonstrations of dose-related safety prior to their use in humans. Aluminum was 'grandfathered' in for use in vaccines, and only proteins in vaccines must be tested for safety. Animal dosage escalation studies of injected forms of aluminum are called for because they have not been conducted to date, and the use of argument by analogy from dietary exposures in adult animals as if they apply to human infants is spurious, filled with errors, and unwarranted assumptions (Lyons-Weiler and Ricketson, 2018 [27]). More, not less, animal science is needed to answer specific questions on mechanisms of aluminum adjuvant-induced autoimmunity.

The evidence presented in this literature review is overwhelming: autoimmunity due to the adjuvantive effects of aluminum combined with the release of oddly and incompletely folded and processed proteins is extremely plausible - for those conditions reviewed. Other autoimmune/ autoinflammatory conditions that should be explored for additional evidence, such as cross-reactive antibodies, of the presence of aluminum in the inflamed tissues and the benefit of chelation include primary biliary cirrhosis, scleroderma, CREST syndrome, polymyositis, Telangiectasia, mixed connective disease, and ankylosing spondylitis (Zioła-Frankowska et al., 2017[208]). The high levels of metal concentrations observed in the cerebral spinal fluid and blood plasma of patients with amyotrophic lateral sclerosis points to failed acquired cellular detoxification syndrome, and because it included aluminum, a potential role for aluminum induced ER stress. And ER stress during placentation is a refined balancing act (Bastia-Ruiz et al., 2017[209]). Individuals seeking conception might consult with their doctor on the wisdom of injecting aluminum in any form.

ER Hyperstress From Genetic and Environmental Risk

It is also worth noting that some genetic variants in the ERAP1 gene, which is down-regulated by thimerosal (Stamogiannos et al., 2016[203]) are associated with ankylosing spondylitis (AS) – an autoimmune form of arthritis in which the vertebrae of the spine can become fused. Individuals with RA are removed from studies of AS, reducing the signal of autoimmunity from vaccination (e.g., Wang et al. 2012[210]). Variants in ERAP1 are also associated with juvenile idiopathic arthritis (Hinks e al., 2011[211]) and psoriasis (Strange et al., 2010[212]). Individuals with LOF-mutations in ERAP1 can be expected to be intolerant of aluminum and mercury from vaccines and other sources, and the harm to ERAP1 expression in the absence of genetic risk can be considered a form of phenomimicry.

Loebel et al. (2016[213]) found antibodies to adrenergic and muscarinic cholinergic receptors in patients with chronic fatigue syndrome – pointing strongly to CFS as an autoimmune disease. It is reported that the same autoantibodies have been found in individuals suffering from malaise and lethargy post-HPV vaccination (HPV Cancer.org, 2017[214), but those results have not yet been published.

Metal cellular detoxification is a biological process that involves complex pathways, and thus some individuals will be less tolerant than others to exposures. Both aluminum and mercury bind to sulfhydryl (sulfur-containing) groups of glutathione. Mercury and aluminum both inhibit cellular detoxification mechanisms and signals. Mutations in any of the hundreds of genes involved in cellular detoxification – which may include mutations in proteins involved in fairly basic cellular functions – will confer reduced capacity. More importantly, genetic sensitivity to mercury (Austin et al., 2014[215]; Westphal et al. 2000[216]) and aluminum (Fosmire et al., 1993[217]) are known. Metals themselves can be antigenic allergens (Kutlu et al., 2016[218]).

Hypersensitivity to aluminum can thwart attempts to immunize with aluminum-containing vaccines (Murphy, 1991[219]). There is also evidence of genetic susceptibility to hypersensitivity to mercury (Austin et al., 2014[215]), and toxicity of ethylmercury is traced to ER-stress (Choi et al., 220). Aluminum can impair P450 mediated microsomal cellular detoxification (Zhu et al., 2017; 221). Aluminum in the brain of people with autism (Mold et al. 2018[222]) likely play a role in chronic microglial activation via the same mechanisms. ER stress and the unfolded protein response has proven central to every autoimmune disorder in which it has been studied (e.g., Pathinayake et al, 2018 [225]; Lee et al. (2015) [226]; Wang et al., [227]). We need to focus on all sources of metals and defects in cellular detoxification, observed in atherosclerosis (Lind et al (2012[228]), multiple sclerosis (Exley et al, 2006; [226]), and ALS (Roos [229]). The role of ER Hyperstress appears to be also be central in ASD (Lyons-Weiler et al. 2018 [30]). Epidemiological studies are variable in the outcome, and pliable to manipulations, and those that have found association of autoimmunity (e.g., Wang et al., 2012 [230] have not led to changes in vaccine formulations.

This review points to how any number of proteins could carry variation that increases protein intrinsic order, leading to genetic ER stress, combined with environmental ER stress leading to ER Hyperstress in the presence of

aluminum and mercury. It is time to respect these minorities' increased specific risk with respect for their differences when considering legislation on vaccine options, and in the medical practice of immunization.

References

1. Rock MT, Yoder SM, Talbot TR et al. Adverse events after smallpox immunizations are associated with alterations in systemic cytokine levels. J Infect Dis. 2004;189:1401-10.
2. Noack M, Miossec P. Th17 and regulatory T cell balance in autoimmune and inflammatory diseases. Autoimmun Rev. 2014; 13(6):668-77.
3. Hu D, Notarbartolo S, Croonenborghs T, Patel B, et al. Transcriptional signature of human pro-inflammatory TH17 cells identifies reduced IL10 gene expression in multiple sclerosis. Nat Commun. 2017;8(1):1600.
4. Hashimoto M Regulatory Th17 in Animal Models of Rheumatoid Arthritis. J Clin Med. 2017;6(7). pii: E73.
5. Safdari V, Alijani E, Nemati M, Jafarzadeh A. Imbalances in T cell-related transcription factors Among patients with Hashimoto's Thyroiditis. Sultan Qaboos Univ Med J. 2017;17:e174-e180.
6. Zayoud M et al. Ras Signaling Inhibitors Attenuate Disease in Adjuvant-Induced Arthritis via Targeting Pathogenic Antigen-Specific Th17-Type Cells. Front Immunol. 2017;8:799.
7. Aizman E. Therapeutic effect of farnesylthiosalicylic acid on adjuvant-induced arthritis through suppressed release of inflammatory cytokines. Clin Exp Immunol. 2014;175:458-67.
8. Terhune TD, Deth RC. A role for impaired regulatory T cell function in adverse responses to aluminum adjuvant-containing vaccines in genetically susceptible individuals. Vaccine. 2014;32:5149-55.
9. Nachamkin I, Allos BM, Ho T. Campylobacter species and Guillain-Barré syndrome. Clin Microbiol Rev. 1998; 11:555-67.
10. Ahmed SS, Volkmuth W, Duca J, Corti L, Pallaoro M, Pezzicoli A et al. Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2. Sci Transl Med 2015; 7:294ra105.
11. US Department of Health and Human Services. Vaccine Injury Table. 2017; https://www.hrsa.gov/sites/default/files/vaccinecompensation/vaccineinjurytable.pdf
12. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, Keenlyside RA, Ziegler DW, Retailliau HF et al. Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977. Am J Epidemiol 1979;110:105–123.
13. Schoenfeld, Y. 2013. Video Q&A: what is ASIA? An interview with Yehuda Shoenfeld BMC Med. 11:118.
14. Bragazzi NL. Advances in our understanding of immunization and vaccines for patients with systemic lupus erythematosus. Expert Rev Clin Immunol. 2017;13(10):939-949.
15. Perricone C and Shoenfeld, Y. Hepatitis B vaccination and undifferentiated connective tissue disease: another brick in the wall of the autoimmune/inflammatory syndrome induced by adjuvants (Asia) Journal of Clinical Rheumatology 2013;19:231–233.
16. Watad A, David P, Brown S, Shoenfeld Y. Autoimmune/Inflammatory Syndrome Induced by Adjuvants and Thyroid Autoimmunity. Front Endocrinol (Lausanne). 2017:7:150. doi: 10.3389/fendo.2016.00150.
17. Colafrancesco S, Perricone C, Shoenfeld Y. Autoimmune/Inflammatory Syndrome Induced by Adjuvants and Sjögren's Syndrome. Isr Med Assoc J. 18:150-3.
18. Colafrancesco S, Perricone C, Priori R, Valesini G, Shoenfeld Y. Sjögren's syndrome: another facet of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA). J Autoimmun. 2014 51:10-6. doi: 10.1016/j.jaut.2014.03.003.
19. Tomljenovic L, Colafrancesco S, Perricone C, Shoenfeld Y. Postural Orthostatic Tachycardia with Chronic Fatigue After HPV Vaccination as Part of the "Autoimmune/Auto-inflammatory Syndrome

Induced by Adjuvants": Case Report and Literature Review. J Investig Med High Impact Case Rep. 2014;2:2324709614527812.
20. Colafrancesco S, Perricone C, Tomljenovic L, Shoenfeld Y. Human papilloma virus vaccine and primary ovarian failure: another facet of the autoimmune/inflammatory syndrome induced by adjuvants. Am J Reprod Immunol. 2013;70:309-16. doi: 10.1111/aji.12151.
21. Watad A. The autoimmune/inflammatory syndrome induced by adjuvants (ASIA)/Shoenfeld's syndrome: descriptive analysis of 300 patients from the international ASIA syndrome registry. Clin Rheumatol. 2018;37(2):483-493.
22. Cheng MP, Kozoriz MG, Ahmadi AA, Kelsall J, Paquette K, Onrot JM. Post-vaccination myositis and myocarditis in a previously healthy male. Allergy Asthma Clin Immunol 2016;12:6. doi: 10.1186/s13223-016-0114-4.
23. Anaya JM, Ramirez-Santana C, Alzate MA, Molano-Gonzalez N, Rojas-Villarraga A. The Autoimmune Ecology. Front Immunol. 2016;26;7:139. doi: 10.3389/fimmu.2016.00139.
24. Morris G, Puri BK, Frye RE. The putative role of environmental aluminium in the development of chronic neuropathology in adults and children. How strong is the evidence and what could be the mechanisms involved? Metab Brain Dis. 2017; 32(5):1335-1355. doi: 10.1007/s11011-017-0077-2.
25. Vadalà M, Poddighe D, Laurino C, Palmieri B. Vaccination and autoimmune diseases: is prevention of adverse health effects on the horizon? EPMA J. 2017;8(3):295-311.
26. Segal Y, Shoenfeld Y. Vaccine-induced autoimmunity: the role of molecular mimicry and immune crossreaction. Cell Mol Immunol. 2018;doi: 10.1038/cmi.2017.151.
27. Lyons-Weiler, J and Ricketson, R. 2018. Reconsideration of the immunotherapeutic pediatric safe dose levels of aluminum. Journal and Trace Elements in Medicine and Biology 2018; 48:67-73.
28. Masson JD, Crépeaux G, Authier FJ, Exley C, Gherardi RK. Critical analysis of reference studies on the toxicokinetics of aluminum-based adjuvants. J Inorg Biochem. 2018; 181:87-95. doi: 10.1016/j.jinorgbio.2017.12.015.
29. Miller, N. Aluminum in Childhood Vaccines is Unsafe. Journal of American Physicians and Surgeons 2016;21: 109-117. www.jpands.org/vol21no4/miller.pdf
30. Lyons-Weiler, J. Autism is an acquired cellular detoxification deficiency syndrome with heterogeneous genetic predisposition. Autism Open Access 2018;8:1-17.
31. Kawahara M, Kato-Negishi M. Link between aluminum and the pathogenesis of Alzheimer's disease: The integration of the aluminum and amyloid cascade hypotheses. Int J Alzheimers Dis. 2011;2011:276393. doi: 10.4061/2011/276393.
32. Aremu DA, Ezomo OF, Meshitsuka S. Gene expression in primary cultured astrocytes affected by aluminum: alteration of chaperons involved in protein folding. Environ Health Prev Med. 2011;16:16-24.
33. Rizvi SH, Parveen A, Ahmad I, Ahmad I, Verma AK, Arshad M, Mahdi AA. Aluminum Activates PERK-EIF2α Signaling and Inflammatory Proteins in Human Neuroblastoma SH-SY5Y Cells. Biol Trace Elem Res. 2016;172(1):108-19.
34. Rizvi MSH, Parveen A, Verma AK, Ahmad I, Arshad M, Mahdi AA. Aluminium induced endoplasmic reticulum stress mediated cell death in SH-SY5Y neuroblastoma cell line is independent of p53. PLoS One. 2014;30;9(5):e98409.
35. Marichal T, Ohata K, Bedoret D, et al. DNA released from dying host cells mediates aluminum adjuvant activity. Nat Med. 2011;17:996-1002.
36. Crépeaux G, Eidi H, David MO, Baba-Amer Y, Tzavara E, Giros B, Authier FJ, Exley C, Shaw CA, Cadusseau J, Gherardi RK. Non-linear dose-response of aluminium hydroxide adjuvant particles: Selective low dose neurotoxicity. Toxicology. 2017; 375:48-57.
37. Zhu L, He Z, Wu F, Ding R6, Jiang Q, Zhang J, Fan M, Wang X, Eva B, Jan N, Liang C, Wu Z. Immunization with advanced glycation end products modified low density lipoprotein inhibits atherosclerosis progression in diabetic apoE and LDLR null mice. Cardiovasc Diabetol. 2014;13:151

38. Kelly-Scumpia KM, Nacionales DC, Scumpia PO, et al. In vivo adjuvant activity of the RNA component of the Sm/RNP lupus autoantigen. Arthritis Rheum. 2007;56:3379-86.
39. Yasar M, Savranlar Y, Karaman H, et al. Effects of propolis in an experimental rat model of allergic rhinitis. Am J Otolaryngol. 2016;37:287-93.
40. Elsakkar MG, Sharaki OA, Abdallah DM. Adalimumab ameliorates OVA-induced airway inflammation in mice: Role of CD4(+) CD25(+) FOXP3(+) regulatory T-cells.. Eur J Pharmacol. 2016;786:100-108.
41. Qi X, Han L, Liu X, Zhi J, Zhao B, Chen D, Yu F, Zhou X. Prostate extract with aluminum hydroxide injection as a novel animal model for chronic prostatitis/chronic pelvic pain syndrome. Urology. 2012;80:1389.e9-15.
42. Brandt EB, Scribner TA, Akei HS, Rothenberg ME. Experimental gastrointestinal allergy enhances pulmonary responses to specific and unrelated allergens. J Allergy Clin Immunol. 118;420-7.
43. Agmon-Levin N, Arango MT, Kivity S, Katzav A, Gilburd B, Blank M, Tomer N, Volkov A, Barshack I, Chapman J, Shoenfeld Y. Immunization with hepatitis B vaccine accelerates SLE-like disease in a murine model. J Autoimmun. 54:21-32.
44. Yang M, Li LH, Wang D, Hou XR, Zhang Y. [Analysis on Influencing Factors of Acupoint Injection of Drugs for Improving Allergic Rhinitis in Rats]. [Article in Chinese] Zhen Ci Yan Jiu. 2016;41:220-4.
45. Xi L, Fan E, Zhao Y, Li Y, Zhang Y, Zhang L. Role of aluminum adjuvant in producing an allergic rhinitis animal model. Genet Mol Res. 2014;13:5173-81.
46. Sagawa K, Nagatani K, Komagata Y, Yamamoto K. Angiotensin receptor blockers suppress antigen-specific T cell responses and ameliorate collagen-induced arthritis in mice. Arthritis Rheum. 2005;52:1920-8.
47. Han S, Lemire J, Appanna VP, Auger C, Castonguay Z, Appanna VD. How aluminum, an intracellular ROS generator promotes hepatic and neurological diseases: the metabolic tale. Cell Biol Toxicol. 2013;29:75-84.
48. Sano R, Reed JC. ER stress-induced cell death mechanisms. Biochim Biophys Acta. 1833;3460-3470.
49. Tovo-Rodrigues et al., 2016. The role of protein intrinsic disorder in major psychiatric disorders. Am J Med Genet B Neuropsychiatr Genet. 2016; 171(6):848-60.
50. Rose S, Wynne R, Frye RE, Melnyk S, James SJ. Increased susceptibility to ethylmercury-induced mitochondrial dysfunction in a subset of autism lymphoblastoid cell lines. J Toxicol. 2015;2015:573701.
51. Eupedia, 2018. Autoimmune Diseases – SNPS. https://www.eupedia.com/genetics/autoimmune_diseases_snp.shtml
52. Gao D, Li T, Li XD, Chen X, Li QZ, Wight-Carter M, Chen ZJ. Activation of cyclic GMP-AMP synthase by self-DNA causes autoimmune diseases. Proc Natl Acad Sci USA. 2015;112(42):E5699-705.
53. Cornejo VH, Hetz C. The unfolded protein response in Alzheimer's disease. Semin Immunopathol. 35(3):277-92.
54. Varma D, Sen D. 2015. Role of the unfolded protein response in the pathogenesis of Parkinson's disease. Acta Neurobiol Exp (Wars). 2015;75(1):1-26.
55. Back SH, Kaufman RJ. Endoplasmic reticulum stress and type 2 diabetes. Annu Rev Biochem. 2012;81:767-93.
56. Lee J, Ozcan U. Unfolded protein response signaling and metabolic diseases. J Biol Chem. 2014;289(3):1203-11.
57. Garaud JC, Schickel JN, Blaison G et al. B cell signature during inactive systemic lupus is heterogeneous: toward a biological dissection of lupus. PLoS One 2011;6:e23900.
58. Lemire, J Mailloux R, Puiseux-Dao S, Appanna VD. Aluminum-induced defective mitochondrial metabolism perturbs cytoskeletal dynamics in human astrocytoma cells J Neurosci Res 2009;87:1474-83.
59. Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, Holl JL. The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics. 2011;128(1):e9-17.

60. Hoyt, AEW, P. Heymann, A Schuyler, S Commins and TAE Platts-Mills. Changes in IgE Levels Following One-Year Immunizations in Two Children with Food Allergy. World Allergy Organization Symposium on Food Allergy and the Microbiome, 2015. https://wao.confex.com/wao/2015symp/webprogram/Paper9336.html
61. Mawson AR, Ray BD, Bhuiyan AR, Jacob B Pilot comparative study on the health of vaccinated and unvaccinated 6- to 12-year-old U.S. children. J Transl Sci 2017;3: DOI: 10.15761/JTS.1000186
62. Anderson HR, Pottier AC, Strachan DP. 1992. Asthma from birth to age 23: incidence and relation to prior and concurrent atopic disease. Thorax. 1992;47:537-42.
63. Wright AL. The epidemiology of the atopic child: who is at risk for what? J Allergy Clin Immunol. 2004;113(1 Suppl):S2-7.
64. Kim JH, Kim JK, Son BK, Oh JE, Lim DH, Lee KH, Hong YC, Cho SI. Effects of air pollutants on childhood asthma. Yonsei Med J. 2005;46:239-44.
65. McDonald K et al.,2008. Delay in diphtheria, pertussis, tetanus vaccination is associated with a reduced risk of childhood asthma. J Allergy Clin Immunol. 121(3):626-31. doi: 10.1016/j.jaci.2007.11.034
66. Li Z, Geng M. [Effect of budesonide on the expression of IL-12 in animal model of minimal persistent inflammation of allergic rhinitis in rats]. [Article in Chinese] Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2015;29:270-4.
67. Kovacova-Hanuskova E, Gavliakova S, Buday T et al. The effect of selective antagonist of H4 receptor JNJ7777120 on nasal symptoms, cough, airway reactivity and inflammation in guinea pigs. Respir Physiol Neurobiol. 2015;216:9-14.
68. Arora P, Ansari SH, Najmi AK, Anjum V, Ahmad S. Investigation of anti-asthmatic potential of dried fruits of Vitis vinifera L. in animal model of bronchial asthma. Allergy Asthma Clin Immunol. 2016;12:42.
69. Arora P, Ansari SH, Anjum V, Mathur R, Ahmad S. Investigation of anti-asthmatic potential of Kanakasava in ovalbumin-induced bronchial asthma and airway inflammation in rats. J Ethnopharmacol. 2017; 197:242-249.
70. Zeng W, Wu C, Dai Y. [Regulatory effects of luteolin on airway inflammation in asthmatic rats]. [Article in Chinese] Zhonghua Yi Xue Za Zhi. 2014;26;94(32):2535-9.
71. Shi YH, Shi GC, Wan HY, Jiang LH, et al. Coexistence of Th1/Th2 and Th17/Treg imbalances in patients with allergic asthma. Chin Med J (Engl). 2011;124:1951–6.
72. Liu F, Yu J, Bai L, Xue Z, Zhang X. Pingchuan formula improves asthma via restoration of the Th17/Treg balance in a mouse model. BMC Complement Altern Med. 2015 16;15:234.
73. Taiwo OA, Sircar KD, Slade MD, et al. Incidence of asthma among aluminum workers. J Occup Environ Med. 2006;48:275-82.
74. Taiwo OA. Diffuse parenchymal diseases associated with aluminum use and primary aluminum production. J Occup Environ Med. 2014;56(5 Suppl):S71-2.
75. Bibi H, Vinokur V, Waisman D, et al. Zn/Ga-DFO iron-chelating complex attenuates the inflammatory process in a mouse model of asthma. Redox Biol. 2014;2:814-9.
76. Gascon M, Sunyer J, Martínez D, Guerra S, Lavi I, Torrent M, Vrijheid M. Persistent organic pollutants and children's respiratory health: the role of cytokines and inflammatory biomarkers. Environ Int. 2014;69:133-40.
77. Karmaus, W. et al. Infections and atopic disorders in childhood and organochlorine exposure. Arch Environ Health 2001; 56:485-492.
78. Hernández AF, Casado I, Pena G, Gil F, Villanueva E, Pla A. Low level of exposure to pesticides leads to lung dysfunction in occupationally exposed subjects. Inhal Toxicol. 2008 20:839-49.
79. Hernández E, Barraza-Villarreal A, Escamilla-Núñez MC et al. 2013. Prenatal determinants of cord blood total immunoglobulin E levels in Mexican newborns. Allergy Asthma Proc 34(5):e27-34.

80. Zivković I, Petrušić V, Dimitrijević R, Stojanović M, Dimitrijević L. Adjuvant dependence of APS pathology-related low-affinity antibodies during secondary immune response to tetanus toxoid in BALB/c mice. Immunol Res. 2013;56:143-9. doi: 10.1007/s12026-012-8378-3.
81. Zivkovic IP, Stojanovic MM, Petrusic VZ, Inic-Kanada AB, Micic MV, Dimitrijevic LA. Network connectivity is shown to change in C57BL/6 mice during a continuing immune response subsequent to tetanus toxoid hyperimmunization. Biol Res. 2010;43:393-402.
82. Pierangeli SS, Harris EN. Induction of phospholipid-binding antibodies in mice and rabbits by immunization with human beta 2 glycoprotein 1 or anticardiolipin antibodies alone. Clin Exp Immunol. 1993;93:269-72.
83. D'alò GL, Zorzoli E, Capanna A, Gervasi G, Terracciano E, Zaratti L, Franco E. Frequently asked questions on seven rare adverse events following immunization. J Prev Med Hyg 2017;58:E13-E26.
84. Rigolet M, Aouizerate J, Couette M, et al. Clinical features in patients with long-lasting macrophagic myofasciitis. Front Neurol. 2014;28;5:230.
85. Martinez-Florez, JA. 2016. Antiphospholipid Syndrome and Kidney Involvement: New Insights. Antibodies 5:17 doi:10.3390/antib5030017
86. FDA, 2017. CFR - Code of Federal Regulations Title 21, Volume 4 [21CFR201.323]
87. Xiao Y, Motomura S, Podack ER. APRIL (TNFSF13) regulates collagen-induced arthritis, IL-17 production and Th2 response. Eur J Immunol. 2008;38:3450-8.
88. Croke CL, Munson EL, Lovrich SD, Christopherson JA, Remington MC, England DM, Callister SM, Schell RF. 2000. Occurrence of severe destructive lyme arthritis in hamsters vaccinated with outer surface protein A and challenged with Borrelia burgdorferi. Infect Immun. 2000;68:658-63.
89. Vudattu, NK, K Strle, AC Steere and EE Drouin. Dysregulation of CD4CD25high T Cells in the Synovial Fluid of Patients with Antibiotic-Refractory Lyme Arthritis. Arthritis & Rheumatism 2013;65:1643-1653.
90. Bamonti F, Fulgenzi A, Novembrino C, Ferrero ME. 2011. Metal chelation therapy in rheumathoid arthritis: a case report. Successful management of rheumathoid arthritis by metal chelation therapy. Biometals. 2011; 24:1093-8. doi: 10.1007/s10534-011-9467-9.
91. Bell, IR and CM Baldwin. 2013. Multiple Chemical Sensitivity. IN Women and Health, 2013 (2nd Ed):1379-1394, Academic Press.
92. Park YJ, Yoo SA, Kim WU. Role of endoplasmic reticulum stress in rheumatoid arthritis pathogenesis. J Korean Med Sci. 2014;29:2-11.
93. Ray P, Black S, Shinefield H, Dillon A, Carpenter D, Lewis E, Ross P, Chen RT, Klein NP, Baxter R; Vaccine Safety Datalink Team. Risk of rheumatoid arthritis following vaccination with tetanus, influenza and hepatitis B vaccines among persons 15-59 years of age. Vaccine. 2011;29:6592-7.
94. Mitchell LA, Tingle AJ, MacWilliam L, et al. HLA-DR class II associations with rubella vaccine-induced joint manifestations. The Journal of infectious diseases 1998;177:5-12.
95. Institute of Medicine. In: Stratton K, Ford A, Rusch E, Clayton EW, eds. Adverse Effects of Vaccines: Evidence and Causality. Washington (DC): National Academies Press (US); 2012.
96. Kim SC, Song YS, Kim YT, et al. Human papillomavirus 16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in 15-25 years old healthy Korean women. J Gynecol Oncol 2011;22:67-75.
97. Jackson LA, Gaglani MJ, Keyserling HL, et al. Safety, efficacy, and immunogenicity of an inactivated influenza vaccine in healthy adults: a randomized, placebo-controlled trial over two influenza seasons. BMC Infect Dis 2010;10:71.
98. Chistiakov DA, Sobenin IA, Orekhov AN, Bobryshev YV. Role of endoplasmic reticulum stress in atherosclerosis and diabetic macrovascular complications. Biomed Res Int. 2014;2014:610140. doi: 10.1155/2014/610140.
99. Zhou AX and I Tabas. The UPR in atherosclerosis. Semin Immunopathol. 35(3):321-32.

100. Tabas I. 2010. The role of endoplasmic reticulum stress in the progression of atherosclerosis. Circ Res. 2010 Oct 1;107(7):839-50. doi: 10.1161/CIRCRESAHA.110.224766.
101. Nishizono S, Kusaba M, Adan Y, Imaizumi K. Induction of atherosclerosis in Brown Norway rats by immunization with ovalbumin. Biosci Biotechnol Biochem. 1999;63:379-83.
102. Lamas GA, Ergui I. Chelation therapy to treat atherosclerosis, particularly in diabetes: is it time to reconsider? Expert Rev Cardiovasc Ther. 2016;14:927-38.
103. Querfeld U. Is atherosclerosis accelerated in young patients with end-stage renal disease? The contribution of paediatric nephrology. Nephrol Dial Transplant. 2002 17:719-22.
104. Jablonski, KL and M Chonchol. Vascular calcification in end-stage renal disease. Hemodial Int. 2013;17(0 1): 10.1111/hdi.12084.
105. Jan M, Meng S, Chen NC, Mai J, Wang H, Yang XF. Inflammatory and autoimmune reactions in atherosclerosis and vaccine design informatics. J Biomed Biotechnol. 2010;2010:459798.
106. Zhou J Lhoták S, Hilditch BA, Austin RC. Activation of the unfolded protein response occurs at all stages of atherosclerotic lesion development in apolipoprotein E-deficient mice. Circulation. 2005;12;111:1814-21.
107. Katz-Agranov, N and G Zandman-Goddard. 2015. Systemic Lupus Erythematosus Induced by Vaccines. Chapter 22 IN: Vaccines and Autoimmunity, Y Shoenfel, N Agmon-Levin and L Tomljenovic (Eds), Wiley.
108. Wang B, Shao X, Wang D, Xu D, Zhang JA. 2017. Vaccinations and risk of systemic lupus erythematosus and rheumatoid arthritis: A systematic review and meta-analysis. Autoimmun Rev. 2017;16(7):756-765.
109. KlackI K, BonfaII E, Ferreira, E, NetoII B. 2012Diet and nutritional aspects in systemic lupus erythematosus Rev. Bras. Reumatol. 52 http://dx.doi.org/10.1590/S0482-50042012000300009
110. Marks ES, Bonnemaison ML, Brusnahan SK, Zhang W, Fan W, Garrison JC, Boesen EI. Renal iron accumulation occurs in lupus nephritis and iron chelation delays the onset of albuminuria. Sci Rep. 2017;7(1):12821.
111. Mandelbrot DA, Santos PW, Burt RK, Oyama Y, et al. Resolution of SLE-related soft-tissue calcification following haematopoietic stem cell transplantation. Nephrol Dial Transplant. 2008;23:2679-84. doi: 10.1093/ndt/gfn036.
112. Guo G, Meng Y, Tan W, Xia Y, Cheng C, Chen X, Gu Z. Induction of apoptosis coupled to endoplasmic reticulum stress through regulation of CHOP and JNK in bone marrow mesenchymal stem cells from patients with systemic lupus erythematosus. J Immunol Res. 2015;2015:183738.
113. Bagavant H, Nandula SR, Kaplonek P, Rybakowska PD, Deshmukh US. Alum, an aluminum-based adjuvant, induces Sjögren's syndrome-like disorder in mice. Clin Exp Rheumatol. 2014;32:251-5.
114. Jeong HS, Lee HK, Ha YJ, Kim DH, Suh IS. Benign lymphoepithelial lesion of parotid gland and secondary amyloidosis as concurrent manifestations in Sjögren's Syndrome. Arch Plast Surg. 2015;42:380-3.
115. Migliore A, Bizzi E, Massafra U, Capuano A, Martin Martin LS. Multiple chemical sensitivity syndrome in Sjögren's syndrome patients: casual association or related diseases? Arch Environ Occup Health. 2006;61:285-7.
116. Ebert EC. Gastrointestinal and hepatic manifestations of Sjogren syndrome. J Clin Gastroenterol. 2012;46:25-30.
117. Pali-Schöll I, Herzog R, Wallmann J, Szalai K, et al. Antacids and dietary supplements with an influence on the gastric pH increase the risk for food sensitization. Clin Exp Allergy. 2010;40(7):1091-8. doi: 10.1111/j.1365-2222.2010.03468.x.
118. Shishehbor F, Behroo L, Ghafouriyan Broujerdnia M, Namjoyan F, Latifi SM. Quercetin effectively quells peanut-induced anaphylactic reactions in the peanut sensitized rats. Iran J Allergy Asthma Immunol. 2010;9:27-34.

119. Ahrens B, Quarcoo D, Buhner S, Reese G, Vieths S, Hamelmann E. Development of an animal model to evaluate the allergenicity of food allergens. Int Arch Allergy Immunol. 2014;164:89-96.
120. Hoyt, AEW, AJ Schuyler, PW Heymann, TAE Platts-Mills, and SP Commins. Alum-containing vaccines increase total and food allergen-specific IgE, and cow's milk oral desensitization increases Bosd4 IgG4 while peanut avoidance increases Arah2 IgE: The complexity of today's child with food allergy. J Allergy Clin Immunol 2016;137:492
121. Tong P, Gao L, Gao J, Li X, Wu Z, Yang A, Chen H. Iron-induced chelation alleviates the potential allergenicity of ovotransferrin in a BALB/c mouse model. Nutr Res. 2017;47:81-89.
122. Genuis SJ. Sensitivity-related illness: the escalating pandemic of allergy, food intolerance and chemical sensitivity. Sci Total Environ. 408(24):6047-61.
123. Heilbrun LP, Palmer RF, Jaen CR, Svoboda MD, Perkins J, Miller CS. Maternal chemical and drug intolerances: potential risk factors for autism and attention deficit hyperactivity disorder (ADHD). J Am Board Fam Med. 2015; 28:461-70. doi: 10.3122/jabfm.2015.04.140192.
124. Bassi N, Luisetto R, Ghirardello A, Gatto M, Bottazzi B, Shoenfeld Y, Punzi L, Doria A. 2012. Vaccination of mice for research purpose: alum is as effective as and safer than complete Freund adjuvant. Reumatismo. 64:380-7.
125. Hood SA. Successful treatment of dialysis osteomalacia and dementia, using desferrioxamine infusions and oral 1-alpha hydroxycholecalciferol. Am J Nephrol. 1984;4:369-74.
126. Levy R, Shohat L, Solomon B. Specificity of an anti-aluminium monoclonal antibody toward free and protein-bound aluminium. J Inorg Biochem. 1998;69:159-63.
127. Cruz-Tapias P, Agmon-Levin N, Israeli E, Anaya JM, Shoenfeld Y. Autoimmune (auto-inflammatory) syndrome induced by adjuvants (ASIA)--animal models as a proof of concept. Curr Med Chem. 2013;20:4030-6.
128. Ameratunga R, Gillis D, Gold M, Linneberg A, Elwood JM. Evidence Refuting the Existence of Autoimmune/Autoinflammatory Syndrome Induced by Adjuvants (ASIA). J Allergy Clin Immunol Pract 2017;5(6):1551-1555.e1. doi: 10.1016/j.jaip.2017.06.033.
129. Kivity S, Arango MT, Molano-González N, Blank M, Shoenfeld Y. Phospholipid supplementation can attenuate vaccine-induced depressive-like behavior in mice. Immunol Res. 2017;65:99-105.
130. Ameratunga R, Langguth D, Hawkes D. Perspective: Scientific and ethical concerns pertaining to animal models of autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA). Autoimmun Rev. 2018;17:435-439. doi: 10.1016/j.autrev.2017.11.033.
131. Sabatos-Peyton CA, Verhagen J, Wraith DC. Antigen-specific immunotherapy of autoimmune and allergic diseases. Curr Opin Immunol. 2010;22(5):609-15. doi: 10.1016/j.coi.2010.08.006.
132. Turkcapar N, Kinikli G, Sak SD, Duman M. Specific immunotherapy-induced Sjögren's syndrome. Rheumatol Int. 2005 26(2):182-4.
133. Linneberg A, Madsen F, Skaaby T. 2012. Allergen-specific immunotherapy and risk of autoimmune disease. Curr Opin Allergy Clin Immunol. 12(6):635-9. doi: 10.1097/ACI.0b013e3283588c8d.
134. Bozek A, Kołodziejczyk K, Bednarski P. 2015. The relationship between autoimmunity and specific immunotherapy for allergic diseases. Hum Vaccin Immunother. 11(12):2764-8. doi: 10.1080/21645515.2015.1087627.
135. Sabatos-Peyton CA, Verhagen J, Wraith DC. Antigen-specific immunotherapy of autoimmune and allergic diseases. Curr Opin Immunol. 2010;22:609-15.
136. Turkalj M, Banic I, Anzic SA. Patient Prefer Adherence. 2017;11:247-257.
137. Flarend RE, Hem SL, White JL, Elmore D, Suckow MA, Rudy AC, Dandashli EA. In vivo absorption of aluminium-containing vaccine adjuvants using 26Al. Vaccine. 1997;15(12-13):1314-8.
138. Vieira, SM, Hiltensperger M, Kumar V et al. et al. Translocation of a gut pathobiont drives autoimmunity in mice and humans science. Science 2018;359:1156-1161.
139. Mu Q, Kirby J, Reilly CM, Luo XM. Leaky gut as a danger signal for autoimmune diseases. Front Immunol. 2017;8:598.

140. Pineton de Chambrun, G, Body-Malapel M, Frey-Wagner I et al. Aluminum enhances inflammation and decreases mucosal healing in experimental colitis in mice. Mucosal Immunol. 2014;7: 589–601.
141. Klarquist J, Janssen EM. The bm12 Inducible Model of Systemic Lupus Erythematosus (SLE) in C57BL/6 Mice. J Vis Exp. 2015;(105):e53319. doi: 10.3791/53319.
142. Morokata T Ishikawa J, Ida K, Yamada T. C57BL/6 mice are more susceptible to antigen-induced pulmonary eosinophilia than BALB/c mice, irrespective of systemic T helper 1/T helper 2 responses. Immunology. 1999;98:345–351.
143. Reddy, AT, Laksmi, SP and Reddy, RC. Murine model of allergen induced asthma. J Vis Exp. 2012;63:3771.
144. Inbar R, 2017. Behavioral abnormalities in female mice following administration of aluminum adjuvants and the human papillomavirus (HPV) vaccine Gardasil. Immunol Res. 2017;65:136-149.
145. Dimitrijević L, Živković I, Stojanović M, Petrušić V, Živančević-Simonović S. Vaccine model of antiphospholipid syndrome induced by tetanus vaccine. Lupus. 2012;21:195-202.
146. Smith, JA Regulation of cytokine production by the unfolded protein response; implications for infection and autoimmunity Front Immunol 2018 doi: 10.3389/fimmu.2018.00422 https://www.frontiersin.org/articles/10.3389/fimmu.2018.00422/full
147. Anwar, A et al. Advanced glycation endproducts, dityrosine and arginine transporter dysfunction in autism - a source of biomarkers for clinical diagnosis, Molecular Autism 2018; DOI: 10.1186/s13229-017-0183-3.
148. Jaronen M, Goldsteins G, Koistinaho J. ER stress and unfolded protein response in amyotrophic lateral sclerosis-a controversial role of protein disulphide isomerase. Front Cell Neurosci 2014;8:402.
149. Doyle KM, Kennedy D, Gorman AM, Gupta S, Healy SJ, Samali A. Unfolded proteins and endoplasmic reticulum stress in neurodegenerative disorders. J Cell Mol Med. 2011;15(10):2025-39.
150. Kaplan, MH and Svec, KH. Immunologic relation of Streptococcal and tissue antigens. III. Presence in human sera of Streptococcal antibody cross-reactive with heart tissue. Association with Streptococcal infection, rheumatic fever, and glomerulonephritis. J Exp Med 1964; 119:651-66.
151. Hughes M, Machardy SM, Sheppard AJ, Woods NC. Evidence for an immunological relationship between Streptococcus mutans and human cardiac tissue. Infect Immun. 1980;27:576-88.
152. Hou S, Kumar A, Xu Z, Airo AM, Stryapunina I, et al. Zika virus hijacks stress granule proteins and modulates the host stress response. J Virol 2017; JVI.00474-17.
153. Clavarino G, Adriouach S, Quesada JL, Clay M et al. Unfolded protein response gene GADD34 is overexpressed in rheumatoid arthritis and related to the presence of circulating anti-citrullinated protein antibodies. Autoimmunity. 2016;49(3):172-8.
154. Dong D, Ni M, Li J, Xiong S et al. Critical role of the stress chaperone GRP78/BiP in tumor proliferation, survival, and tumor angiogenesis in transgene-induced mammary tumor development. Cancer Res. 2008;68(2):498-505.
155. Ambarus C, Yeremenko N, Tak PP, Baeten D. Pathogenesis of spondyloarthritis: autoimmune or autoinflammatory? Curr Opin Rheumatol. 2012;24:351-8.
156. Grootjans J, Kaser A, Kaufman RJ, Blumberg RS. The unfolded protein response in immunity and inflammation. Nat Rev Immunol. 2016;16:469-84.
157. Osorio F, Lambrecht BN, Janssens S. Antigen presentation unfolded: identifying convergence points between the UPR and antigen presentation pathways. Curr Opin Immunol. 2018; 52:100-107.
158. Piovesan D. 2018. MobiDB 3.0: more annotations for intrinsic disorder, conformational diversity and interactions in proteins. Nucleic Acids Res. 2018;46:D471-D476.
159. Demicheli V, Rivetti A, Debalini MG, Di Pietrantonj C. Vaccines for measles, mumps and rubella in children. Cochrane Database of Systematic Reviews. 2012;2CD004407
160. Hernán MA, Jick SS, Olek MJ, Jick H. Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study. Neurology. 2004;63:838-42.

161. Ahmed, S and Steinman L. Narcolepsy and influenza vaccination-induced autoimmunity Ann Transl Med. 2017;5:25.
162. Bruzzese, V, Zullo, A, Hassan, C. Connective tissue disease following hepatitis B vaccination. Journal of Clinical Rheumatology. 2013 19;280–281.
163. Perricone C, Shoenfeld Y. Hepatitis B vaccination and undifferentiated connective tissue disease: another brick in the wall of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA). J Clin Rheumatol. 2013;19:231-3.
164. Gatto M, Agmon-Levin N, Soriano A, Manna R, Maoz-Segal R, Kivity S, et al. Human papillomavirus vaccine and systemic lupus erythematosus. Clin Rheumatol (2013) 32:1301–7.10.1007/s10067-013-2266-7
165. Couette M, Boisse MF, Maison P, et al. Long-term persistence of vaccine-derived aluminum hydroxide is associated with chronic cognitive dysfunction. J Inorg Biochem. 2009:103:1571-8.
166. Levart, TK. Post-vaccine glomerulonephritis in an infant with hereditary C2 complement deficiency: case study. Croat Med J. 2013;54: 569–573.
167. Bogdanos DP, Smith H, Ma Y, Baum H, Mieli-Vergani G, Vergani D. A study of molecular mimicry and immunological cross-reactivity between hepatitis B surface antigen and myelin mimics. Clin Dev Immunol. 2005;12(3):217-24.
168. Innis, MD. Autoimmune tissue scurvy misdiagnosed as child abuse. Clinical Medicine Research 2013 2:154-157.
169. Basra,G., P Jajoria and E Gonzalez. 2012. Rheumatoid arthritis and swine influenza vaccine: a case report. Volume 2012 (2012), Article ID 785028, 3 pages https://www.hindawi.com/journals/crirh/2012/785028/#B3
170. Verstraeten, T, Cohet, C, Dos Santos G et al. Pandemrix™ and narcolepsy: a critical appraisal of the observational studies. Human Vaccines & Immunotherapeutics 2016; 12: 187–193.
171. Meyboom RH, Fucik H, Edwards IR. Thrombocytopenia reported in association with hepatitis B and A vaccines. Lancet. 1995;345:1638.
172. Cecinati V, Principi N, Brescia L, Giordano P, Esposito S. Vaccine administration and the development of immune thrombocytopenic purpura in children Hum Vaccin Immunother. 2013;9(5):1158-62. doi: 10.4161/hv.23601.
173. O'Leary ST, Glanz JM, McClure DL, Akhtar A, et al. The risk of immune thrombocytopenic purpura after vaccination in children and adolescents. Pediatrics 2012;129(2):248-55. doi: 10.1542/peds.2011-1111.
174. Tomljenovic, L and Shaw C. Death after quadrivalent human papillomavirus (HPV) vaccination: causal or coincidental? Pharmaceutical Regulatory Affairs: Open Access 2012; S12-001:1-11.
175. Gomes SM, Glover M, Malone M, Brogan P. Vasculitis following HPV immunization. Rheumatology (Oxford) 2013 ;52:581–2.10.1093/rheumatology/kes168
176. Souayah N, Michas-Martin PA, Nasar A, Krivitskaya N, Yacoub HA, Khan H, et al. Guillain-Barré syndrome after Gardasil vaccination: data from Vaccine Adverse Event Reporting System 2006-2009. Vaccine 2011;29:886–9.10.1016/j.vaccine.2010.09.020
177. Pugnet G, Ysebaert L, Bagheri H, Montastruc J-L, Laurent G. Immune thrombocytopenic purpura following human papillomavirus vaccination. Vaccine 2009;27:3690.10.1016/j.vaccine.2009.04.004
178. Alvarez-Soria MJ, Hernandez-Gonzalez A, Carrasco-Garcia de Leon S, del Real-Francia MA, Gallardo-Alcaniz MJ, Lopez-Gomez JL. [Demyelinating disease and vaccination of the human papillomavirus]. Rev Neurol 201;52:472–6.
179. Redhead K, Quinlan GJ, Das RG, Gutteridge JM. Aluminium-adjuvanted vaccines transiently increase aluminium levels in murine brain tissue. Pharmacol Toxicol. 1992;70:278-80.
180. Tomljenovic L, Shaw CA. Mechanisms of aluminum adjuvant toxicity and autoimmunity in pediatric populations. Lupus. 2012;21(2):223-30.

181. Franchi L, Núñez G. The Nlrp3 inflammasome is critical for aluminium hydroxide-mediated IL-1beta secretion but dispensable for adjuvant activity. Eur J Immunol. 38(8):2085-9.
182. Li H, Willingham SB, Ting JP, Re F. Cutting edge: inflammasome activation by alum and alum's adjuvant effect are mediated by NLRP3. J Immunol. 2008;181:17-21.
183. Han S, Lemire J, Appanna VP, Auger C, Castonguay Z, Appanna VD. How aluminum, an intracellular ROS generator promotes hepatic and neurological diseases: the metabolic tale. Cell Biol Toxicol. 2013;29:75-84.
184. Pahari S, Chatterjee D, Negi S, Kaur J, Singh B, Agrewala JN. Morbid sequences suggest molecular mimicry between microbial peptides and self-antigens: a possibility of inciting autoimmunity. Front Microbiol. 2017;8:1938.
185. Goines, PE and Ashwood, P. Cytokine dysregulation in autism spectrum disorders (ASD): Possible role of the environment. Neurotoxicol Teratol. 2013;36:67-81.
186. Augustyniak D, Majkowska-Skrobek G, Roszkowiak J, Dorotkiewicz-Jach A. Defensive and offensive cross-reactive antibodies elicited by pathogens: the good, the bad and the ugly. Curr Med Chem. 2017;24:4002-4037.
187. Segal Y, Shoenfeld Y. Vaccine-induced autoimmunity: the role of molecular mimicry and immune crossreaction. Cell Mol Immunol. 2018; doi: 10.1038/cmi.2017.151.
188. Berger, A. Science commentary Th1 and Th2 responses: what are they? BMJ. 2000;321: 424.
189. Fulgenzi AE, Vietti D, Ferrero ME. 2014. Aluminium involvement in neurotoxicity. Biomed Res Int. 2014;2014:758323.
190. Exley C, Mamutse G, Korchazhkina O, Pye E, Strekopytov S, Polwart A, Hawkins C. 2006. Elevated urinary excretion of aluminium and iron in multiple sclerosis. Mult Scler. 2006;12:533-40.
191. Zanella SG, Roberti di Sarsina P. 2013. Personalization of multiple sclerosis treatments: using the chelation therapy approach. Explore (NY). 2013 9(4):244-8.
192. Di Lorenzo F, Di Lorenzo B. Iron and aluminum in Alzheimer's disease. Neuro Endocrinol Lett. 2013;34:504-7.
193. Fulgenzi A, Zanella SG, Mariani MM, Vietti D, Ferrero ME. A case of multiple sclerosis improvement following removal of heavy metal intoxication: lessons learnt from Matteo's case. Biometals. 2012;25(3):569-76.
194. Luján L, Pérez M, Salazar E, et al. Autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA syndrome) in commercial sheep. Immunol Res 2013;56(2-3):317-324.
195. Trost B, Lucchese G, Stufano A, Bickis M, Kusalik A, Kanduc D. No human protein is exempt from bacterial motifs, not even one. Self Nonself. 2010; 1:328-334.
196. Gershwin, ME. The long and latent road to autoimmunity. Cellular and Molecular Immunology 2018;1-4.
197. Khan Z, Combadière C, Authier FJ, et al. Slow CCL2-dependent translocation of biopersistent particles from muscle to brain. BMC Med 2013;11:99.
198. Bjørklund G, Stejskal V, Urbina MA, Dadar M, Chirumbolo S, Mutter J. Metals and Parkinson's disease: Mechanisms and biochemical processes. Curr Med Chem. 2017; doi: 10.2174/0929867325666171129124616.
199. Mitkus RJ, King DB, Hess MA, Forshee RA, Walderhaug MO. Updated aluminum pharmacokinetics following infant exposures through diet and vaccination. 2011;29:9538-43.
200. Yang J, Qi F, Yang Y, Yuan Q, Zou J, Guo K, Yao Z. Neonatal hepatitis B vaccination impaired the behavior and neurogenesis of mice transiently in early adulthood. Psychoneuroendocrinology 2016;73:166-176. doi: 10.1016/j.psyneuen.2016.08.002
201. Sheth SKS, Li Y, Shaw CA. Is exposure to aluminium adjuvants associated with social impairments in mice? A pilot study. J Inorg Biochem 2018;181:96-103. doi: 10.1016/j.jinorgbio.2017.11.012.
202. Petrik MS, Wong MC, Tabata RC, Garry RF, Shaw CA. Aluminum adjuvant linked to Gulf War illness induces motor neuron death in mice. Neuromolecular Med 2007;9:83-100.

203. Stamogiannos A, Papakyriakou A, Mauvais FX, van Endert P, Stratikos E. Screening Identifies Thimerosal as a Selective Inhibitor of Endoplasmic Reticulum Aminopeptidase 1. ACS Med Chem Lett. 2016;7:681-5.
204. Smith SW The role of chelation in the treatment of other metal poisonings. J Med Toxicol. 2013;9:355-69.
205. Buffoli B, Foglio E, Borsani E, Exley C, Rezzani R, Rodella LF. Silicic acid in drinking water prevents age-related alterations in the endothelium-dependent vascular relaxation modulating eNOS and AQP1 expression in experimental mice: an immunohistochemical study. Acta Histochem. 2013;115(5):418-24.
206. Sun R, Ren H, Wei J. Effects of astrogaloside on the inflammation and immunity of renal failure patients receiving maintenance dialysis. Exp Ther Med. 2018;15:2307-2312.
207. Jones K, Linhart C, Hawkins C, Exley C. 2017. Urinary excretion of aluminium and silicon in secondary progressive multiple sclerosis. EBioMedicine. 2017;26:60-67.
208. Zioła-Frankowska A, Kubaszewski Ł, Dąbrowski M, Frankowski M. Interrelationship between silicon, aluminum, and elements associated with tissue metabolism and degenerative processes in degenerated human intervertebral disc tissue. Environ Sci Pollut Res Int. 2017;24:19777-19784.
209. Bastida-Ruiz D, Aguilar E, Ditisheim A, Yart L, Cohen M. Endoplasmic reticulum stress responses in placentation - A true balancing act. Placenta. 2017;57:163-169.
210. Wang, C-M et al., 2012. ERAP1 genetic variations associated with HLA-B27 interaction and disease severity of syndesmophytes formation in Taiwanese ankylosing spondylitis Arthritis Research & Therapy 201214:R125
211. Hinks A, Martin P, Flynn E, et al. Subtype specific genetic associations for juvenile idiopathic arthritis: ERAP1 with the enthesitis related arthritis subtype and IL23R with juvenile psoriatic arthritis. Arthritis Res Ther 2011;13:R12.
212. Strange A, Capon F, Spencer CC, et al. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. Nat Genet 2010;42:985–90.
213. Loebel M, Grabowski P, Heidecke H et al. Antibodies to β adrenergic and muscarinic cholinergic receptors in patients with Chronic Fatigue Syndrome. Brain Behav Immun. 2016;52:32-39.
214. HPV Cancer.org 2017. Status of Jesper Mehlens Research in the HPV Vaccine 28 Feb 2017 https://www.hpv-cancer.org/status-paa-jesper-mehlsens-forskning-inden-hpv-vaccinen/
215. Austin DW, Spolding B, Gondalia S, Shandley K, Palombo EA, Knowles S, Walder K. Genetic variation associated with hypersensitivity to mercury. Toxicol Int. 2014;21(3):236-41. doi: 10.4103/0971-6580.155327.
216. Westphal GA, Schnuch A, Schulz TG, Reich K, et al. Homozygous gene deletions of the glutathione S-transferases M1 and T1 are associated with thimerosal sensitization. Int Arch Occup Environ Health. 2000; 73(6):384-8.
217. Fosmire GJ, Focht SJ, McClearn GE. Genetic influences on tissue deposition of aluminum in mice. Biol Trace Elem Res. 1993;37:115-21.
218. Kutlu A, Ucar R, Aydin E, Arslan S, Calıskaner AZ. Could aluminum be a new hidden allergen in type 1 hypersensitivity reactions when used as a drug additive? Postepy Dermatol Alergol. 2016;33(3):243-5.
219. Murphy J. Toxic chemicals in vaccines, pp. 39-58. Role of aluminum sensitivity in delayed persistent immunisation reactions. *J Clinical Pathology* 1991;44:876-877.
220. Choi JY, Won NH, Park JD, Jang S, et al. Ethylmercury-induced oxidative and endoplasmic reticulum stress-mediated autophagic cell death: involvement of autophagosome-lysosome fusion arrest. Toxicol Sci. 2016;154(1):27-42.
221. Zhu Y, Han Y, Zhao H, Li J, Hu C, Li Y, Zhang Z. 2013. Suppressive effect of accumulated aluminum trichloride on the hepatic microsomal cytochrome P450 enzyme system in rats. Food Chem Toxicol. 51:210-4.

222. Mold M, Umar D, King A, Exley C. Aluminium in brain tissue in autism. J Trace Elem Med Biol. 2018; 46:76-82.
223. Favoino E, Favia EI, Digiglio L, Racanelli V, Shoenfeld Y, Perosa F. Effects of adjuvants for human use in systemic lupus erythematosus (SLE)-prone (New Zealand black/New Zealand white) F1 mice. Clin Exp Immunol. 2014;175:32-40.
224. Shaw CA, Petrik MS. Aluminum hydroxide injections lead to motor deficits and motor neuron degeneration. J Inorg Biochem. 2009;103:1555-62.
225. Pathinayake PS, Hsu AC, Waters DW et al. Understanding the unfolded protein response in the pathogenesis of asthma. Front Immunol. 2018;9:175.
226. Lee WS, Sung MS, Lee EG, Yoo HG, Cheon YH, Chae HJ, Yoo WH. A pathogenic role for ER stress-induced autophagy and ER chaperone GRP78/BiP in T lymphocyte systemic lupus erythematosus. J Leukoc Biol. 2015;97:425-33.
227. Wang J, Cheng Q, Wang X, Zu B, Xu J, Xu Y, Zuo X, Shen Y, Wang J, Shen Y. Deficiency of IRE1 and PERK signal pathways in systemic lupus erythematosus. Am J Med Sci. 2014;348(6):465-73.
228. Lind PM, Olsén L, Lind L. Circulating levels of metals are related to carotid atherosclerosis in elderly. Sci Total Environ. 2012;416:80-8.
229. Roos PM, Vesterberg O, Syversen T, Flaten TP, Nordberg M. Metal concentrations in cerebrospinal fluid and blood plasma from patients with amyotrophic lateral sclerosis. Biol Trace Elem Res. 2013;151(2):159-70. doi: 10.1007/s12011-012-9547-x.
230. Wang IJ, Huang LM, Guo YL, Hsieh WS, Lin TJ, Chen PC. Haemophilus influenzae type b combination vaccines and atopic disorders: a prospective cohort study. J Formos Med Assoc. 2012; 111:711-8.