

# The Paradigm of ASIA (Autoimmune/Inflammatory Syndrome Induced by Adjuvants): A Concept in Evolution

Alessandra Soriano MD

Department of Clinical Medicine and Rheumatology, Campus Bio-Medico University, and Periodic Fevers Research Centre, Catholic University of Sacred Heart – A. Gemelli Hospital, Rome, Italy

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In 2011 Shoenfeld and Agmon Levin described a new syndrome which they termed ASIA – Autoimmune/Inflammatory Syndrome Induced by Adjuvants, summarizing for the first time the spectrum of immune mediated diseases triggered by an adjuvant stimulus such as chronic exposure to silicone, pristane, aluminum and other adjuvants, or by infectious components that may also act as adjuvants [1,2]. All these environmental factors were found to induce autoimmunity in both animal models and humans [3]. The term “adjuvant” derives from the Latin verb *adjuvare*, which means to aid. In 1989, in his seminal introduction to the Cold Spring Harbor Symposium on Quantitative Biology *Approaching the Asymptote? Evolution and Revolution of Immunology*, Janeway defined adjuvants as the “immunologist’s dirty little secret” because of their ability to enhance the immune response by intensifying both the humoral and cellular arms [4]. In fact, since the 1930s, adjuvants have been used as a ‘dirty little trick’ to allow decrease of the antigen dose in vaccines, or even in immunization frequency, to inhibit reactions between antigens in polyvalent vaccines and to stimulate the immune response in subjects with impaired response to vaccinations because of concurrent immunosuppressive therapies.

Glenny and colleagues [5] described the first adjuvant effect of an aluminum compound in 1926, hypothesizing a “depot” effect and the ability to control the release of the antigen [6]. Later on, these hypotheses were questioned [7]. Today we know that an immunologic adjuvant is able to increase innate and adaptive immune responses to the injected antigen by means of several mechanisms. Indeed, the identification of Toll-like receptors as pattern-recognition receptors – responsible for recognizing evolutionary conserved molecules (i.e., lipopolysaccharide, skeletal cell wall components) and critical for sensing infections – added further insight to our understanding of the mechanisms of innate immunity in recent decades and, subsequently, of adjuvant function mechanisms. Adjuvants may act not only via TLR-dependent mechanisms – by up-regulation of cytokines and MCH class II co-stimulatory molecules, promotion of dendritic cell migration to the T cell area of lymph node – but also via TLR-independent mechanisms by activating another class of PRR, the NOD-like receptors, ultimately responsible for the activation of a molecular platform called “inflammasome,” as shown in the case of aluminum [8].

Undoubtedly, vaccines represent one of the greatest advances of modern medicine; they are considered safe and effective by the medical community for both the general population and many categories of subjects at risk, such as the elderly and immunocompromised individuals.

Adverse reactions and post-immunization phenomena following different

TLR = Toll-like receptors

PRR = pattern recognition receptors

types of vaccines have been described in the medical literature since 1950. However, they remain rare, as confirmed by several studies on the safety, efficacy and effectiveness of vaccines in patients of different ages (children, adults, elderly).

In the present issue of this journal, Green et al. [9] describe an episode of acute hemolytic anemia that occurred in a 29 year old woman 2 days after she received an influenza vaccine; the diagnosis was paroxysmal nocturnal hemoglobinuria. The authors hypothesized that the influenza vaccine triggered complement activation in two possible pathways: a) response to the presentation of the viral antigen itself – which varies every year in seasonal influenza vaccines, or b) response to the adjuvant via the mechanisms of the recently described “ASIA.” Interestingly, the patient had received a flu shot a year before without experiencing any adverse effect. Although the exact composition of the administered vaccine was not specified in the article (i.e., whether the influenza vaccine was adjuvanted or not, which preservatives were used, the vaccine brand and lot number, etc.), both the supposed pathophysiological mechanisms of complement activation may be plausible, given the likewise plausible temporal relationship with the vaccine administration.

It is well-known that molecular mimicry is one of the most common mechanisms by which infections or vaccines induce autoimmunity [10,11]; also, the administered viral antigen is potentially able to determine complement system activation via the classical, alternative, or lectin pathway. Nevertheless, as Shoenfeld and Agmon-Levin stressed [12,13], the

increased risk of autoimmunity and post-vaccination phenomena among recipients of a certain vaccine may stem not only from its antigenic mediated responses but also from other constituents of the vaccine, such as yeast [14], adjuvants and preservatives. With specific regard to complement activation by adjuvants, it was recently showed by Güven and co-authors [15] that aluminum hydroxide is able to activate the three complement pathways with major involvement of the alternative complement pathway, confirming previous evidence in the literature and adding further proof of its adjuvant properties.

The 'ASIA' syndrome includes in its definition four medical conditions: silicosis, the Gulf War syndrome, the macrophagic myofasciitis syndrome, and post-vaccination phenomena. Post-vaccination phenomena are rare conditions that may be explained as protean clinical manifestations of specific autoimmune, rheumatic or inflammatory diseases, but also as non-specific autoimmune, rheumatic or inflammatory manifestations. Major and minor criteria have been proposed to determine the diagnosis of ASIA. Exposure to external stimuli (vaccines, adjuvants, infections) prior to the appearance of clinical manifestations is considered a major criterion.

Following the description of "ASIA," retrospective analyses of several post-vaccination phenomena have been performed and reported in the literature. Thus, the clinical spectrum of this syndrome appears to be expanding based on increasing evidence in both animal models and humans,

which renders the paradigm of the syndrome itself 'a concept in evolution' [3,16].

The case described by Green et al. [9] is the first report of a hemolytic episode of paroxysmal nocturnal hemoglobinuria triggered by influenza vaccine, supporting the hypothesis that vaccines may act as triggers of immune mediated phenomena that do not necessarily manifest as a clear autoimmune disease or by the appearance (transient or stable) of autoantibodies. The spectrum of post-immunization diseases caused by immune mediated phenomena is possibly wider and further studies are needed to find common denominators. With this aim, the implementation of active surveillance registries of ASIA cases worldwide will contribute further insight and proof of concept.

#### Corresponding author:

**Dr. A. Soriano**

Dept. of Clinical Medicine and Rheumatology,  
Campus Bio-Medico University, Rome, Italy

**Phone:** (39-622) 541-1340

**Fax:** (39-622) 541-456

**email:** soriano.alessandra@gmail.com

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## Capsule

### Sugar sabotage in diabetes

In patients with diabetes, too much of a good thing – glucose – in the bloodstream causes the debilitating loss of biological functions and can eventually lead to death. Scientists continue to home in on the precise mechanisms by which this occurs, in hope of mitigating the damage. Warren and team have found a mechanism by which excess glucose can alter the functions of vascular endothelial cells, one of the main sites of complications in diabetes. In mouse endothelial cells, too much glucose leads to the overproduction of reactive oxygen species in the mitochondria.

This excess of ROS causes the phosphorylation of the receptor for vascular endothelial growth factor (VEGF) within the Golgi, rendering the receptor vulnerable to proteolysis. This reduces the levels of VEGF receptor at the cell surface, where it would be able to detect circulating VEGF. Thus, cells chronically exposed to excess glucose become less responsive to VEGF, which is necessary for the proper growth, function, and survival of endothelial cells.

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Eitan Israeli