# The Mosaic of Autoimmunity
# A Classical Case of Inhalation of a Polyclonal Activating Factor in a Genetically and Hormonally Susceptible Patient Leading to Multiple Autoimmune Diseases

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The "mosaic of autoimmunity," a term coined over a decade ago [1], describes the multifactorial origin and diversity of expression of autoimmune diseases. The term implies that different combinations of the many factors involved in autoimmunity produce varying and unique clinical pictures that represent the wide spectrum of autoimmune diseases. Most of the factors involved in autoimmunity can be categorized into four groups: genetic, immune defects, hormonal, and environmental [1].

The following case report represents a classic example of the concept of autoimmunity developing as a mosaic, and demonstrates how factors from each of the above categories combine to produce a variety of autoimmune diseases in one individual.

## Patient Description

A 45 year old non-smoking Caucasian woman had worked as an engineer at an energy research center for 8 years. When she was 30 years old an accident occurred at work and she inhaled polyanethol sulfonic acid. Her past medical history prior to the incident was unremarkable, apart from two hospitalizations. The first, for the investigation of fever when she was 19 years old, revealed increased thyroid iodine uptake and she was treated with thiouracil. Her second hospitalization, at the age of 24, was for abdominal pains. On both occasions her erythrocyte sedimentation rate and differential blood count were considered normal.

Shortly after the aforementioned accident involving PSP she was hospitalized due to inflammation of the right knee and fever, which was treated successfully. However, she subsequently underwent a series of hospitalizations and tests, and within a period of 2 years was diagnosed as suffering from systemic lupus erythematosus, thyrotoxicosis (Hashimoto's disease), polyarthralgia, Raynaud's syndrome, relapsing polychondritis, and vasculitis. Her blood results were as follows: antinuclear factor 1:168 (speckled and homogenous), anti-thyroid cytoplasmic titer 1:40, anti-dsDNA 12% in amonium sulphate precipitate (normal 10%), C3 > 80 mg/dl (normal 55–120 mg/dl) and C4 16 mg/dl (normal 20–50). In addition, she was found to have hypergammaglobulinemia with immunoglobulin G 1,900 mg/dl (normal $1,250 \pm 300$ mg/dl), IgA 200 mg/dl (normal $210 \pm 50$) and IgM 209 mg/dl (normal $125 \pm 50$ mg/dl). Other antibodies found included: anticardiolipin, antithyroid microsomal, anti-Tg, antiparietal, antigliadin, antireticulin, and anti-smooth muscle. ESR and differential blood count were considered normal. Treatment consisted of plaquanil, intravenous Ig and corticosteroids.

Two years ago she was diagnosed with Sjogren's syndrome, polyneuropathy multiplex, temporal epilepsy and celiac disease with lactose intolerance. Her HLS tissue typing is A2, A3, B8, B14, Bw6, DR3, DR7, DRW53, DQW2.

PSP = polyanethol sulfonic acid

## Comment

The patient described is a middle-aged woman with HLA tissue typing B8/DR3 and mild complement deficiency. The higher propensity of autoimmune diseases in females is well documented and is thought to result from the effects of estrogen (i.e., the hormonal factor) [1]. The HLA B8/DR3 haplotype is recognized as particularly prevalent in SLE (the genetic factor) [1,2]. Furthermore, immune defects such as immunoglobulin abnormalities, complement deficiencies, suppressor T cell defects and spontaneous polyclonal B cell activation are often found in persons who develop autoimmune diseases (immune deficiency factors) [1,2]. Our patient was found to have low levels of C4 and elevated levels of IgG, consistent with abnormalities found in persons with autoimmune disease (humoral *and* genetic factors).

However, until the inhalation of PSP, an anionic detergent used extensively in microbiology, our patient was in good health. PSP was found to be a potent polyclonal B cell activator in a process dependent on macrophages and macrophage-related factors (the environmental

Ig = immunoglobulin
ESR = erythrocyte sedimentation rate
SLE = systemic lupus erythematosus

factor) [3]. Polyclonal B cell activation has been recognized as playing a major role in the pathogenesis of autoimmune diseases (mechanisms) [1]. A polyclonal antibody response is mounted against thymus-independent antigen, causing a large number of B cells to proliferate and mature into antibody-forming cells independent of antigen stimulation. In addition, PSP was found to interact with the complement system in a complex manner, inhibiting both classical and alternative pathways of complement activation [4]. It is known that antibody-dependent cell-mediated cytotoxicity and natural killing are inhibited by PSP [5]. Many environmental agents have been implicated in inducing autoimmune diseases, including ultraviolet radiation, infections, drugs, and smoking [1]. It is indeed plausible to consider PSP as an environmental agent that acted as a "trigger" factor causing the immune state of our patient.

While the clustering of more than one autoimmune disease is a well-known phenomenon [1], the clustering of at least five autoimmune diseases in one individual is considered highly uncommon. Thus, in the patient described here it would seem that the combination of genetic susceptibility, female gender and the inhalation of a biologically active substance (a polyclonal activator) constitutes the pieces of the mosaic that presented with the development of an assortment of autoantibodies and autoimmune diseases.

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