



## Forum

# Vaccination and Autoimmunity—'Vaccinosis': A Dangerous Liaison?

Y. Shoenfeld and A. Aron-Maor

*Department of Internal Medicine B,  
Sheba Medical Center, the Research Unit  
of Autoimmune Diseases, Sheba Medical  
Center, Tel Hashomer and the Sackler  
Faculty of Medicine, Tel Aviv University,  
Israel*

The question of a connection between vaccination and autoimmune illness (or phenomena) is surrounded by controversy. A heated debate is going on regarding the causality between vaccines, such as measles and anti-hepatitis B virus (HBV), and multiple sclerosis (MS). Brain antibodies as well as clinical symptoms have been found in patients vaccinated against those diseases. Other autoimmune illnesses have been associated with vaccinations. Tetanus toxoid, influenza vaccines, polio vaccine, and others, have been related to phenomena ranging from autoantibodies production to full-blown illness (such as rheumatoid arthritis (RA)). Conflicting data exists regarding also the connection between autism and vaccination with measles vaccine.

So far only one controlled study of an experimental animal model has been published, in which the possible causal relation between vaccines and autoimmune findings has been examined: in healthy puppies immunized with a variety of commonly given vaccines, a variety of autoantibodies have been documented but no frank autoimmune illness was recorded. The findings could also represent a polyclonal activation (adjuvant reaction). The mechanism (or mechanisms) of autoimmune reactions following immunization has not yet been elucidated. One of the possibilities is molecular mimicry; when a structural similarity exists between some viral antigen (or other component of the vaccine) and a self-antigen. This similarity may be the trigger to the autoimmune reaction. Other possible mechanisms are discussed.

Even though the data regarding the relation between vaccination and autoimmune disease is conflicting, it seems that some autoimmune phenomena are clearly related to immunization (e.g. Guillain-Barre syndrome).

The issue of the risk of vaccination remains a philosophical one, since to date the advantages of this policy have not been refuted, while the risk for autoimmune disease has not been irrevocably proved. We discuss the pros and cons of this issue (although the temporal relationship (i.e. always 2–3 months following immunization) is impressive).

© 2000 Academic Press

**Key words:** vaccine, autoimmunity, autoantibodies, measles, hepatitis, Guillain-Barre syndrome, rheumatoid arthritis, SLE, multiple sclerosis, autism

## Introduction

In 1996 we published a review [1] of the reported cases of vaccine-induced autoimmune phenomena (in particular those related to hepatitis B (HBV) recombinant vaccine), as well as possible mechanisms for these reactions. We wish now to update and expand this review.

In 1993 it was reported in the Journal of the American Medical Association (JAMA) [2] that a causal relationship had been found between several vaccines and a number of autoimmune disorders, such as that between diphtheria, tetanus toxoids and oral polio vaccine and the Guillain-Barre syndrome.

Over the years numerous reports have raised the questions whether vaccines can cause autoimmune disease, and how safe are vaccines in persons already diagnosed with autoimmune conditions. In this article we will address each of these questions separately. There is a wide spectrum of disorders that have been

Correspondence to: Department of Internal Medicine B, Sheba Medical Center-Tel Hashomer, 52621, Israel. Fax: 972-3-5352855. E-mail: [shoenfel@post.tau.ac.il](mailto:shoenfel@post.tau.ac.il)

connected (temporally and/or causally) with vaccination. Many of those are autoimmune. We will refer to several major groups of disorders and to a number of the most commonly used vaccines and we will review the existing body of evidence connecting them.

## Can Vaccines Cause Autoimmune Diseases?

### Neurological manifestations

#### *The Guillain-Barre syndrome (GBS)*

GBS is a transient neurological disorder characterized by areflexic motor paralysis with mild sensory disturbances. In the patients cerebrospinal fluid (CSF) there is an acellular rise of total protein associated with inflammatory demyelination of the peripheral nerves [3]. The aetiology of GBS remains unknown, however there is increasing evidence suggesting an autoimmune aetiology [4]. Autoantibodies to various myelin-associated glyco-conjugates are described in GBS patients [5]. Prior viral infections are often associated with GBS [6, 7], in particular herpes virus [8], Epstein-Barr virus [9], cytomegalovirus [10], measles [11], and many others. Approximately 30% of the cases of GBS are preceded by *Campylobacter jejuni* infection [12] as detected by serologic tests. In 1995 Terryberry *et al.* [13] published the results of a study in which they examined the CSF of GBS patients for the presence of antibodies against 18 myelin autoantigens. These results suggest a multi-infectious etiology of GBS or an increased susceptibility of GBS patients to infection. We concluded that GBS is probably both a humoral and a cellular autoimmune disease induced by infection with multiple micro-organisms. The presence of microbe-specific antibodies, and T cells, with cross-reactivity to various nerve-sheath components, initiates inflammatory demyelination and shedding of peripheral-nerve autoantigens [14]. Vaccines contain live (attenuated) or killed infectious organisms, or parts of them. Presumably by a similar mechanism, vaccines can induce an autoimmune reaction. Indeed, a recognized temporal association exists between vaccination (with several vaccines) and the manifestation of GBS [2, 15].

**GBS and Influenza vaccine.** In the autumn of 1976 after a government-sponsored mass-inoculation program in which 45 million adults received influenza virus (the 'swine-flu' virus) vaccine [16] the incidence of GBS increased by a factor of four to eight. The concern caused among physicians by this occurrence applied especially to those patients who had a history of GBS [16]. In the NEJM of December 1998 [17] Lasky *et al.* report a slight increase of GBS incidence (one to two additional cases per million vaccinated persons) after recent (1992-1993) influenza vaccination programs. This study constitutes epidemiologic evidence that influenza strains other than the 'swine flu' may increase the risk of inducing GBS [18]. **Table 1**

**Table 1.** Vaccines associated to GBS

	Type of vaccine
GBS	Tetanus toxoid [2,16] Bacille Calmette-Guerin (BCG) [16] Rabies [16] Smallpox [16] Mumps [16] Rubella [16] Hepatitis B [16] Diphtheria [2] Poliovirus [2, 16]

**Table 2.** Vaccines associated with arthritis

	Type of vaccine
Arthritis	Tetanus [40,42] Typhoid [40] Paratyphoid [40] Polio [40] Mumps [41] Diphtheria [40] Rubella [41] Smallpox [40] Parvovirus B19 [40] Hepatitis C [42] Hepatitis B [46,47]

summarizes the vaccines that have been related to induction of GBS.

There are no studies that specifically address the question of the risk of relapse after vaccination. Therefore, it seems prudent to delay immunization for a year in all patients after a neurological illness [19] since there may be a threat of relapse (especially after tetanus toxoid) [19]. Patients with inflammatory demyelinating polyradiculopathy should not be put at risk by exciting the immune system with an immunization, unless the risk of contracting the disease poses a greater potential threat than the risk of GBS relapse.

#### *Multiple Sclerosis (MS)*

MS is a disease characterized by central nervous system (CNS) demyelination and progressive paralysis. It is considered an autoimmune disease of unknown aetiology in which the pathologic process is caused by a cell-mediated autoimmune process directed against nerve-sheath myelin. In a recent study [20] autoantibodies specific for the central nervous system myelin/oligodendrocyte glycoprotein were identified. These autoantibodies were specifically bound to disintegrating myelin around axons in lesions of acute multiple sclerosis.

**Multiple Sclerosis and Hepatitis B vaccine.** A heated debate over the possible adverse effects of HBV vaccine is going on in the United States and Europe, and

has been reported in *Science* [21]. More than 600 cases of illnesses, many with MS-like symptoms, of people who had received the recombinant HBV vaccine, have been collected in France. A growing fraction of people who have been vaccinated against HBV claim to have experienced serious side effects. Their complaints cover a wide spectrum of diseases, among which many of an autoimmune nature and nervous system disorders. Those include rheumatoid arthritis, optic neuritis, and neurodegenerative disorders that resemble MS. The temporal association of multiple sclerosis (MS) with HBV vaccination has been reported on few occasions [22, 23]; neurological symptoms and signs, as well as magnetic resonance imaging documenting central nervous system (CNS) demyelination have occurred days to weeks after HBV vaccination. On the other hand, a study sponsored by the French government in 1997 found that vaccinated people were less likely to have MS [21].

Already many of those who have been immunized with the HBV vaccine are seeking compensation from the government and manufacturers, or demanding that mandatory vaccination be stopped.

**Multiple Sclerosis and measles vaccine.** There are several lines of evidence that support the possibility that MS may be an age-dependent host response to measles. MS patients have higher titers of measles antibody than healthy controls and also paramyxovirus inclusions have been found in brain cells of MS patients [24]. The older the age of infection with measles the more complications (especially neurological: encephalitis—subacute sclerosing panencephalitis (SSPE)). Measles tends to occur at an earlier age in tropical and sub-tropical areas, where MS is rare, than in temperate areas where it is more common [24]. Therefore, in these areas where measles is contracted at a later age a high level of 'herd immunity' to measles is achieved later (only by adolescence as compared to age 5 in the tropical areas). Though there is still not much evidence, it seems that the later a high level of herd immunity is acquired in a population, the higher the incidence of MS in that population [24]. Therefore, a hypothesis has been raised that measles might be one cause of MS. However, even though the incidence of measles dropped precipitously after measles vaccination began in the United States in 1963, no effect was seen (approximately 30 years later) on the incidence of MS [25].

Additional neurological conditions (such as optic neuritis) have been documented after vaccination with live or attenuated viruses (against measles, mumps, polio, vaccinia, rubella, influenza) [26, 27].

### Autism

The behavioural syndrome of autism in children is considered to be a neuro-developmental disorder identified by neuropsychiatric manifestations that include few or no imaginative and language skills, repetitive rocking and self-injurious behavior, and abnormal responses to sensations, people, events and

objects. The cause of the syndrome is not known but the aetiology may be multifactorial, including environmental, genetic, immunological and as yet undiscovered biochemical and neuropathological factors.

An immune hypothesis involving autoimmunity as one possible pathogenetic mechanism in autism has been suggested [28] based on a family study of infantile autism in the presence of autoimmune disease. Antibodies against myelin basic protein (MBP) have been found in the sera of autistic children [29] further supporting the autoimmunity linkage as a pathogenetic mechanism in autism.

If an immunological assault (perhaps secondary to a viral infection) were to occur prenatally or postnatally during infancy or early childhood, it could possibly result in poor myelination or abnormal function of the axon myelin [29]. An association was found between anti-viral and brain autoantibodies in autistic children. The measles-IgG titers were moderately higher in autistic children compared to normal controls (but not significantly higher) [30]. The higher the measles-viral antibody titer the greater the chance of brain autoantibody [30]. These findings support the assumption that a virus-induced immune response may play a causal role in the pathogenesis of autism. A recent report [31] has raised concern about a possible causal relation between autism and the measles-mumps-rubella (MMR) vaccine as well as with a new chronic inflammatory bowel syndrome. This entity differs histologically from ulcerative colitis or Crohn's disease: on ileocolonoscopy performed on children that presented with autism (or developmental regression) after MMR vaccination, lymphoid nodular hyperplasia (LNH) of the bowel was found. This is a reactive swelling of the lymphoid (immune) tissue of the ileal and colonic lining. Symptoms include abdominal pain and change in bowel habits. LNH may be acute and transient (following viral infections) or chronic and persistent. Autistic children with this finding were also found to be immune-deficient [32], lacking in one or more lymphocyte subsets or in immunoglobulin IgG subclasses; findings consistent with an acquired immunodeficiency. The finding of persistent LNH may represent chronic viral infection. The connection between the gastrointestinal findings and the behavioral disturbance is hypothetically explained by the possibility that the primary site of damage in autism is outside the brain, causing an arrest in the normal development of the brain and its function. The measles component of the MMR vaccine has been implicated in the aetiology of this syndrome.

All this having been said, other studies failed to demonstrate the presence of measles virus in lesions of inflamed bowel from these children. Even though a temporal association was sometimes reported between the MMR vaccine, gastrointestinal symptoms and developmental regression, data is conflicting on whether a causal association exists between the measles (or the MMR) vaccine and autism [33]. Recently, an epidemiological study was published [34], reassessing the association between the MMR

vaccine and autism. Autistic children born since 1979 were identified and information from clinical records was linked to immunization data. It was found that there was a steady increase in cases by year of birth with no sudden change in the trend line after the introduction of the MMR vaccine. Also there was no difference in age at diagnosis between children who were vaccinated before or after the age of 18 months, and those never vaccinated. There was no temporal association between the onset of autism within 1 or 2 years after MMR vaccination. Developmental regression was not clustered in the months after vaccination. The conclusion of this study (and an associated editorial) was that the analyses of the existing data do not support a causal association between MMR vaccine and autism (or at least not one frequent enough, so that it could be identified in the large regional sample examined in the study).

Additional neurological deficits have been reported in associated with the MMR vaccine (mainly with the measles component of the vaccine). There are several reports of sensory-neural hearing loss following vaccination with live measles virus (hearing loss being a well recognized complication of measles infection) [35, 36]. (Sensory-neural hearing loss has been reported in association with some autoimmune disorders such as the antiphospholipid antibody syndrome and SLE) [37–39]. There have also been reported several cases of gait disturbance after MMR immunization [40] even though so far no systematic study has addressed this issue.

## Joint Manifestations

### Arthritis

Arthritis is a common complication of wild *rubella* virus in adults, but it occurs less often in children. Teenage girls and fertile women are most prone to develop arthritis. The arthritis caused by rubella usually resolves without leaving any permanent sequelae. However there are cases when the arthritis developed as a complication of rubella (or some other viral infection) represents the first manifestation of a systemic, chronic rheumatological disease such as rheumatoid arthritis. The frequency of the articular manifestations is age- and sex-dependent, but also dependent on the strain of vaccine [41].

**Arthritis and MMR vaccine.** The incidence of joint manifestations was assessed 6 weeks after immunization with the MMR vaccine [42]. The study included 2658 immunized- and 2359 non-immunized- (but eligible for immunization) children. There was an increased risk of joint symptoms (arthralgia or arthritis) in the immunized children, 6 weeks after immunization. It was concluded that the rubella component of the vaccine was the most likely to have caused the joint symptoms reported. The risk of frank arthritis was less than after wild rubella infection.

### Rheumatoid arthritis (RA)

RA is a chronic inflammatory polyarthritis of unknown aetiology. There is increased concordance of disease in monozygotic *vs.* dizygotic twins and a strong association of disease with MHC class two molecules.

The question has been asked *whether immunization can trigger rheumatoid arthritis?* [43]. In a study conducted in 1993 [43] 19 (3%) of approximately 600 patients with arthritis reported the onset of their arthritis in the 6 weeks after receiving tetanus immunization. Twelve of these patients satisfied the ARA criteria for the diagnosis of RA. Two additional patients that had reported having been immunized against influenza and hepatitis B, did not satisfy the criteria for RA. There are case series of healthy people who had been immunized against a variety of viruses (tetanus, typhoid, paratyphoid, mumps, diphtheria, polio, smallpox) who had developed either a transient rise in rheumatoid factor (RF) or some form of arthritis [44, 45]. There are also some reports of RA developing following various immunizations [46, 47]. Other studies however, disprove a causal relation between vaccination and RA [47], finding that the incidence of RA among the vaccinated patients was not higher than that among the general population.

Symmons *et al.* [43] suggest three possible explanations to the apparent association between immunization and the development of arthritis:

1. That it represents the chance occurrence of two common phenomena—immunization and arthritis.
2. That immunization precipitates a specific form of arthritis that is distinct from RA (post-immunization arthritis) and that is usually self-limited.
3. That immunization is one of the factors which can trigger the development of RA (as can infections).

**Arthritis and Hepatitis B vaccine.** Only a few cases of arthritis after hepatitis vaccination have been reported and there are but few cases of frank RA developing after such immunization. Three cases of vaccination-induced arthritis are reported [48] with different resulting disease. Two of the patients showed a pattern resembling reactive arthritis without serological findings suggestive of RA and with a slowly remitting course. One additional patient developed RA with a relapsing and remitting course, with symptoms that improved only slightly over the years following the onset of the disease. The patient was female, had a significant serum titer of RF and she expressed HLA-DR4.

An additional series of 11 patients who developed RA after HBV recombinant vaccine inoculation is described [49]. All individuals were healthy prior to vaccination and they developed persistent polyarthritis fulfilling the ACR criteria for RA. Five subjects expressed HLA-DR4, and HLA class II genes with the RA shared motif were identified in nine of 11 patients examined. These studies suggest that genetic factors linked to MHC class II molecules may represent a risk factor for post-vaccine arthritis (even though there are

undoubtedly other determining factors, given the frequency of these HLA class II molecules in the healthy population).

**Arthritis and BCG vaccine.** Oligo- and poly-articular arthritis has been noted in approximately 3% of patients treated with intravesicular BCG (for bladder carcinoma) 1–3 months after start of treatment [50]. The arthritis is sterile and HLA-B27 has been found in several of these patients, a fact that reinforces the resemblance to reactive arthritis [51].

### Other Manifestations

#### *Systemic Lupus Erythematosus (SLE)*

SLE is a systemic autoimmune disease. Its aetiology is believed to be multifactorial since presentation (or flare-up) of the disease has been observed after exposure to infectious (viral and bacterial) agents, sunlight (or ultra-violet radiation), drugs and various chemicals. Genetic factors also play an important role in determining who will develop SLE and when.

Viral infections have been causally associated to SLE [52–58]. There are also cases of lupus presenting after vaccination.

**SLE and HBV vaccine.** The case of a healthy 43-year-old woman is described [59]. The patient received recombinant HBV vaccine 2 weeks prior to development of bilateral leg oedema. The diagnosis of SLE was made based on serological findings (high anti-nuclear and anti-DNA antibody titers), a decrease in serum complement, and a renal biopsy which showed diffuse proliferative glomerulonephritis with extracapillary proliferation and positive immunofluorescence for different immunoglobulins and complement factors. The appearance of the clinical manifestations of SLE after immunization suggests that the vaccine may have had a precipitating role in the immune phenomena.

Acute disseminated systemic lupus erythematosus was diagnosed in a healthy 24-year-old woman 4 months after completion of the immunization series (three monthly vaccine injections and a booster) with recombinant HBV vaccine. Her 7-year-old daughter developed idiopathic thrombocytopenic purpura 10 months after the first vaccine against HBV [60]. Three additional cases of SLE following hepatitis B vaccine have been reported. Symptoms appeared 15 days after the first vaccination in two cases [61, 62] and after the third injection in the latter [63]. Cutaneous lupus erythematosus and severe buccal aphthosis has been described in a 6-year-old boy following hepatitis B vaccination [64]. Both cutaneous and oral symptoms subsided with chloroquine therapy.

**Lupus vulgaris and BCG vaccine.** Cases of lupus vulgaris have been described in the literature [65–69] following BCG inoculation (around 60 cases). The risk of developing lupus vulgaris after a single dose of BCG is extremely low; multiple BCG inoculations

increase the risk [68]. Acid fast cultures from the lesions have usually been negative [67, 68].

Factors that might be responsible for the development of the lesions after BCG inoculation are the inherent resistance of the individual, virulence of the BCG organism, the amount of the inoculum and the technique of inoculation. Clinical and histologic features of BCG-induced lupus vulgaris do not differ from those of the spontaneous disease.

The BCG in bladder carcinoma does not directly destroy the tumour cells. Instead it increases the local immune response (cytokine production and inflammatory reaction) eventually eliminating the tumor cells [69]. In laboratory animals (more specifically—NOD (non-obese diabetic) mice), mycobacteria has been noted to precipitate an SLE-like syndrome (via an adjuvant-like activity) [70]. Reactivity to the mycobacterial 64 kDa heat shock protein (HSP 65) has been implicated in the development of adjuvant arthritis in rats, and may be involved in the pathogenesis of some autoimmune diseases in humans (such as rheumatoid arthritis) [71]. The magnitude of the autoimmune response to HSP 65, however, is not related to the development of autoimmune disease. It has also been observed that modulation of the immune response to HSP is one way to prevent autoimmune disease [72]. In some cases, at least, treatment of autoimmune disease by immunization with HSP 65 may be feasible.

#### *Diabetes Mellitus and immunization*

It has been suggested [73] that immunization (in general) after 2 months of age is associated with an increased risk of diabetes mellitus, in humans and in rodents. Latterly the vaccine more specifically connected to the risk of diabetes was the *Haemophilus influenzae* type b vaccine [74]. Other studies have been performed on large populations [75] and have not found any statistical links between *H. influenzae* type b vaccine and diabetes. A very recent study [76] aimed at determining the effect and the timing of *H. influenzae* type b vaccination on the risk of diabetes mellitus type I. In this study 128,936 children born between October 1983 and September 1985 and 116,352 children born between October 1985 and August 1987, were included. The children were divided into three cohorts. Cohort no. 1 received the usual immunizations, excepting *H. influenzae*. Cohorts 2 and 3 received all immunizations, including the *H. influenzae* vaccine; those in cohort 2 first received the vaccine at 3 months of age, and those in cohort 3 first received it at 24 months. The results showed no statistical difference in the cumulative incidence of type I diabetes at age 10. The authors conclusion was that it is unlikely that *H. influenzae* type b vaccination or its timing cause type I diabetes in children.

In March 1998 a workshop was convened at the Johns Hopkins School of Public Health to address concerns about the relation between immunization and diabetes mellitus. The panel concluded that 'selective vaccines are protective against type I diabetes but the data in humans are inconclusive and

**Table 3.** Vaccines associated with systemic autoimmune symptoms or renal involvement

	Type of Vaccine
Systemic autoimmune disease	Smallpox [66] Asiatic influenza [66] Pertussis [69] Tetanus toxoid [69]
Renal involvement	Polio vaccine [69] Smallpox [70] Tetanus toxoid [70] Influenza [70]

no vaccines have been shown to increase the risk of diabetes type I in humans' [77].

#### Systemic autoimmune phenomena after immunization

Systemic and especially renal involvement are described in relation to several vaccines (Table 3). A number of patients were described [78] who developed systemic symptoms (gastrointestinal, dermatological, respiratory) with involvement of the kidneys and evidence of glomerulonephritis (GN). On renal biopsy immunofluorescence studies were positive—mainly with anti-C3 and anti-IgG conjugates. The disease in these patients developed after receiving a variety of vaccines [79–81] (Table 3) and their outcomes differed significantly: two patients died of renal failure, five patients recovered completely, and one patient remained with persistent glomerular changes [78].

Systemic vasculitis was described in three patients, all cases having occurred after vaccination against hepatitis B [82]. The vasculitis manifested with skin lesion (palpable purpura), gastrointestinal symptoms (abdominal pain), joint symptoms (arthralgias) and renal dysfunction with proteinuria.

### Is there any risk in vaccinating patients with autoimmune diseases?

This question was addressed in many studies over the years, and several vaccines given to patients with various autoimmune conditions were examined.

Swine-influenza vaccination was well tolerated by MS patients. The vaccine did not seem to influence the course of the disease and the patients did not experience more exacerbations than non-vaccinated patients [83–84]. The rate of toxic reactions was similar to that encountered after conventional influenza vaccine [85].

This brings us to the widely used influenza vaccine. Because of the popularity and the widespread use of this vaccine, its effects were examined in many autoimmune conditions. Apparently MS patients have tolerated influenza immunization well [86] and have had the same incidence of systemic reactions as the general population. Transient exacerbations of MS during fever (a well-known

occurrence) have been observed and have subsided with defervescence. These exacerbations were not specific for influenza and the patients should be treated with antipyretics. Based on clinical and MRI assessment of MS patients after influenza vaccination it was concluded once again that this vaccine is safe in MS [86, 87]. Influenza vaccine did not cause any worsening of the disease in SLE patients either [88, 89]. Response to immunization in lupus patients, however (as measured by antibody titers) was lower than in healthy controls [89, 90]. Nevertheless, since morbidity and mortality with influenza infections may be greater in SLE patients, they should receive the immunization [90].

In rheumatoid arthritis (RA) there are still doubts about the usefulness and safety of influenza vaccine. In those patients, as in those with SLE, the immune response to vaccination is poor [91]. It seems that the vaccine has no noxious effect on RA patients and the frequency of flares is not greater after vaccination [91, 92].

Based on the same considerations as with SLE patients it may be helpful to immunize RA patients against influenza in order to prevent not only the potential complications of influenza (in these immunocompromised patients), but also the articular flares that sometimes follow influenza infection.

### Possible mechanisms of induction of autoimmune phenomena by vaccines

One of the mechanisms suggested is the 'molecular mimicry' theory, where an antigen of the recombinant vaccine (as in the case of HBV vaccine) [21] or of the attenuated live virus (as with oral polio vaccine) [1] may resemble a host antigen. The structural resemblance enables the start of the autoimmune process (as may be the case in lyme arthritis [93]).

The immunization may also imply the appearance of, or increase in immune complexes [51] which can in turn cause the vasculitis noted in several cases, or the exacerbation of existing autoimmune symptoms (such as worsening of renal function [78]).

The genetic predisposition of the patient represents a very important factor in the development of autoimmune disorders after vaccination [1, 47].

A comparison may be made between the case of vaccines and autoimmunity and the case of silicone and autoimmunity ('siliconosis'). Numerous women with silicone breast implants have been described in connection with the development of autoimmune phenomena. A wide range of autoantibodies was found in both symptomatic and asymptomatic women with silicone breast implants [94] (of various durations). Similarly, a wide range of autoimmune phenomena is related to vaccines. Perhaps the pathogenic mechanism is similar in both cases: namely an adjuvant effect. It is therefore possible that since in the MMR vaccine there is three times the amount of adjuvant as in a single vaccine, it may trigger autoimmune phenomena more often.

The issue was not addressed regarding the women with silicone breast implants, but there may also exist a genetic tendency in those who developed autoantibodies, and even more so in those who were symptomatic.

## Experimental models

The first (and to our knowledge—the only) controlled experimental model to test the effects of vaccination on the immune system was performed recently by Hogenesch *et al.* [95], in dogs. The incentive for the study was the frequent complaints of dog owners that their dogs got ill after they received the mandatory vaccines. The purpose of the study was to investigate the effects of vaccination in young dogs (who had not been previously immunized).

The goals of the experiment were:

1. To determine if vaccination (of dogs) affects the immune system, and whether it results in autoimmunity.
2. To determine the mechanism by which vaccination results in autoimmunity (if this occurs).
3. To develop alternative vaccination strategies—not accompanied by adverse side effects.

The investigators used two litters of five dogs each: 1) the study group—were immunized with a commonly used, commercially available, multivalent vaccine. The dogs were immunized at 8, 10, 12, 16 and 20 weeks of age, and with an inactivated rabies vaccine at 16 weeks of age. 2) The control group—received subcutaneous injections of sterile saline at the same time points.

The dogs that were vaccinated developed titers against the viruses they were vaccinated against (rabies, canine distemper virus and canine parvovirus-9). The non-vaccinated dogs remained seronegative.

At 22 weeks of age, in the vaccinated dogs, there was a significant increase in the titer of IgG antibodies reactive with 10 of 17 antigens. There was no increase in the non-vaccinated dogs. Among the various antibodies, a significant increase was observed for fibronectin and laminin. Gross and light microscopic examination of the dogs' tissues (post mortem) revealed no significant lesions.

Vaccination did not cause immunosuppression, and it did induce autoantibodies and antibodies to conserved heterologous antigens. There was no evidence of autoimmune disease in any of the immunized animals, even though the experiment was terminated at 22 weeks of age, well before any clinical signs of autoimmune disease usually become apparent. The authors mention similar serological findings in a follow-up study, in dogs that were immunized with the multivalent vaccine only and with the rabies vaccine only.

A marked increase in autoantibodies to myoglobin and myosin was observed in both groups, and was attributed to the frequent bleedings of the dogs (that undoubtedly caused some tissue trauma).

The most strikingly increased titers of autoantibodies were directed against fibronectin and laminin—both widely distributed throughout the body (fibronectin—a component of the extracellular matrix and plasma). Both these antibodies (anti-fibronectin and anti-laminin) have been found in human patients with a variety of autoimmune diseases: SLE, rheumatoid arthritis, and vasculitis. These autoantibodies have been experimentally induced in various animal models [96, 97], and have been implicated in the development of glomerulopathy with granular deposits suggestive of immune complex deposition. No evidence of glomerular disease was found in the immunized dogs. It is possible that the immune response observed was the result of polyclonal activation (adjuvant reaction). In support of this hypothesis is the large number of autoantibodies and antibodies found in the immunized dogs. Three other possible mechanisms are suggested by the authors: 1) cross-reactivity with vaccine components (or contaminants); 2) 'bystander activation' of self-reactive lymphocytes; 3) somatic mutation of immunoglobulin variable genes.

It is apparent that susceptibility to vaccine-induced autoimmunity is also determined by genetic factors. So that it is likely that a small proportion of the immunized animals that have developed autoantibodies, will at some time in the future also develop autoimmune disease.

## Summary

There are several conclusions that in our opinion can be drawn in summary of the above review:

1. For the general population, vaccines are a safe and a beneficial procedure that prevents diseases (especially childhood diseases) with a high morbidity and mortality.
2. There are subjects who, subsequent to vaccination (apparently), have developed diseases that they may not have developed had they not been vaccinated. It is not *sine qua non* that these people would naturally have developed autoimmune conditions, even though they may carry the genetic potential.
3. So far we are unable to identify those subjects (IgA deficiency, complement component deficiency, HLA-DR specific?) who will most probably develop autoimmune conditions after immunization (since not all who have the genetic predisposition end up with post-vaccine autoimmune illness).
4. Would those subjects who acquired autoimmune illnesses after immunization, have acquired those illnesses had they been exposed to the infection? They may have, or they may not. Since the vaccine also contains adjuvant material we cannot definitely rule out the possible that not the infectious component of the vaccine was responsible for the autoimmune phenomena, but the adjuvant.

As for patients already known to have autoimmune diseases, it seems that most vaccines are well tolerated

by them, not causing more flare-ups or exacerbation than would occur spontaneously, as part of the natural history of the disease. We still need to investigate whether an individual tendency exists for post-immunization autoimmune disease, such as a family member who has an autoimmune condition or if the individuals affected carry (in a greater proportion) certain HLA antigens (such as HLA-DR2, 3, 4 which are more reactive to specific immunogenic stimuli).

## References

- Cohen A.D., Shoenfeld Y. 1996. Vaccine-induced autoimmunity. *J. Autoimmune*. **9**: 699–703
- Stratton K.R., Howe C.J., Johnston R.B. 1994. Adverse events associated with childhood vaccines other than pertussis and rubella. *JAMA* **271**: 1602–1605
- Ropper A.H. 1992. The Guillain–Barre syndrome. *New Engl. J. Med.* **326**: 1130–1136
- Rostami A.M. 1993. Pathogenesis of immune-mediated neuropathies. *Pediatr. Res.* **33**: 590–594
- Fredman P., Vedeler C.A., Nyland H., Aarli J.A., Svennerholm L. 1991. Antibodies in sera from patients with inflammatory demyelinating polyradiculoneuropathy reactive with ganglioside LM1 and sulfatide of peripheral nerve myelin. *J. Neurol.* **238**: 75–79
- Melnick S.C. 1964. Role of infection in the Guillain–Barre syndrome. *Neurol. Neurosurg. Psychiatry* **27**: 395–407
- Pepose J.S. 1982. A theory of virus-induced demyelination in the Landry–Guillain–Barre syndrome. *J. Neurol.* **227**: 93–97
- Dowling P.C., Cook S.D. 1981. Role of infection in Guillain–Barre syndrome: laboratory confirmation of herpes virus in 41 cases. *Ann. Neurol.* **9(suppl)**: 44–55
- Van Doorn P.A., Brand A., Vermeulen N. 1988. Anti-neuroblastoma cell-line antibodies in inflammatory demyelinating polyneuropathy: inhibition in vitro by intravenous immunoglobulins. *Neurology* **38**: 1592–1595
- Schmitz H., Enders G. 1977. Cytomegalovirus as a frequent cause of Guillain–Barre syndrome. *J. Med. Virol.* **1**: 21–27
- Grose C., Spizland I. 1976. Guillain–Barre syndrome following administration of live measles vaccine. *Am. J. Med.* **60**: 441–443
- Gruenewald R., Ropper A.H., Lior H., Chan J., Lee R., Molinaro V.S. 1991. Serologic evidence of *Campylobacter jejuni* and *E. coli* enteritis in patients with Guillain–Barre syndrome. *Arch. Neurol.* **48**: 1080–1082
- Terryberry J., Sutjita M., Shoenfeld Y., Gilburd B., Tanne D., Lorber M., Alosachie I., Barka N., Lin H.C., Youinou P. 1995. Myelin- and microbe-specific antibodies in Guillain–Barre syndrome. *J. Clin. Lab. Analysis* **9**: 308–319
- Abu-Shakra M., Shoenfeld Y. 1993. *Natural autoantibodies*. Y. Shoenfeld, D. Isenberg, eds. CRC Press, Boca-Raton, p. 15–33
- Koski C.L. 1992. Humoral mechanisms in immune neuropathies. *Neurol. Clin.* **10**: 629–649
- Ropper A.H., Victor M. 1998. Influenza vaccination and the Guillain–Barre syndrome. *New Engl. J. Med.* **339**: 1845–1846
- Lasky T., Terracciano G.J., Magder L., Koski C.L., Ballesteros M., Nash D., Clark S., Haber P., Stolley P.D., Schonberger L.B., Chen R.T. 1998. The Guillain–Barre syndrome and the 1992–1993 and 1993–1994 influenza vaccines. *New Engl. J. Med.* **339**: 1797–1801
- Langmuir A.D., Bregman D.J., Kurland L.T., Nathanson N., Victor M. 1984. An epidemiologic and clinical evaluation of Guillain–Barre syndrome reported in association with the administration of swine influenza vaccines. *Am. J. Epidemiol.* **79**: 841–879
- Hughes R.A., Chondhary P.P., Osborn M., Rees J.H., Sanders E.A. 1996. Immunization and risk of relapse of Guillain–Barre syndrome or chronic inflammatory demyelinating polyradiculoneuropathy. *Muscle Nerve* **19**: 1230–1231
- Genain C.P., Cannella B., Hauser S.L., Raine C.S. 1999. Identification of autoantibodies associated with myelin damage in multiple sclerosis. *Nature Med.* **5**: 170–175
- Marshall E. 1998. A shadow falls on Hepatitis B vaccination effort. *Science* **281**: 630–1
- Herroelen L., de Keyser J., Ebinger G. 1991. Central nervous system demyelination after immunization with recombinant Hepatitis B vaccine. *Lancet* **338**: 1174–1175
- Nadler J.P. 1993. Multiple sclerosis and Hepatitis B vaccination. *Clin. Infect. Dis.* **17**: 928–929
- Alter M. 1976. Is multiple sclerosis an age-dependent host response to measles? *Lancet* **28**: 456–457
- Currier R.R.D. 1996. Measles vaccination has had no effect on the occurrence of multiple sclerosis. *Arch. Neurol.* **53**: 1216
- Riikonen R. 1989. The role of infection and vaccination in the genesis of optic neuritis and multiple sclerosis in children. *Acta. Neurol. Scand.* **80**: 425–431
- Hull T.P., Bates J.H. 1997. Optic neuritis after influenza vaccination. *Am. J. Ophthalmol.* **124**: 703–704
- Weizman A., Weizman R., Szekely G.A., Wijssenbeek H., Livni E. 1982. Abnormal immune response to brain tissue antigen in the syndrome of autism. *Am. J. Psychiat.* **7**: 1462–1465
- Singh V.K., Warren R.P., Odell J.D., Warren W.L., Cole P. 1993. Antibodies to myelin basic protein in children with autistic behaviour. *Brain Behav. Immun.* **7**: 97–103
- Singh V.K., Sheren X.L., Yang V.C. 1998. Serological association of measles virus and human herpesvirus-6 with brain autoantibodies in autism. *Clin. Immunol. Immunopathol.* **89**: 105–108
- Lee J.W., Melgaard B., Clementa C.J. 1998. Autism, inflammatory bowel disease and MMR vaccine. *Lancet* **351**: 905–909
- Gupta S., Aggarnal S., Heads C. 1996. Brief report: Dysregulated immune system in children with autism: beneficial effects of intravenous immunoglobulins on autistic characteristics. *J. Autism. Develop. Dis.* **26**: 439–450
- Peltola H., Patja A., Leinikki P., Valle M., Davidkin I., Paunio M. 1998. No evidence for measles, mumps and rubella vaccine-associated inflammatory bowel disease or autism in a 14 year prospective study. *Lancet* **351**: 1327–1328
- Taylor B., Miller E., Farrington C.P., Petropoulos M.C., Favot-Mayaud I., Li J., Waight P.A. 1999. Autism and measles, mumps and rubella vaccine: no epidemiological evidence for a causal association. *Lancet* **353**: 2026–2029



35. Brodsky L., Stanievich J. 1998. Sensorineural hearing loss following live measles vaccination. *Int. J. Pediatric Otolaryngol.* **16**: 159–163
36. Stewart B.J.A., Prabhu P.U. 1993. Reports of sensorineural hearing loss after measles, mumps and rubella immunization. *Arch. Dis. Childhood* **69**: 153–154
37. Paira S.O. 1998. Sudden sensory-neural hearing loss in patients with systemic lupus erythematosus or lupus-like syndrome and antiphospholipid antibodies. *J. Rheumatol.* **25**: 2476–2477
38. Brey R.L. 1998. Neurological manifestations of antiphospholipid antibody syndrome. *Lupus* **7**: S67–74
39. Naarendorp M. 1998. Sudden sensoryneural hearing loss in patients with systemic lupus erythematosus or lupus-like syndromes and antiphospholipid antibodies. *J. Rheumatol.* **25**: 589–592
40. Plesner A.M. 1995. Gait disturbances after measles, mumps and rubella vaccine. *Lancet* **345**: 316
41. Grasland A., Vinceneux P. 1999. Rheumatic manifestations of vaccination. *Rheumat. Eur.* **28**: 25–27
42. Benjamin C.M., Chew C.G., Silman A.J. 1992. Joint and limb symptoms in children after immunization with measles, mumps and rubella vaccine. *BMJ* **304**: 1075–1077
43. Symmons D.P.M., Chakravarty K. 1993. Can immunization trigger rheumatoid arthritis. *Ann. Rheum. Dis.* **52**: 843–844
44. Aho K., Kottinen A., Rajasalmi M., Werger O. 1962. Transient appearance of rheumatoid factor in connection with profilactic vaccinations. *Acta. Path. Microbiol. Scand.* **56**: 478–479
45. Peeler R.N., Kadull P.J., Cluff L.E. 1956. Intensive immunization of man: evaluation of possible adverse consequences. *An. Intern. Med.* **63**: 44–57
46. Robertson P.W., Leonard B.J. 1956. Some delayed complications of inoculation. *BMJ* **2**: 1029–1032
47. Kurland L.T., Molgaard C.A., Kurland E.M., Erdtman F.J., Stebbing G.E.T. 1984. Lack of association of swine flu vaccine and rheumatoid arthritis. *May. Clin. Proc.* **59**: 816–821
48. Gross K., Combe C., Kruger K., Schattenkirschner M. 1995. Arthritis after hepatitis B vaccination. *Scand. J. Rheumatol.* **24**: 50–52
49. Pope J.E., Stevens A., Howson W., Bell D.A. 1998. The development of rheumatoid arthritis after recombinant hepatitis B vaccine. *J. Rheumatol.* **25**: 1687–1693
50. Tischler M., Shoenfeld Y. 1996. Tuberculose et immunité: ou en sommes-nous? *Ann. Inst. Pasteur* **7**: 133–136
51. Belmatong E., Levy-Ojebbour, Appelboom T., De Gennes C., Peltier A.P., Meyer O., Kahn M.F., Carbon C. 1993. Polyarthritis in four patients treated with intravesical BCG for bladder carcinoma. *Rev. Rhum.* **60**: 130–131
52. James J.A., Kaufman K.M., Farris A.D., Taylor-Albert E., Lehman T.J., Harley J.B. 1997. An increased prevalence of Epstein–Barr virus infection in young patients suggests a possible etiology for systemic lupus erythematosus. *J. Clin. Invest.* **100**: 3019–3026
53. Vaughan J.H. 1997. The Epstein–Barr virus and systemic lupus erythematosus. *J. Clin. Invest.* **100**: 2939–2940
54. Dror Y., Blachar Y., Cohen P., Livni N., Rosenmann E., Ashkenazi A. 1998. Systemic lupus erythematosus associated with acute Epstein–Barr virus infection. *Am. J. Kidney Dis.* **32**: 825–828
55. Incaprera M., Rindi L., Bazzichi A., Garzelli C. 1998. Potential role of the Epstein–Barr virus in systemic lupus erythematosus autoimmunity. *Clin. Exp. Rheumatol.* **16**: 289–294
56. Dostal C., Newkirk M.M., Duffy K.N., Paleckova A., Bosak V., Cerna M., Zd'arsky E., Zvarova J. 1997. Herpes viruses in multicase families with rheumatoid arthritis and systemic lupus erythematosus. *Ann. N. Y. Acad. Sci.* **815**: 334–337
57. Keen G.A., Yeats J. 1996. Epstein–Barr virus-induced systemic lupus erythematosus. *S. Afr. Med. J.* **86**: 850
58. Matsukawa Y. 1996. Epstein–Barr virus-induced systemic lupus erythematosus. *S. Afr. Med. J.* **86**: 850–851
59. Tudela P., Marti S., Bonal J. 1992. Systemic lupus erythematosus and vaccination against hepatitis B. *Nephron* **62**: 236
60. Finielz P., Lam-Kam-Sang L.F., Guiserix J. 1998. Systemic lupus erythematosus and thrombocytopenic purpura in two members of the same family following hepatitis B vaccine. *Nephrol. Dial. Transplant* **13**: 2420–2421
61. Tudela P., Marti S., Bonal J. 1992. Systemic lupus erythematosus and vaccination against hepatitis B. *Nephron* **62**: 236
62. Guiserix J. 1996. Systemic lupus erythematosus following Hepatitis B vaccine. *Nephron* **74**: 441
63. Mamoux V., Dumont C. 1994. Lupus erythemateux disseminé et vaccination contre l'hépatite B. *Arch. Pediatr.* **1**: 307–308
64. Grezard P., Chafi M., Philippot V., Perrot H., Faisant M. 1996. Cutaneous lupus erythematosus and buccal aphthosis after hepatitis B vaccination in a 6-year-old child. *Ann. Dermatol. Venereol.* **123**: 657–659
65. Ramirez O., Ramirez R. 1986. Lupoid syndrome in BCG-itis. Report of a case. *Med. Cutano Ibero Lat. Am.* **14**: 87–89
66. Stewart W.M., Lecroq C., Damon B. 1968. Lupus after BCG vaccination: three familial cases. *Bull. Soc. Er. Dermatol. Syphilis* **75**: 846–848
67. Misery L., Combemale P. 1993. Systemic urticaria disclosing post-vaccine lupus tuberculosis. *Ann. Dermatol. Venereal.* **120**: 233–235
68. Rodrigues A., Coelho R.D., Pereira F. 1990. Lupus vulgaris after BCG vaccine; A clinical case. *Med. Cutan. Ibero. Lt. Am.* **18**: 224–226
69. Izumi A.K., Matsunaga J. 1982. BCG vaccine-induced lupus vulgaris. *Arch. Dermatol.* **118**: 171–172
70. Baxter A.G., Horsfall A.C., Healey D., Ozegbe P., Day S., Williams D.G., Cooke A. 1994. Mycobacteria precipitate an SLE-like syndrome in diabetes-prone NOD mice. *Immunology* **83**: 227–231
71. Karopoulos C., Rowley M.J., Handley C.J., Strugnell R.A. 1995. Antibody reactivity to mycobacterial 65 kDa heat shock protein: relevance to autoimmunity. *J. Autoimmun.* **8**: 235–248
72. Feige U., van Eden W. 1996. Infection, autoimmunity and autoimmune disease. *EXS* **77**: 359–373
73. Classen D.C., Classen J.B. 1997. The timing of pediatric immunization and the risk of insulin-dependent diabetes mellitus. *Infect. Dis. Clin. Pract.* **6**: 449–454

74. Classen J.B., Classen D.C. 1999. Public should be told that vaccines may have long-term adverse effects. *BMJ* **318**: 193
75. Blom L., Nystrom L., Dahlquist G. 1991. The Swedish childhood diabetes study. Vaccinations and infection as risk determinants for diabetes in childhood. *Diabetologica*. **34**: 176–181
76. Karvonen M., Zygimantas C., Tuomilehto J. 1999. Association between type 1 diabetes and *Haemophilus influenzae* type b vaccination: birth cohort study. *BMJ* **318**: 1169–1172
77. The Institute for Vaccine Safety Diabetes Workshop Panel. Childhood immunizations and type 1 diabetes: summary of an Institute for Vaccine Safety Workshop. 1999. *Pediatr. Infect. Dis. J.* **18**: 217–222
78. Joeekes A.M., Gabriel J.R.T., Goggin J. 1972. Renal disease following prophylactic inoculation. *Nephron* **9**: 162–170
79. Freud P., Maffia A.J., Hosbach R.E., Valicenti P.W. 1960. Smallpox vaccination followed by acute renal failure. *Amer. J. Dis. Child.* **99**: 98–100
80. Stefanini M., Piomelli S., Ostrovski J.F., Colpoys W.P. 1958. Acute vascular purpura following immunization with asiatic influenza vaccine. *New Engl. J. Med.* **259**: 9–12
81. Bishop W.B., Carlton R.F., Fanders L.L. 1966. Diffuse vaculitis and death after hyperimmunization with pertussis vaccine. Report of a case. *New Engl. J. Med.* **274**: 661–669
82. Le Hello C., Cohen P., Bousser M.G., Letellier P. 1999. Suspected hepatitis B vaccination related vasculitis. *J. Rheumatol.* **26**: 191–192
83. Bamford C.R., Sibley W.A., Laguna J.F. 1978. Swine influenza vaccination in patients with multiple sclerosis. *Arch. Neurol.* **35**: 242–243
84. Kurland L.T., Molgaard C.A., Kurland E.M., Wiederholt W.C., Kirkpatrick J.W. 1984. Swine flu vaccine and multiple sclerosis. *JAMA* **251**: 2672–2675
85. Sibley W.A., Bamford C.R., Laguna J.F. 1976. Influenza vaccination in patients with multiple sclerosis. *JAMA* **236**: 1965–1966
86. Salvetti M., Pisani A., Bastianello S., Millefiorini E., Buttinelli C., Pozzilli C. 1995. Clinical and MRI assessment of disease activity in patients with multiple sclerosis after influenza vaccination. *J. Neurol.* **242**: 143–146
87. Miller A.E., Morgante L.A., Buchwald L.Y., Nutile S.M., Coyle P.K., Krupp L.B., Doscher C.A., Lublin F.D., Knobler R.L., Trantas F., Kelley L., Smith C.R., La Rocca N., Lopez S. 1997. A multicenter, randomized, double-blind, placebo-controlled trial of influenza immunization in multiple sclerosis. *Neurology* **48**: 312–314
88. Brodman R., Gilfillan R., Glass D., Schur P.H. 1978. Influenzal vaccine response in systemic lupus erythematosus. *Ann. Intern. Med.* **88**: 735–740
89. Williams G.W., Steinberg A.D., Reinertsen J.L., Klassen L.W., Decker J.L., Dolin R. 1978. Influenza immunization in systemic lupus erythematosus. A double-blind trial. *Ann. Intern. Med.* **88**: 729–734
90. Ristow S.C., Douglas R.G., Condemi J.J. 1978. Influenza vaccination of patients with systemic lupus erythematosus. *Ann. Intern. Med.* **88**: 786–789
91. Cimmino M.A., Serio B., Accardo S. 1995. Influenza vaccination in rheumatoid arthritis. *J. Rheumatol.* **22**: 1802
92. Heron A., Dettleff G., Hixon B., Brandwin L., Orbals D., Hornick R., Hahn B. 1979. Influenza vaccination in patients with rheumatic diseases. Safety and efficacy. *JAMA* **242**: 53–56
93. Dickman S. 1998. Possible cause found for lyme arthritis. *Science* **281**: 631
94. Zandman-Goddard G., Blank M., Ehrenfeld M., Gilburd B., Peter J., Shoenfeld Y. 1999. A comparison of autoantibody production in asymptomatic and symptomatic women with silicone breast implants. *J. Rheumatol.* **1**: 73–77
95. Hogenesch H., Azcona-Olivera J., Scott-Montcrieff C., Snyder P.W., Glickman L.T. 1999. Vaccine-induced autoimmunity in the dog. *Adv. Vet. Med.* **41**: 733–747
96. Murphy-Ullrich J.E., Oberley T.D., Mosher D.F. 1984. Detection of autoantibodies and glomerular injury in rabbits immunized with denatured human fibronectin monomer. *Am. J. Pathol.* **117**: 1–11
97. Abrahamson D.R., Caulfield J.P. 1982. Proteinuria and structural alterations in rat glomerular basement membranes induced by intravenously injected anti-laminin immunoglobulin G. *J. Exp. Med.* **156**: 128–145