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A review of hepatitis B vaccination

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Hepatitis B is one of the most important infectious causes of acute and chronic liver disease both in the US and worldwide. In order to combat the life-threatening effects of hepatitis B infection, recombinant hepatitis B vaccines have been developed. The medical and scientific communities have generally accepted that recombinant hepatitis B vaccine – a highly purified, genetically engineered, single antigen vaccine – is a safe vaccine. Information is presented showing that hepatitis B vaccine contains yeast, aluminium, thimerosal and hepatitis B surface antigen epitopes, which may result in hepatitis B vaccine being associated with autoimmune diseases among susceptible adult vaccine recipients. There is little doubt that the benefits of this vaccine overall far outweigh its risks. Physicians and patients should evaluate the risks and benefits of hepatitis B vaccination and, together, make an informed consent decision as to whether to undergo vaccination. Individuals who experience an adverse reaction to hepatitis B vaccination should report it to the Vaccine Adverse Event Reporting System database and be advised that they may be eligible for compensation from the no-fault National Vaccine Injury Compensation Program, administered by the US Court of Claims. The authors strongly urge that additional research be conducted into the molecular basis of adverse events following hepatitis B vaccine administration, so that further recommendations may be made on how to improve their safety profiles.

Keywords: aluminium, autoimmune, hepatitis B surface antigen (HBsAg), hepatitis B virus (HBV), thimerosal, VAERS, yeast

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1. Introduction

In the US and worldwide, hepatitis B is one of the most important infectious causes of acute and chronic liver disease. Each year, prior to the introduction of universal childhood vaccination in the US, approximately 300,000 people in the US acquired new hepatitis B virus (HBV) infection; 25,000 were reported with acute hepatitis [1,2]. Between 18,000 and 30,000 people became HBV carriers, adding to a pool of 750,000 – 1,000,000 HBV carriers at risk of chronic liver disease, including chronic active hepatitis, cirrhosis and primary hepatocellular carcinoma (PHC). Between 4000 and 5000 people died annually due to HBV; 300 deaths were due to fulminant hepatitis, 3000 – 4000 due to cirrhosis, and 600 – 1000 due to PHC. The Centers for Disease Control and Prevention (CDC) estimated the direct costs of HBV infection in the US to have exceeded $500 million annually [3].

HBV is transmitted by percutaneous or permucosal exposure to infected blood via sexual contact with infected individuals, and perinatally from an infected mother to an infant [4,5]. In the US, infection occurs primarily in adults at risk due to lifestyle or exposure in the workplace. Groups at risk include parenteral drug abusers, homosexual men, individuals who have heterosexual contact with multiple partners, individuals who live in households with HBV carriers, haemophiliacs, haemodialysis

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patients and staff, the institutionalised developmentally disabled and those who care for them, and healthcare and public safety workers who are in contact with human blood and body fluids [1]. Perinatal exposure to infected mothers results in 19,000 infants being exposed to HBV annually, 4500 of whom would become HBV carriers if preventive treatment was not administered. Certain US populations, including Alaskan natives and Pacific Islanders, are at high risk of disease; 5 – 15% of such individuals are HBV carriers, and disease transmission occurs primarily during childhood [6].

In the US, 97% of reported disease cases and an estimated 75% of new HBV carriers result from infection in adults [7]. Although few cases of acute hepatitis B are reported in infants or children, 25% of new HBV carriers result from infection of infants or young children. In 1988, parenteral drug abuse and heterosexual transmission accounted for ~ 50% of reported disease cases, while homosexual activity and occupationally-acquired infection accounted for ~ 13%, a proportion that has decreased substantially in the last 5 years. Approximately 30% of cases cannot be directly linked to high-risk behaviour and are therefore not accessible to preventive efforts [7,8].

2. Vaccine development

Following identification of the causative agent and the development of serological tests for the hepatitis B surface antigen (HBsAg), screening of human blood has largely eliminated transfusion-related HBV infection [9,10]. Effective vaccines against HBV were developed in the late 1970s. The last decade has seen the wide availability of effective vaccines, including the development of new vaccines by recombinant DNA technology. During the 1970s, several groups developed vaccines from the plasma of HBV carriers. These vaccines were prepared by purifying the non-infectious, 22 nm HBsAg particles from plasma using biophysical techniques, and treating the purified HBsAg with heat or chemicals to inactivate remaining HBV and other biological agents present in the original plasma pool. Plasma-derived vaccines developed in the US (Merck, Sharp and Dohme), France (Pasteur Institute) and the Netherlands (Dutch Red Cross) were shown to be safe and highly effective in both adults at high risk of infection and in infants born to HBV carrier mothers [11-17]. Plasma-derived vaccines have also been developed in Japan and Korea, and the latter are being used extensively in programmes in Asia [18-20].

Genetically engineered vaccines, developed and licensed in the 1980s, are most commonly produced by inserting the gene for HBsAg into the yeast *Saccharomyces cerevisiae* [21,22]. Following growth of the yeast, a vaccine is prepared by lysing the yeast to free HBsAg particles, which are separated from yeast components by biochemical and biophysical methods. The amino acid sequence of the protein produced by yeast is identical to that of the plasma-derived product, but the recombinant protein is not glycosylated whereas the natural protein is. Vaccine particles are 20 – 21 nm in size, and are slightly smaller and less regular than the plasma-derived product. Other first-generation recombinant vaccines have been produced in mammalian cell lines (CHO [Chinese hamster ovary]) into which the HBsAg gene has been inserted; these vaccines do contain glycosylated HBsAg and are thus chemically more similar to the plasma-derived vaccines [23]. Two recombinant vaccines produced in yeast (Recombivax™, Merck, and Energix™, GlaxoSmithKline) are available in the US and many countries worldwide; an additional recombinant vaccine produced in mammalian cells and which also contains pre-S2 antigen (Merieux) is available in some countries in Europe [21-23]. Recombinant vaccines are also being produced in Japan, and may become widely available in the future.

In the US, licensed hepatitis B vaccines are recommended for use in the childhood vaccination schedule and among the high-risk adult population to be given as a three-dose series, consisting of two priming doses given 1 month apart, followed by a third dose given 6 months after the first [1]. An alternative schedule, consisting of three primary doses at 1-month intervals, followed by a fourth dose 12 months after the first, has been approved for one vaccine. The priming doses induce detectable antibody to HBsAg in 70 – 85% of healthy adults and children, but the titre of antibody (50 – 300 IU/l) is relatively low. The final dose induces adequate antibody in > 90% of healthy adults and 95% of children and infants, and increases antibody titres to 1000 – 3000 IU/l in adults and > 5000 IU/l in children [11,24-26].

3. Hepatitis B vaccine safety

The medical and scientific communities have generally accepted that hepatitis B vaccine – a highly purified, genetically engineered, single antigen vaccine – is a safe vaccine. The CDC states that there is no confirmed scientific evidence that hepatitis B vaccine causes chronic illness, including multiple sclerosis (MS), chronic fatigue syndrome, rheumatoid arthritis or autoimmune disorders. Furthermore, two surveillance studies of adverse events in the US after hepatitis B vaccination have shown no association between hepatitis B vaccine and the occurrence of serious adverse events [27,28].

Currently, there are two manufacturers of hepatitis B vaccine in the US. In their package inserts, both companies state that their hepatitis B vaccines are 'generally well-tolerated.' However, both companies go on to warn that, as with any vaccine, it is possible that expanded commercial use of the vaccine could reveal rare adverse reactions. The manufacturers warn that hypersensitivity to yeast or any other component of the vaccine is a contraindication to vaccination. In addition, the manufacturers report that anaphylaxis, erythema mutliforme, arthritis, abnormal liver function tests, Guillain–Barré syndrome, neuritis, MS, optic neuritis, thrombocytopenia, transverse myelitis, and alopecia have all been reported following the commercial use of recombinant hepatitis B vaccines.

Table 1. Summary of important reactions after recombinant hepatitis B vaccine.

Reaction	Sex	Age (years)	Dose no.	Onset	Duration	Ref.
Erythema nodosum	F	43	1	4 days	Several weeks	[29]
Lichen planus-1	F	19	2	2 months	3 months	[30]
Lichen planus-2	M	50	2	1 month	6 weeks	[31]
Polyarthritis and erythema nodosum-1	M	31	1	1 day	6 weeks	[32]
Polyarthritis-2	F	41	1	2 weeks	7 months	[32]
Reiter's syndrome	M	29	2	4 weeks	4 months	[33]
Rheumatoid arthritis-1	F	49	1	24 h	NR	[34]
Rheumatoid arthritis-2	F	17	1	3 days	2 years (residual)	-
Rheumatoid arthritis-3	F	25	3	1 day	2 years (residual)	-
Rheumatoid arthritis-4	F	34	-	11 days	2 years (residual)	-
Vasculitis	F	45	1	2 days	1 week	[35]
SLE	F	43	1	2 weeks	NR	[36]
Glomerulonephritis	M	21	3	6 weeks	Few days	[37]
Evan's syndrome	M	33	2	2 days	2 months	[38]
Thrombocytopenia purpura-1	F	15	3	4 weeks	4 months	[39]
Thrombocytopenia purpura-2	F	21	2	3 weeks	2 months	[39]
Thrombocytopenia purpura-3	M	19	3	20 days	2 years (residual)	-
Thrombocytopenia purpura-4	F	21	1	4 weeks	4 months	-
Thrombocytopenia purpura-5			2	4 weeks	2 months	-
Acute posterior multifocal placoid pigment epitheliopathy-1	M	31	4	3 days	9 months (residual)	[40]
Acute posterior multifocal placoid pigment epitheliopathy-2	M	30	3	2 weeks	4 months (residual)	[41]
Optic neuritis-1	F	42	-	4 days	6 months (residual)	-
Optic neuritis-2	M	47	1	7 days	3 months (residual)	-
CNS demyelination-1	F	26	3	6 weeks	3 weeks (residual)	[42]
CNS demyelination-2	F	28	2	6 weeks	3 months (residual)	[42]
Transverse myelitis-1	M	40	1	2 weeks	6 weeks (residual)	[43]
Transverse myelitis-2	F	22	-	4 days	6 months (residual)	-

*Female:male ratio = 2.3.

MS: Multiple sclerosis; NR: Not reported; SLE: Systemic lupus erythematosus.

Table 1. Summary of important reactions after recombinant hepatitis B vaccine *(continued)*.

Reaction	Sex	Age (years)	Dose no.	Onset	Duration	Ref.
MS	F	43	1	7 – 10 days	4 weeks (residual)	[44]
Cerebellar ataxia	F	26	2	10 days	4 months	[45]
Chronic fatigue syndrome	F	51	3	9 days	2 years (residual)	-
Demyelinating polyneuropathy	F	45	3	2 days	1 year (residual)	-
Lymphadenopathy immunodeficiency	F	31	3	14 days	2 years (residual)	-
Peripheral neuropathy	F	15	3	3 days	2 years (residual)	-
Mean	*	32	2.0	15 days	242 days	-
Standard deviation	-	11	0.9	15 days	269 days	-

*Female:male ratio = 2.3.

MS: Multiple sclerosis; NR: Not reported; SLE: Systemic lupus erythematosus.

There are a number of case reports of arthritic, neurological, immunological and gastrointestinal (GI) adverse reactions reported in the scientific literature following adult hepatitis B vaccination [29-45]. In addition, a series of case reports in the authors' possession note serious adverse events following adult hepatitis B vaccination. A review of published and the authors' own case reports of adverse events following adult hepatitis B vaccination are summarised in Table 1. This table shows that:

- Adverse events have been primarily observed in adult (32 ± 11-years-old) females (female:male ratio = 2.3) within several weeks of immunisation (15 ± 15 days).
- Residual effects are often observed for prolonged periods (242 ± 269 days) with adverse events fairly evenly distributed in the vaccine schedule (2.0 ± 0.9).

In addition to an evaluation of adverse reactions following hepatitis B vaccination noted in case reports, the authors have analysed the Vaccine Adverse Events Reporting System (VAERS) database. This epidemiological database, maintained by the CDC since 1990, requires that all adverse reactions be reported to this database as mandated by US law. The protocol for reporting all serious reactions to VAERS requires written and telephonic confirmation by the CDC. The CDC follows up all serious reactions 1 year after they occur to determine whether or not the patients have recovered. The FDA inquires into all deaths reported to the VAERS database by contacting the patient's healthcare provider and physician. The FDA also continually monitors reports to the VAERS database to determine whether any vaccine or vaccine lot has a higher than expected incidence rate of events. The VAERS Working Group of the CDC, the FDA and the authors analyse and publish epidemiological studies based upon analyses of the VAERS database. A recent study by the CDC's VAERS Working Group states that VAERS is simple to use and flexible by design, and the data are available in a timely fashion [46]. The authors and others find that the massive size of the VAERS database offers a unique and useful tool for analysing adverse reactions to vaccines. The authors have retrospectively examined arthritic, immunological, neurological and GI adverse events following adult hepatitis B vaccination in the VAERS database using Microsoft Access [47-57]. The terms for the adverse events were based upon descriptions by those reporting them, and by defined reporting fields within the VAERS database. The number of male and female event reports were examined, as were the mean and standard deviation of age in years and the mean standard deviation of onset in days. The incidence rates of adverse events following adult hepatitis B vaccination were determined using the Biologic Surveillance Summaries of the CDC to estimate the number of doses administered during the time periods examined. The authors subscribe to the premise that another vaccine administered to a similarly-aged population should exhibit a non-statistically significant difference in the incidence rate of adverse events reported to the VAERS database. In the authors' analysis, an adult tetanus–diphtheria (Td) vaccine population served as a control group. The assumption of equal reactogenicity that forms the basis of the authors' null hypothesis, considers that the vaccine under study and the control population will be similarly influenced by factors in the VAERS database and the Biologic Surveillance Summaries of the CDC. Accordingly, the incidence of adverse events following adult hepatitis B vaccination was compared against the incidence rate of adverse events in an adult vaccine control group to determine the relative risk, attributable risk, percentage association and statistical significance. The relative risk was determined by dividing the incidence rate of the event following adult hepatitis B vaccination by the incidence rate

Table 2. Relative risk, attributable risk, percentage association and statistical significance of adverse reactions following adult hepatitis B vaccination.

Type of reaction	Relative risk	Attributable risk	Percentage association	Statistical significance
Arthritis	5.8	4.8	85	$p < 0.01$
Chronic arthritis	15.0	14.0	94	$p < 0.0001$
Myelitis	6.6	5.6	87	$p < 0.05$
Chronic myelitis	15.0	14.0	94	$p < 0.0001$
Vasculitis	11.0	10.0	92	$p < 0.05$
Chronic vasculitis	19.0	18.0	95	$p < 0.05$
Guillain–Barré syndrome	2.0	1.0	67	NS
Neuropathy	1.9	0.9	66	NS
Chronic neuropathy	3.3	2.3	77	$p < 0.01$
Chronic neuritis	7.3	6.3	88	$p < 0.0001$
Thrombocytopenia	11.0	10.0	92	$p < 0.01$
Chronic thrombocytopenia	-	-	100	$p < 0.05$
Chronic GI disease	15.0	14.0	92	$p < 0.0002$
MS	23.0	22.0	96	$p < 0.01$
Chronic MS	19.0	18.0	95	$p < 0.0001$
Cerebellar ataxia	4.4	3.4	81	$p < 0.01$

GI: Gastrointestinal; MS: Multiple sclerosis; NS: Not significant.

of the event following the adult vaccine control group. Attributable risk was determined by subtracting 1 from the relative risk. Percentage association was calculated by dividing the relative risk by the relative risk + 1, and multiplying this computed value by 100. In the authors' statistical analysis, a 2 x 2 contingency table was employed. The statistical package contained in Corel's Quattro Pro was used with a p value of 0.05 accepted as statistically significant.

Table 2 summarises the relative risk, attributable risk, percentage association and statistical significance of various serious adverse events previously analysed following adult hepatitis B vaccination based upon an analysis of the VAERS database. Table 3 summarises the number of male and female event reports, the mean age and standard deviation, and the mean onset and standard deviation. These analyses reveal an association between adult hepatitis B vaccination and arthritic, immunological, neurological, GI and dermatological adverse reactions. The relative risks of adverse events following adult hepatitis B vaccination ranged from 1.9 to 23.0 in comparison to an adult Td vaccination control based upon an analysis of the VAERS database. Serious adverse events developed in the adult female population within a few days to weeks following vaccination.

3.1 Potential immunological mechanisms responsible for severe adverse events reported following adult hepatitis B vaccination

The effector mechanisms of specific immunity, i.e., the complement cascade, phagocytosis, the presence of the cells of inflammation and the release of cytokines by immune cells, are not themselves specific for foreign antigens – they are nonspecific homeostatic mechanisms for the elimination of pathogenic microbes and other foreign antigenic substances. Since they are nonspecific, the effector mechanisms often result in local and systemic injury to tissues that represent 'self.' Under normal circumstances, the pathological sequelae of effector mechanisms are controlled and self-limited, and they tend to naturally diminish as the foreign antigen is eliminated. Furthermore, most individuals are tolerant of their own antigens and do not develop immune (autoimmune) responses against self (autologous) tissues. However, when responses against foreign antigens fail to be controlled within physiological limits, or when tolerance of self fails to be maintained, disorders leading to disease ensue. The disorders that have their source in aberrant, excessive or uncontrolled immune reactions are referred to as hypersensitivity diseases. The manufacturers of recombinant-type hepatitis B vaccine warn about hypersensitivity to any component of the vaccine as a contraindication to receiving an injection of vaccine. The potential inducers of immunological responses in recombinant hepatitis B vaccine include: thimerosal (a mercury derivative preservative), aluminium (an adjuvant), yeast (5% remaining following HBsAg purification from yeast) and HBsAg.

Immunological disease due to immune responses against self-antigens are referred to as autoimmune diseases. MS and

Table 3. Adverse reactions following adult hepatitis B vaccination.

Type of reaction	Number of female reports	Number of male reports	Mean age (years)	Mean onset (days)	Incidence per 10 million vaccinations
Arthritis	16	7	33.9 ± 11.8	8.4 ± 7.3	14.0
Myelitis	8	1	29.1 ± 9.9	3.3 ± 4.9	5.6
Vasculitis	5	1	38.3 ± 16.1	11.3 ± 9.3	4.3
Guillain–Barré syndrome	2	4	29.8 ± 12.5	9.7 ± 10.0	4.3
Neuropathy	6	6	38.2 ± 12.2	9.9 ± 17.3	8.1
Thrombocytopenia	7	6	27.3 ± 11.6	9.5 ± 7.9	8.0
MS	7	1	38.1 ± 11.4	47.8 ± 50.6	5.4
Cerebellar ataxia	7	2	35.6 ± 10.8	1.6 ± 2.0	6.1

MS: Multiple sclerosis.

Table 4. A summary of immunological disease classifications.

Type of hypersensitivity	Pathological immune mechanisms	Mechanisms of tissue injury and disease
Type I: immediate hypersensitivity	IgE antibody	Mast cells and their mediators (vasoactive amino acids, arachidonic acid metabolites, cytokines)
Type II: antibody-mediated	IgM, IgG antibodies against tissue or cell surface antigen	1. Complement activation 2. Recruitment and activation of neutrophils and macrophages 3. Abnormalities in receptor function
Type III: immune complex-mediated	Immune complexes of circulating antigens and IgM or IgG antibodies	1. Complement activation 2. Recruitment and activation of leukocytes
Type IV: T cell-mediated	1. $CD4^+$ (DTH) 2. $CD8^+$ CTLs (T cell-mediated cytolysis)	1. Activated macrophages, cytokines 2. Direct target cell lysis, cytokines

CTL: Cytolytic T lymphocyte; DTH: Delayed-type hypersensitivity.

systemic lupus erythematosus (SLE) are considered to be autoimmune diseases, as are some forms of polyarteritis nodosa (systemic vasculitis), which occur as a late consequence of HBV infection, and are due to the deposition in arteries of immune complexes comprising HBsAg and specific antibodies. Other immune complex-mediated diseases in which autoantibodies are produced include arthritis and glomerulonephritis. Myasthenia gravis, Graves' disease, insulin-resistant diabetes mellitus and pernicious anaemia are examples of autoimmune diseases where autoantibodies result in functional abnormalities without the involvement of any other effector mechanisms. Table 4 gives a general classification of immunological diseases by type of hypersensitivity. Of particular interest are Types I, III and IV, as these are most pertinent to the hypersensitivity responses exhibited by responser individuals who adversely react to one or more injections of recombinant-type hepatitis B vaccine.

Types I and III hypersensitivity have been reported in human responses to yeast antigens, and Type IV hypersensitivity has also been cited as being involved in such responses. Type IV hypersensitivity has been reported in human responses to small metal ions (i.e., mercury and aluminium). Type III responses include immunological diseases produced by immune complexes made up of a soluble antigen (i.e., HBsAg) and a specific antibody.

Such complexes form in the circulation and may deposit in the walls of vessels almost anywhere in the body, therefore they may be considered to be systemic in nature. Antibodies that are autoantibodies, and which may be produced against foreign antigen that is immunologically crossreactive with a component of self-tissues, can cause disease by activating the same effector mechanisms as immune complexes. The demonstration of antibody-mediated disease is commonly based on three criteria, amongst which the second is the more readily demonstrable. These are:

- The demonstration of antibodies or immune complexes deposited in tissues.
- The presence of anti-tissue antibodies or immune complexes in the circulation.

Table 5. Forms of immunological reactions in the skin.

	Immediate hypersensitivity (Type I)	Immune complex-mediated injury (Type III)	DTH (Type IV)
Induced by	Antigens evoking IgE response	Antigens evoking IgM and IgG antibodies	Protein antigens; xenobiotics that bind to self-proteins
Form of cutaneous reaction	Urticaria; wheal	Arthus reaction	Contact sensitivity
Onset after antigen challenge	Immediate: minutes Late phase: 8 – 10 h	Arthus: ~ 2 – 6 h Serum sickness: 7 – 10 days	Usually 24 – 72 h
Pathological lesion	Oedema; vascular dilation; local smooth muscle contraction	Necrotising vasculitis	Perivascular cell infiltrates and oedema
Antibody involved	IgE	IgG (C' fixing), IgM	None
Effector cells	Mast cells and basophils with bound IgE	Neutrophils and monocytes	$CD4^+$ T cells, $CD8^+$ T cells
Secreted mediators, effector molecules	Mast cell-derived mediators; vasoactive amines; lipid mediators	C' products as: membrane attack complex; anaphylatoxins	Cytokines (notably IFN and TNF)

DTH: Delayed-type hypersensitivity.

- Clinicopathological similarities with experimental diseases (in animal models) that are shown to be antibody-mediated by the adoptive transfer of such an antibody into a naive animal.

The importance of T lymphocytes as agents of human immunological disease has been well recognised since the 1980s because of two technological breakthroughs, namely, the production of monospecific (monoclonal) antibodies that identify distinct functional and phenotypic subsets of T cells, and the development of methods for the isolation and propagation of T cells *in vitro* from tissue sources. T cells that cause tissue injury may be autoreactive or they may be specific for foreign protein antigens present in or bound to self-cells and -tissues. T cells injure tissues by the same mechanisms that are responsible for cell-mediated immunity against microbes, namely:

- T cells of the $CD4^+$ subset secrete cytokines which activate macrophages. Such activation gives rise to delayed-type hypersensitivity (DTH) reactions. Tissue injury results from the products of activated macrophages.
- $CD8^+$ or cytolytic T lymphocytes (CTLs) directly lyse target cells bearing certain major histocompatibility complex (MHC)-associated foreign antigens. Such lysis occurs in the absence of any other effector mechansim.

Table 5 summarises forms of immunological reactions in the skin (denoting the type of hypersensitivity). All three types of hypersensitivity reactions have been experienced in humans reporting adverse events to recombinant hepatitis B vaccines.

It is generally accepted that autoimmunity results from a breakdown or failure of the mechanisms that are normally responsible for maintaining tolerance to self. The commonly stated events or factors that predispose to autoimmune diseases are:

- Multiple factors, including genetic predisposition, microbial infections (including viral agents) and immunological abnormalities.
- Immune response to disseminated antigens (e.g., DNA in SLE) and the formation of circulating immune complexes producing systemic disease, i.e., aberrant regulation or polyclonal activation of clones of lymphocytes.
- Production of higher than normal quantities of high affinity antibodies as a result of help provided by autoreactive T cells.

Immunological crossreactions of foreign- and self-antigens give rise to autoimmune disease where the response is directed against homologous, normal self-antigen. Since autoimmune responses induced by such immunological crossreactions are likely to generate autoantibodies specific for one or a few related antigens, it is also likely that the lesions that develop are organ- or tissue-specific, e.g., nerve tissue.

Autoimmunity also results from antigen-independent stimulation of self-reactive clones that are not deleted during development. Polyclonal activators may stimulate a large number of T or B lymphocytes irrespective of antigenic specificity, and often without interacting with antigen receptors. This form of autoimmunity is generally associated with the production of multiple autoantibodies and gives rise to systemic rather than organ-specific autoimmune disease, e.g., SLE. Polyclonal T cell activation has been invoked as a mechanism of autoimmunity, and it is known that adjuvants, or bacterial 'super antigens', can stimulate large numbers of T cells, amongst which there are clones specific for, but normally unresponsive to, self-antigens.

4. Conclusions and expert opinion

Case reports and the authors' previous analyses of the VAERS database show that recombinant hepatitis B

vaccination is associated with a number of serious adverse events. SLE, MS, allergic neuritis and other serious autoimmune diseases have been reported as being temporally related to injection with recombinant hepatitis B vaccine. The presence of extraneous antigen(s), a thimerosal preservative, an aluminium adjuvant, and crossreactive epitopes in the HBsAg in recombinant hepatitis B vaccines, may work synergistically to produce autoimmunity in susceptible individuals.

The authors have published that in order to improve the safety profile of vaccines, they need to be a single antigen, highly-purified, and tested to determine whether the epitopes they contain are crossreactive with human lymphocytes [54]. Furthermore, such vaccines should be packaged as single-dose, sealed vials so that preservatives are not necessary, and they should contain enough antigenic material to ensure that adjuvants are not necessary.

Hepatitis B is a disease with far-reaching and potentially devastating consequences. Hepatitis B vaccine has greatly reduced the incidence of the disease in vaccinated populations. In evaluating the potential risks and benefits of hepatitis B vaccination, there is little doubt that the benefits of this vaccine overall far outweigh its risks. It is also clear that the risk of contracting hepatitis B is largely dependent on lifestyles and life situations. Therefore, an informed consent decision as to whether to undergo vaccination should be realised between physician and patient based upon evaluation of the risks and benefits of hepatitis B vaccination. Those patients experiencing an apparent hepatitis B vaccine-related adverse event should report it to the VAERS, and should be advised of their eligibility to seek compensation from the National Vaccine Injury Compensation Program (NVICP) administered by the US Court of Claims. In light of the evidence in the form of a large number of case reports, epidemiology statistics and biological mechanisms showing a direct link between serious acute and chronic adverse reactions to hepatitis B vaccination, further molecular research should be conducted to allow for design of a safer hepatitis B vaccination.

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