Subject: Dr. Scheibner Article - Adjuvants in Vaccines

Date: Mon, 30 Apr 2001 12:29:08 -0700

ADVERSE EFFECTS OF ADJUVANTS IN VACCINES by Viera Scheibner (Part 1)

Part 2 is below

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ADVERSE EFFECTS OF ADJUVANTS IN VACCINES

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Nexus Dec 2000 (Vol 8, No1)

ADJUVANTS, PRESERVATIVES AND TISSUE FIXATIVES IN VACCINES

Vaccines contain a number of substances which can be divided into the following groups:

1. Micro-organisms, either bacteria or viruses, thought to be causing certain infectious diseases and which the vaccine is supposed to prevent. These are whole-cell proteins or just the broken-cell protein envelopes, and are called antigens.

2. Chemical substances which are supposed to enhance the immune response to the vaccine, called adjuvants.

3. Chemical substances which act as preservatives and tissue fixatives, which are supposed to halt any further chemical reactions and putrefaction (decomposition or multiplication) of the live or attenuated (or killed) biological constituents of the vaccine.

All these constituents of vaccines are toxic, and their toxicity may vary, as a rule, from one batch of vaccine to another.

In this article, the first of a two-part series, we shall deal with adjuvants, their expects role and the reactions (side effects).

ADJUVANTS

The desired immune response to vaccines is the production of antibodies, and this is enhanced by adding certain substances to the vaccines. These are called adjuvants (from the Latin adjuvare, meaning "to help").

The chemical nature of adjuvants, their mode of action and their reactions (side effect) are highly variable. According to Gupta et al. (1993), some of the side effects can be ascribed to an unintentional stimulation of different mechanisms of the immune system whereas others may reflect general adverse pharmacological reactions which are more less expected.

There are several types of adjuvants. Today the most common adjuvants for human use are aluminium hydroxide, aluminium phosphate and calcium phosphate. However, there are a number of other adjuvants based on oil emulsions, products from bacteria (their synthetic derivatives as well as liposomes) or gram-negative bacteria, endotoxins, cholesterol, fatty acids, aliphatic amines, paraffinic and vegetable oils. Recently, monophosphoryl lipid A, ISCOMs with Quil-A, and Syntex adjuvant formulations (SAFs) containing the threonyl derivative or muramyl dipeptide have been under consideration for use in human vaccines.

Chemically, the adjuvants are a highly heterogenous group of compounds with only one thing in common: their ability to enhance the immune response-their adjuvanticity. They are highly variable in terms of how they affect the immune system and how serious their adverse effects are due to the resultant hyperactivation of the immune system.

The mode of action of adjuvants was described by Chedid (1985) as: the formation of a depot of antigen at the site of inoculation, with slow release; the presentation of antigen immunocompetent cells; and the production of various and different lymphokines (interleukins and tumour necrosis factor).

The choice of any of these adjuvants reflects a compromise between a requirement for adjuvanticity and an acceptable low level of adverse reactions.

The discovery of adjuvants dates back to 1925 and 1926, when Ramon (quoted by Gupta et al., 1993) showed that the antitoxin response to tetanus and diphtheria was increased by injection of these vaccines, together with other compounds such as agar, tapioca, lecithin, starch oil, saponin or even breadcrumbs.

The term adjuvant has been used for any material that can increase the humoral or cellular immune response. to an antigen. In the conventional vaccines, adjuvants are used to elicit an early, high and long-lasting immune response. The newly developed purified subunit or synthetic vaccines using biosynthetic, recombinant and other modern technology are poor immunogens and require adjuvants to evoke the immune response.

The use of adjuvants enables the use of less antigen to achieve the desired immune response, and this reduces vaccine production costs. With a few exceptions, adjuvants are foreign to the body and cause adverse reactions.

Part 1 deals with the following types of adjuvants (after Gupta et al, 1993):

Oil emulsions
- Freund's emulsified oil adjuvants (complete and incomplete)
- Arlacel A
- Mineral oil
- Emulsified peanut oil adjuvant (adjuvant 65)

Mineral compounds

Bacterial products
- Bordetella pertussis
- Corynebacterium granulosumderived P40 component
- Lipopolysaccharide
- Mycobacteriwn and its components
- Cholera toxin

Liposomes

Immunostimulating complexes (ISCOMs)

Other adjuvants
- Squalene

Oil Emulsions

In the 1960s, emulsified water-in-oil and water-in-vegetable-oil adjuvant preparations used experimentally showed special promise in providing exalted "immunity" of long duration (Hilleman, 1966). The development of Freund's adjuvants emerged from studies of tuberculosis. Several researchers noticed that immunological responses in animals to various antigens were enhanced by introduction into the animal of living Mycobacterium tuberculosis. In the presence of Mycobacterium, the reaction obtained was of the delayed type, transferrable with leukocytes. Freund measured the effect of mineral oil in causing delayed-type hypersensitivity to killed mycobacteria. There was a remarkable increase in complement-fixing antibody response as well as in delayed hypersensitivity reaction.

Freund's adjuvant consists of a water-in-oil emulsion of aqueous antigen in paraffin (mineral) oil of low specific gravity and low viscosity. Drakeol 6VR and Arlacel A (mannide monooleate) are commonly used as emulsifiers.

There are two Freund's adjuvants: incomplete and complete. The incomplete Freund's adjuvant consists of water-in-oil emulsion without added mycobacteria; the complete Freund's adjuvant consists of the same components but with 5 mg of dried, heat-killed Mycobacterium tuberculosis or butyricum added.

The mechanism of action of Freund's adjuvants is associated with the following three phenomena:

1. The establishment of a portion of the antigen in a persistent form at the injection site, enabling a gradual and continuous release of antigen for stimulating the antibody;

2. The provision of a vehicle for transport of emulsified antigen throughout the lymphatic system to distant places, such as lymph nodes and spleen, where new foci of antibody formation can be established; and,

3. Formation and accumulation of cells of the mononuclear series which are appropriate to the production of antibody at the local and distal sites.

The pathologic reaction to the Freund's adjuvants starts at the injection site with mild erythema and swelling followed by tissue necrosis, intense inflammation and the usual progression to the formation of a granulomatous lesion. Scar and abscess formation may occur. The reactions observed following the administration of the complete adjuvant are generally far more extensive than with the incomplete adjuvant. The earliest cellular response is polymorphonuclear, then it changes into mononuclear and later includes plasmocytes. The adjuvant emulsion may be widely disseminated in varrious organs, depending on the route of inoculation, with the development of focal granulomatous lesions at distal places. Various gram-negative organisms may show a potentiating effect of the adjuvant, similar to that displayed by mycobacteria.

The earliest use of oil emulsion adjuvants was made with the influenza, vaccine by Friedwald (1944) and by Henle and Henle (1945). Following their promising results on animals, Salk (1951) experimented with such adjuvants on soldiers under the auspices of the US Armed Forces Epidemiological Board. He used a highly refined mineral oil, and developed a purified Arlacel A emulsifier which was free of toxic substances, such as oleic acid which had caused sterile abscesses at the injection site, and he administered the vaccine by intramuscular route.

Subsequently, Miller et al. (1965) reported their, failure to enhance the antibody and protective response to types 3, 4 and 7 adenovirus vaccines in mineral oil adjuvant compared with aqueous vaccine. Unpublished studies have revealed the need for an adequate minimal amount of antigen to trigger an antibody response to the emulsified preparations.

Salk et al. (1953) applied Freund's adjuvant to poliomyelitis vaccine, and later followed with extensive testing of killed crude as well as purified polio virus vaccine in animals and humans, where the reactions in humans were considered inconsequential.

Grayston et al. (1964) reported highly promising results with the trachoma vaccine using an oil adjuvant. However, the trachoma vaccine lost its relevance because, as demonstrated by Dolin et al. (1997) in their 37 years of research in a sub-Saharan village, the dramatic fall in the disease occurrence was closely connected with improvements in sanitation, water supply, education and access to health care. According to Dolin et al. (1997), the decline in trachoma occurred without any trachoma-specific intervention.

Allergens in Freund's adjuvant deserve special attention because they can be dangerous. These dangers include an overdose, i.e., the immediate release of more than the tolerated amount of properly emulsified vaccine in sensitive persons, or the breaking of the emulsion with the release of all or part of the full content of the allergen within a brief period of time. Long-term delayed reactions include the development of nodules, cysts or sterile abscesses requiring surgical incision. It is also likely that some allergens used, such as house dust or mould, might have acted like mycobacteria to potentiate the inflammatory response. Such reactions have been reduced with the use of properly tested and standardised reagins.

One must also consider that the first application of Freund's adjuvants was made at a time when modern concepts of safety were non-existent Indeed, mineral oil adjuvants have not been approved for human use in some countries, including the USA.

Mineral Compounds

Aluminium phosphate or aluminium hydroxide (alum) are the mineral compounds most commonly used as adjuvants in human vaccines. Calcium phosphate is another adjuvant that is used in many vaccines. Mineral salts of metals such as cerium nitrate, zinc sulphate, colloidal iron hydroxide and calcium chloride were observed to increase the antigenicity of' the toxoids, but alum gave the best results.

The use of alum was applied more than 70 years ago by Glenny et al. (1926), who discovered that a suspension of alum-precipitated diphtheria toxoid had a much higher immunogenicity than the fluid toxoid. Even though a number of reports stated that alum-adjuvanted vaccines were no better than plain vaccines (Aprile and Wardlaw, 1966), the use of alum as an adjuvant is now well established. The most widely used is the antigen solution mixed with pre-formed aluminium hydroxide or aluminium phosohate under controlled conditions. Such vaccines are now called aluminium-adsorbed or aluminium-adjuvanted. However, they are difficult to manufacture in a physico-chemically reproducible way, which results in a batch-to-batch variation of the same vaccine. Also, the degree of antigen absorption to the gels of aluminium phosphate and aluminium hydroxide varies. To minimise the variation and avoid the non-reproducibility, a specific preparation of aluminium hydroxide (Alhydrogel) was chosen as the standard in 1988 (Gupta et al., 1993).

The aluminium adjuvants allow the slow release of antigen, prolonging the time for interaction between antigen and antigen-presenting cells and lymphocytes. However, in some studies, the potency of adjuvanted pertussis vaccines was more than that of the plain pertussis vaccines, while in others no effect was noted. The serum agglutinin titres, after vaccination with adjuvanted pertussis vaccines, were higher than those of the plain vaccines, with no difference in regard to protection against the disease (Butler et al., 1962). Despite these conflicting results, aluminium compounds are universally used as adjuvants for the DPT (diphtheriapertussis-tetanus) vaccine. Hypersensitivity reactions following their administration have been reported which could be attributed to a number of factors, one of which is the production of IgE along with IgG antibodies.

It was suggested that polymerased toxoids, such as the so-called glutaraldehyde-detoxifled purified tetanus and diphtheria toxins, should be used instead of aluminium compounds. They are used combined with glutaraldehyde-inactivated pertussis vaccine.

Calcium phosphate adjuvant has been used for simultaneous vaccination with diphtheria, pertussis, tetanus, polio, BCG, yellow fever, measles and hepatitis B vaccines and with allergen (Coursaget et al., 1986). The advantage of this adjuvant has been seen to be that it is a normal constituent of the body and is better tolerated and absorbed than other adjuvants. It entraps antigens very efficiently and allows slow release of the antigen. Additionally, it elicits high amounts of IgG-type antibodies an much less of IgE-type (reaginic) antibodies.

Bacterial Products

Micro-organisms in bacterial infections and the administration of vaccines containing whole killed bacteria and some metabolic products and components of various micro-organisms have been known to elicit antibody response and act as immunostimulants. The addition of such micro-organisms and substances into vaccines augments the immune response to other antigens in such vaccines.

The most commonly used micro-organisms, whole or their parts, are Bordetella pertussis components, Corenybacterium derived P40 component, cholera toxin and mycobacteria.

.B. pertussis components

The killed Bordetella pertussis has a strong adjuvant effect on the diptheria and tetanus toxoids in the DPT vaccines. However, there are a number of admitted and well-describe reactions to it, such as convulsion, infantile spasms, epilepsy, sudden infant death syndrome (SIDS), Reye syndrome, Guilain-Barre syndrome, transverse myelitis and cerebral ataxia. Needless to say, the causal link to it is often (even though not always) vehemently disputed and generally considered "coincidental".

Paradoxically, in one case of shaken baby syndrome in which the baby developed subdural and retinal haemorrhages from the disease whooping cough, doctors accused the father of causing these injuries and strenuously denied that the disease pertussis can and does cause such haemorrhages-forgetting that this is the very reason why pertussis vaccine was developed against such potentially devastating disease in the first place. Such devastating effects are caused by the pertussis toxin, the causative agent of the disease (pertussis is a toxin-mediated disease), employed as the active ingredient in all pertussis vaccines whether whole-cell or acellular (Pittman, 1984).

Gupta et al. (1993) concluded that PT is too toxic to be administered to humans, but chemically detoxified or genetically inactivated PT may not exhibit the adjuvant effects comparable to the native PT.

.Corynebacterium-derived P40

P40 is a particulate fraction isolated from Corynebacterium granulosum, composed of the cell wall peptidoglycan associate with a glycoprotein. In animals, it displays a number of activities such as stimulation of the reticulo-endothelial system, enhancement of phagocytosis and activation of macrophages.

P40 abolishes drug-induced immunosuppression and increase non-specific resistance to bacterial, viral, fungal and parasitic infections. It induces the formation of IL-2, tumour necrosis factor, and interferon alpha and gamma (Bizzini et al., 1992). In clinical trials, P40 was claimed to be efficacious in the treatment of recurrent infections of the respiratory and genito-urinary tracts. Allergens coupled to P40 have been said to be instrumental in desensitising allergic patients without any side effects.

.Lipopolysaccharide (LPS)

LPS is an adjuvant for both humoral and cell-mediated immunity. It augments the immune response to both protein and polysaccharide antigens. It is too toxic and pyrogenic, even in minute doses, to be used as an adjuvant in humans.

.Mycobacterium and its components

Interestingly, Mycobacterium and its components, as originally formulated, were too toxic to be used as adjuvants in humans. However, the efforts to detoxify them resulted in the development of N-acetyl muramyl-L-alanyl-D-isoglutamine, or muramyl dipeptide (MDP). When given without antigen, it increased nonspecific resistance against infections with bacteria, fungi, parasites, viruses, and even against certain tumours (McLaughlin et al., 1980). However, MDPs are potent pyrogens (maybe that's why they may be effective against certain tumours-my comment) and their action is not completely understood; hence they are not acceptable for use in humans.

.Cholera Toxin

A major drawback with cholera toxin as a mucosal adjuvant is its intrinsic toxicity.

Liposomes

Liposomes are particles made up of concentric lipid membranes containing phospholipids and other lipids in a bilayer configuration separated by aqueous compartments. They have been used parenterally in people as carriers of biologically active substances (Gregoriadis, 1976) and considered safe.

Immunostimulating complexes (ISCOMs)

ISCOMs (DeVries et al., 1988; Morein et al., 199&, Lovgren : al., 1991) represent an interesting approach to stimulation of the humoral and cell-mediated immune response towards amphipathic antigens. It is a relatively stable but non-covalently-bound complex of saponin adjuvant Quil-A, cholesterol and amphipathic antigen in a molar ratio of approximately 1:1:1. The spectrum of viral capsid antigens and non-viral amphipathic antigens of relevance for human vaccination, incorporated into ISCOMs, comprises influenza, measles, rabies, gp340 from EB-virus, gp120 from HIV, Plasmodium falciparum and Trypanosoma cruzi.

ISCOMs have been shown to induce cytotoxic T-lymphocyte (CTL). Following oral administration, some types of CTLs were found in mesenteric lymph nodes and in the spleen, and specific IgA response could be induced.

ISCOMs have only been used in veterinary vaccines, partly due to their haemolytic activity and some local reactions all reflecting the detergent activity of the Quil-A molecule.

Other Adjuvants: Squalene

Squalene is an organic polymer with some antigenic epitopes which might be shared with other organic polymers acting as immunostimulators. It has been used in experimental vaccines since 1987 (Asa et aL, 2000) and it was used in the

experiments vaccines given to a great number of the participants in the Gulf War. These included those who were not deployed but received the same vaccines as those who were deployed.

The adjuvant activity of non-ionic block copolymer surfactants was demonstrated when given with 2% squalene-in-water emulsion. However, this adjuvant contributed to the cascade of reactions called "Gulf War syndrome", documented in the soldiers involved in the Gulf War. The symptoms they developed included arthritis, fibromyalgia, lymphadenopathy, rashes, photosensitive rashes, malar rashes, chronic fatigue, chronic headaches, abnormal body hair loss, non-healing skin lesions, aphthous ulcers, dizziness, weakness, memory loss, seizures, mood changes, neuropsychiatric problems, anti-thyroid effects, anaemia, elevated ESR (erythrocyte sedimentation rate), systemic lupus erythematosus, multiple sclerosis, ALS (amyotrophic lateral sclerosis), Raynaud's phenomenon, Sjorgren's syndrome, chronic diarrhoea, night sweats and low-grade fevers.

This long list of reactions shows just how much damage is done by vaccines, particularly when potentiated by powerful "immunoenhancers" such as squalene and other adjuvants. Interestingly, vaccinators as a rule consider such problems as mysterious and/or coincidental with vaccines. Since the administration of a multitude of vaccines to the participants (and prospective participants) in the Gulf War is well-documented (in fact, veterans claim they were given many more than were even recorded), this list of observed reactions further incriminates the vaccines as causing such problems.

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Nexus Feb 2001 (Vol 8, Number 2)

IMMUNOLOGY PRINCIPLES: ANTIBODY RESPONSE

To explain the action of adjuvants, we should look into immunology. The theory of vaccine efficacy is based on the ability of vaccines to evoke the formation of antibodies. This is of varying efficacy, depending on the nature of the antigen(s) and the amount of antigenic substance administered.

However, the mechanisms for the diversity of immune reactions are complex, and to this day are not quite known and understood. There are numerous theories, the favoured one being antibody response as the sign of immunisation (acquiring immunity).

Specific immunity to a particular disease is generally considered to be the result of two kinds of activity: the humoral antibody and the cellular sensitivity.

The ability to form antibodies develops partly in utero and partly after birth in the neonatal period. In either case, immunological competence-the ability to respond immunologically to an antigenic stimulus-appears to originate with the thymic activity.

The thymus initially consists largely of primitive cellular elements which become peripheralised to the lymph nodes and spleen. These cells give rise to lymphoid cells, resulting in the development of immunological competence. The thymus may also exert a second activity in producing a hormqne-lilce substance which is essential for the maturation of immunological competence in lymphoid cells. Such maturation also takes place by contact with thymus cells in the thymus.

Stimulation of the organism by antigen results in proliferation of cells of the lymphoid series accompanied by the formation of immunocytes, and this leads to the antibody production. Certain lymphocytes and possibly reticulum cells may be transformed into immunoblasts, which develop into immunologically active ("sensitised") lymphocytes and plasmocytes (plasma cells). Antibody formation is connected with plasma cells, while cellular immunity reactions are mainly lymphocytic.

None of the theories for antibody formation comprehends all the biological and chemical data now available. However, several principal theories have been considered at length.

The so-called instructive theory holds that the antigen is brought to the locus of antibody synthesis and there imposes in some way the synthesis of the specific antibody with reactive sites which are complementary to the antigen.

The clonal selection theory, evolved by Burnett (1960), presupposes that the information requisite to the synthesis of the antibody is part of the genetics. While the body develops a wide range of clones of cells necessary to cover all antigenic determinants by random mutation during early embryonic life, those clones which are capable of reacting with antigens of the body ("self') are destroyed, leaving only those cells which are not oriented to self ("non-self'). Upon stimulation by a foreign antigen, the clones of the cells corresponding to the particular foreign antigen are stimulated to proliferate and to produce the antibody.

Other researchers demonstrated that there are at least four different antigens formed by descendants of a single cloned cell. By this mechanism, the information for antibody synthesis is contained in the genetic material of each cell (DNA) but is normally repressed. The antigen then assumes the role of a de-repressor and initiates (provokes) the RNA synthesis for a particular messenger, resulting in the corresponding antibody production. The antigen would instruct the genetically predisposed capability of multipotential cells as to which antibody to produce and might also command the cells to proliferate, resulting in clones of properly instructed cells.

There are two possible mechanisms for the elimination of antibodies against self: immunological nonresponsiveness and immunological paralysis. There are several states of immunological nonresponsiveness; one is illustrated by the exposure of a foetus or newborn to an antigen prior to the development of its ability to recognise the antigen as non-self (immunological incompetence). Immunological paralysis results from the injection of a very large amount of antigen into immunologically competent individuals. Nonspecific immunological suppression by cortisone, ACTH, nitrogen mustards and irradiation is also well known.

Cellular sensitivity, also known as delayed or cellular hypersensitivity, depends on the development of immunologically reactive or "sensitive" lymphocytes and possibly other cells which react with the corresponding antigen to give a typical delayed-type reaction after a period of several hours, days or even weeks.

Cellular hypersensitivity depends on the original antigenic stimulation and a latent period, and is specific in its response. Delayed-type hypersensitivity is characteristic of the body's response to various infectious agents such as viruses, bacteria, fungi, spirochetes and parasites. It is also characteristic of the body's response to various chemicals, such as mercury, endotoxins, antibiotics, various drugs and many other substances foreign to the body.

The induction of a hypersensitivity reaction requires the presence in the tissues of the whole organism or certain derivatives of it, in addition to the specific antigen such as a lipid in addition to tubercle bacillus protein. Sensitisation to a non-infectious substance must be mediated through the skin or mucuous membranes which probably provide further necessary co-factors.

A delayed hypersensitivity reaction may be enhanced experimentally by the employment of the antigen in a mineral oil adjuvant with added Mycobacterium tuberculosis or by injection of the antigen directly into the lymphatics. The delayed hypersensitivity response is accompanied by mild to severe inflammation which may cause cell injury and necrosis. The inflammatory response which occurs in delayed-

type hypersensitivity may not be protective, and in many instances may even be harmful (e.g., rejection of grafts is directly linked to delayed hypersensitivity).

IMMUNOPATHOLOGY OF HYPERSENSITIVITY REACTIONS:

Immediate Hypersensitivity This is the antibody-type reaction that is a secondary consequence to the beneficial effect of the combination of an antibody with its antigen.

Arthus-type Reaction This reaction results from the precipitative union of a large amount of antigen with a highly reactive antibody in the blood vessels, and leads to vascular damage. The cascade of events includes spastic contraction of the arterioles, endothelial damage, formation of leukocyte thrombi, exudation of fluid and blood cells into the tissues, and sometimes ischemic necrosis. Periarteritis nodosa results from a similar antigen-antibody reaction and is characterised by inflammation of the smaller arteries and periarterial structures. it is accompanied by proliferation of the intima and two types of occlusion: (a) by proliferation or thrombosis; or (b) by the formation of nodules containing neutrophils and eosinophils.

Anaphylaxis

Injection of antigen and its combination with antibody may cause release from the cells (especially mast-cell fixed basophils) of physiologically active substances such as histamine, serotonin, acetyicholine, slow-reacting substances (SRS) and heparin. They act on smooth muscle and blood vessels and cause anaphylactic (hypersensitivity) shock, asthma attack, allergic oedema, rhinitis or hay fever, and accumulation of fluid in the joints.

Atopy

Atopy is caused by the union of antigen-usually pollens, dust, milk, wheat and animal danders-with a peculiar type of antibody (reagin). This reaction is relatively heat-labile and cannot be demonstrated by in vitro procedure. It has a special affinity for the skin and for familial predisposition to the disease. The reaction is nevertheless similar to other immediate-type sensitivities, with the release of histamine and its manifestation principally as asthma (breathing paralysis), hay fever, urticaria, angioedema and infantile eczema.

Delayed Hypersensitivity

The typical pathology of delayed hypersensitivity due to infectious agents involves perivascular infiltration of lymphocytes and histiocytes with the destruction of the antigen-containing parenchyma in the infiltrated area. The visual manifestations may vary from slight erythema and oedema to a violent reaction with progressive tissue destruction and necrosis. Local reactions include papular rose spots of typhoid fever, meningitis and a variety of infectious diseases, and contact sensitivities to plant and chemical substances manifesting as erythema, followed by papule and vesicle formation with resultant tissue damage and desquamation. Systemic reactions may accompany severe local reactions or may result from inhalation of the allergenic substances. Humoral antibodies do not seem to play a role in delayed hypersensitivity reaction. The reactivity is transferred only by cells, presumably sensitised lymphocytes, and it is unlikely that histamine or other physiologically active substances play a role in the reaction. The reaction extends to any or all tissues where the offending antigen may occur.

Isoimmunological Disease
This is the result of an immunological reaction of a member of the same species to the tissue of another member of the same species. A blood transfusion reaction in a person given an incompatible blood type is a typical example. Another example is erythroblastosis fetalis, which results from the transfer of antibodies against the red blood cells of the foetus to the foetal circulation. Homograft rejection of tissues or organs between nonisologous members of a species is also immunologically based.

Immunological Disease Resulting from Adsorption of Foreign Substances Under certain circumstances, foreign substances such as medications may combine with cells to render them antigenic. Subsequent exposure to such a foreign substance results in lytic, agglutinative or other types of cell-destructive activity. Such a reaction may involve red blood cells (drug-induced anaemias), platelets (drug-induced thrombocytopemc purpura), and leukocytosis (drug-induced agranulocytosis).

Bacteria or viruses may also alter cell surfaces by coating or by unmasking antigens through enzymatic activity which may render them vulnerable to immunological destruction.

Autoimmune Disease
Under certain circumstances, the body may respond immunologically to its own components or to intrinsic substances which are related antigenically to the host's own tissues. The circulating antibody or sensitised cells which are produced are then active in causing cellular injury to the tissues or organs of the body which bear the corresponding antigen.

Waksman (1962) proposed several mecnamsms of autoimmunisation, such as:

1.Vaccination with organ-specific antigens which are isolated from the lymphatic channels and bloodstream and are not recognised as self when brought into contact with the immunologic process. They are represented in the central and peripheral nervous systems, lens, uvea, testes, thyroid (thyroglobulin), kidneys and other organs.

2.Vaccination against constituents of tissues which have been altered antigenetically by various factors. These include myocardial infarction, X-irradiation, enzymatic or other chemical alteration, and changes induced by infectious disease agents or by drugs. Erythrocytes, platelets and leucocytes are the most affected cells. Various organs may also be affected.

3.Vaccination with heterologous antigens which are sufficiently different to permit an immunological response but sufficiently alike to react with autologous antigens.

4.Alteration of the immunological apparatus so as to result in the failure of recognition of self. This occurs in neoplasia of the lymphatic system and in experimental grafting of immunologically competent heterologous lymphatic tissues under conditions which suppress the host's response to the graft and give rise to the wasting "runt disease" or "homologous disease".

5.Possible hereditary or other immunological abnormality. This is represented by a hyper-reactivity to antigens or other aberrations without apparent antigenic

stimulation. Such mechanisms might be related to certain forms of the "collagen diseases", such as systemic lupus erythematosus in which there is an antibody against a diversity of antigens.

6.Experimentally, Freund's mineral oil adjuvant (usually with added mycobacteria) and certain bacteria or bacterial toxins may so alter the host as to bring about a ready response to unaltered normal homologous tissue. These "experimental autoallergies" include a wide variety of organs and tissues, and are now being employed as model systems for investigation of autoimmune phenomena.

Both humoral antibody and sensitised cells may function in autoimmune disease. Auto-antibodies seem to be involved in reactions with cells which are easily accessible, such as the formed elements of the blood (in haemolytic anaemia, leucopeni thrombocytopenia), vascular endothelium, vascular basement membrane including the glomerulus (in acute glomerulonephritis and ascites cells (neoplastic immunity).

Production of lesions in the solid vascularised tissues appears to depend on delayed hypersensitivity reactions with sensitised lymphoid cells (such as in allergic encephalomyeitis, thyroiditis, subacute and chronic glomerulonephritis, orchitis, adrenalitis and many other diseases).

It is quite obvious now that the same autoimmune mechanisms are responsible for the same diseases in human beings and that the extent of such damage is enormous and keeps increasing with more and more vaccines added to to "recommended" schedule.

Indeed, vaccines such as the pertussis vaccine are actually used to induce autoimmune diseases in laboratory animals, the best and most publicised example being the so-called experimental allergic encephalomyelitis (EAE). When, as expected, these unfortunate animals develop EAE from the pertussis vaccine, the causal link is never disputed; yet when babies after vaccination with the same vaccines develop the same symptoms of EAE as the laboratory animals, the causal link to the administered vaccine is always disputed and usually considered "coincidental". Lately, innocent parents and other carers have been accused of causing the symptoms of vaccine darn age by allegedly shaking their babies.

Systemic lupus erythematosus is one of the innumerable recognised side effects of a number of vaccinations. One of the best papers (if not the best on this is by Ayvazian and Badger (1948), and it has not lost any of its punch and relevance since it was published. They describe three cases of nurses who were literally vaccinated to death. The authors surveyed a group of 750 nurses who trained at a large municipal hospital between 1932 and 1946, and detailed the cases of three nurses who were vaccinated with a multitude of vaccines over a period of time and developed and succumbed to disseminated lupus erythematosus.

Typically, these nurses were given the following tests and vaccines in short succession: the Schick test; three days later, the Dick test; seven days later, typhoid-paratyphoid vaccine; seven days later, another typhoid-paratyphoid vaccine (a double dose); seven days later, the third typhoid-paratyphoid vaccine; and seven days later, the fourth typhoid-paratyphoid vaccine. Every time, the recipient

developed local erythema and/or fever and malaise, but it did not deter the doctor from administering yet another series of vaccines, starting only 14 days after the first lot of tests and typhoid-paratyphoid vaccines.

This time, after all these injections, one of the trainee nurses was given her first injection of scarlet fever streptococcus toxin with "no ill results". One week later, she was given the second injection of streptococcus toxin, after which she developed joint pains and fever. She did not report these reactions to the health office. Nine days later, she returned and received the third injection of a fourfold dose of streptococcus, after which she developed severe arthralgia in the fingers and knees and a sore throat.

She was hospitalised for five days and discharged with the diagnosis "Dick-toxin reaction". Only five days later her inoculations were continued, first in lower and then in gradually increasing doses so that the series included a total of 10 instead of the usual seven injections. Epinephrine was administered with each of these injections of streptococcus toxin and toxin-antitoxin.

Two months after the last lot, the trainee nurse was re-admitted to the hospital with swelling and pain of the ankles and toes and tenderness of the joints of both hands, which had been constant since the first Dick test five months earlier. The diagnosis was "rheumatic arthritis". She was given aspirin, but two weeks later the pain came back and she developed chills and fever, sore throat and cough. One month later, the trainee nurse was re-admitted to hospital for two weeks, and during this admission a streptococcus vaccine was started in small doses, but because of her severe reaction "further vaccines were refused". The diagnosis after this admission was "rheumatoid arthritis and infectious mononucleosis". Four months later, the trainee nurse noticed skin eruptions over her nose and both cheeks, and her saliva became foul. The skin and cheeks, upper lips and the bridge of the nose were covered with purplish red, mottled and indurated rash eruptions. Two months later, the eruptions spread over much of the body. A year later, the trainee nurse died, but not before developing severe symptoms of high fever, tachycardia, diarrhoea and showing abnormal blood tests.

It was not enough that this unfortunate trainee nurse died; there were another two cases reported, almost identical to the first case. We shall never know bow many of the remaining 747 trainee nurses developed less lethal, but still health-incanacitating. reactions.

If someone said that this type of "medical treatment' had been given to the inmates of the Nazi concentration camps, I would not be surprised. However, this type of "medical treatment" was and is being given with impunity to millions of babies, children, teenagers and adults in so-called free and democratic countries as well as in the Third World. Meanwhile, the health authorities refuse to accept that vaccines cause such reactions and even deaths.

VACCINATION: A SAFETY WARNING The conclusions which follow the study of relevant medical and immunological literature dealing with vaccines and the adjuvants used in vaccines is that the absolute safety of these substances can never be guaranteed. According to Gupta et al. (1993), the toxicity of adjuvants can be ascribed in part to the unintended stimulation of various mechanisms of the immune

response. That's why the safety and adjuvancy must be balanced to get the maximum immune stimulation with minimum side effects.

My conclusion is that such balance is impossible to achieve, even if we fully understood the immune system and the full spectrum of deleterious effects of foreign antigens and other toxic substances such as vaccine and drug adjuvants and medications on the immune system of humans, and particularly on the immature immune system of babies and small children. Injecting any foreign substance straight into the bloodstream will only cause anaphylactic (sensitisation) reactions. Nature, over thousands and thousands of years, has developed effective immune responses; yet man, without respect for nature, demonstrably causes more harm than good.

Vaccination procedures are a highly politically motivated non-science, whose practitioners are only interested in injecting multitudes of vaccines without much interest or care as to their effects. Data collection on reactions to vaccines is only paid lip service, and the obvious ineffectiveness of vaccines to prevent diseases is glossed over.

The fact that natural infectious diseases have beneficial effect on the maturation and development of the immune system is ignored or deliberately suppressed.

Consequently, parents of small children and any potential recipients of vaccines and any orthodox medications should be wary of any member of the medical establishment (which is little more than a highly politicised business system) extolling the non-existent virtues of vaccination. Even though Australian law requires doctors to warn patients about all side-effects of all medications and procedures of a material nature, whether the patient asks or not, doctors as a rule do not uphold this important law.

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