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CHILDHOOD VACCINES AND INDUCTION OF ALLERGIC AND AUTOIMMUNE DISORDERS: FACTS AND FICTION

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SUMMARY

During the past century, there has been either a total elimination or a dramatic decline in the global prevalence of many common, sometimes fatal human infectious diseases. Although a number of societal changes have contributed to such a decline, the introduction of specific vaccines appears to be the single most important approach underlying the disappearance of many serious childhood infections. Interestingly, however, this period has also been characterized by the increasing evidence of many other pathologic states, including respiratory and intestinal allergic or autoimmune diseases and other immunologically mediated disease processes. The later part of the 20th century has also seen emergence of many new disease states, such as HIV, autism, and antibiotic resistant microorganisms.

Because of the apparent temporal association observed between introduction and large-scale use of vaccines against infectious diseases and the increasing prevalence of allergic and autoimmune diseases, the use of childhood vaccines has been subject of intense global discussion and concerns. Such concerns and discussions have been fuelled by anecdotal reports of serious occasional side effects, followed by other recent observational studies, and the rapid dissemination of their results through modern mass media. This review summarizes the available evidence for the role of natural infections, or their available vaccine counterparts in the mechanisms of protection against or the pathogenesis of allergic or autoimmune disorders in man.

Available carefully controlled studies have suggested that some vaccines will have infrequent and rarely even serious reactions. Some vaccines have also been associated with the development of transient allergic or autoimmune reactivity. However, these observations have also documented that childhood vaccines do not cause, and are not responsible for the recent surge in the incidence of some allergic or autoimmune disease. Childhood vaccines are highly effective and safe and continue to represent the best available approach to prevention of many serious infectious diseases of man.

INTRODUCTION

For the contemporary medical practitioner who completed medical training after the late 1970's, and the general public who were born after the late

Table 1: Impact of childhood vaccines: 2008•

Disease	% Reduction in morbidity-mortality post vaccine introduction
Diphteria, measles, polio rubella Congenital rubella syndrome, smallpox	>99
Mumps, tetanus, pertussis	>90
Hepatitis A	87
Hepatitis B	80
Haemophilus type B	>99
Streptococcus pneumoniae	34-25

• Roush et al., 2007

1960's, it is difficult to identify with or fathom the emotional impact of the high morbidity and mortality that was the rule for many infectious diseases in the North American Continent and Europe until about 50 years ago, and still continues to be a major societal problem in many parts of the world.

Most individuals today have never seen a case of smallpox, plague, measles, poliomyelitis, congenital rubella, mumps, diphtheria, tetanus, or meningitis due to *Hemophilus influenzae* type B. These diseases have been either eradicated or effectively controlled in most parts of the developed world. Currently efforts are underway to effect their control or elimination throughout the rest of the world. The possible reasons underlying the decline of these childhood diseases include; improvement in socio-economic conditions; introduction of sanitation and public hygiene; improvement in nutrition and introduction of dietary supplements; changes in the ecology and environment; and introduction of antimicrobials, chemotherapeutic and chemoprophylactic agents. However, the single most important reason for the decline of infectious diseases is the introduction of vaccines against specific childhood infections. Smallpox has been eliminated globally, the morbidity and mortality of *Hemophilus influenzae* type B, diphtheria, measles, polio, rubella, has declined by >99%, mumps, tetanus, pertussis by >90%, hepatitis A and B by 80-87%, and of *Streptococcus pneumoniae* by 25-34% (Table 1). In addition to their impact on disease prevention, the introduction of childhood vaccines have significantly improved other societal functions, including school, social and employment-related work attendance. It is estimated that in the United States alone, the introduction of vaccines have prevented >33,000 deaths annually, saved over 10 billion dollars in direct costs in each birth cohort, and resulted in over 33 billion dollars in savings by prevention of disability and loss of productivity (*Roush* and *Murphy*, 2007; *Stratton* et al., 1999).

Despite these phenomenal societal gains, many justifiable concerns have been raised about the role of modern day immunization practices, largely because of the somewhat parallel increase in the incidence of many allergic and autoimmune diseases. In order to address these issues in some detail, this review will attempt to consider available evidence for the role of naturally acquired infections in the mechanism

of protection against, or the pathogenesis of allergic and autoimmune disease. Based on this evidence, it will then be attempted to determine if childhood immunization against such infectious diseases do similarly contribute to the development or outcome of such autoimmune or allergic disease states.

DEVELOPMENT OF ALLERGY OR AUTOIMMUNITY

Concurrent with the improvement of socioeconomic conditions, and the introduction of community sanitation, and improvements in nutrition between the 19th and 20th centuries in many societies, there has also been a discernable increase in the incidence of disease states such as asthma, eczema, urticaria, angioedema, food allergies, systemic lupus erythematosis, rheumatoid arthritis, diabetes mellitus, inflammatory bowel disease and other autoimmune or immunologically mediated diseases (*Bach*, 2002). Autoimmune reactions represent auto reactive B and T cell responses directed toward self-antigens or neoantigens generated in the host. Many microbial antigens exhibit mimicry for certain host tissue (self) antigens. On the other hand, allergic reactions represent immune responses to non-self antigens such as vaccine antigen(s), or other components in the vaccine preparations which may elicit specific IgE, immune complexes, delayed type or cytotoxic T cell mediated hypersensitivity responses. Finally, expression of host tissue damage may be directly related to tissue replication of infectious vaccine antigens, and direct cytotoxicity, independent of host immune response (*Kamradt* and *Mitchison*, 2001). The incidence of allergic disorders (asthma, food allergy, and atopy) has manifested a dramatic increase during the past 5 decades especially in the technologically advanced Western hemisphere and other developed parts of the world. Similarly, the incidence of several autoimmune diseases has increased mostly over the past few years. These include diabetes mellitus, multiple sclerosis, rheumatoid arthritis, systemic lupus and other autoimmune disorders. These diseases have been seen with increasing frequency in age groups often selected for national immunization programs. It is estimated that about 5-8% (14-22 million) of the population in the United States is affected by one or more autoimmune disorder. The prevalence of allergic disorders is estimated to be even higher in some parts of the world (*National Institutes of Health*, 2000). Autoimmune disorders can involve any human body site. At least 15 distinct clinical disorders have well defined evidence of autoimmune immunologic reactivity. A number of autoimmune diseases have been reproduced in experimental animal models. These include experimental allergic encephalitis (EAE), rheumatoid arthritis, myocarditis, diabetes mellitus, and inflammatory bowel disease. Recent data have demonstrated that autoimmune disorders affect women disproportionately more than men. It is estimated that over 78.8% (6-7 million) subjects with autoimmune disorders in the United States are female. The reason for high prevalence in women remains to be defined. However, experimental data have suggested that sex hormones may significantly amplify autoimmune responses and, possibly other forms of hypersensitivity. Recently, it has been observed that sex hormones, especially oestrogen, progesterone, and testosterone determine the outcome of Th1 vs. Th2 type T cell responses by their abil-

Table 2: Impact of natural infections on development of protection against or induction of allergy

Development of protection against allergy (immunity)	Induction of allergic disease (pathology)
BCG	Bordetella pertussis
Bifidobacterium lactis	**Chlamydia pneumoniae**
Chlamydia pneumoniae	**Chlamydia trachomatis**
Chlamydia trachomatis	Mycoplasma pneumoniae
Lactic acid bacteria	Staphylococcus aureus
Lactobacillus rhamnosus	**Influenza A virus**
Listeria monocytogenes	Metapneumovirus
Mycobacterium tuberculosis	Rhinovirus
Hepatitis A virus	**Respiratoir syncytiaal virus (RSV)**
Influenza A virus	Anisakis simplex
Respiratoir syncytiaal virus (RSV)	Ascaris sp.
Heligmosomoides polygyrus	Fasciola hepatica
Hookworm sp.	**Nippostrongylus brasiliensis**
Nippostrongylus brasiliensis	**Strongyloides stercoralis**
Strongyloides stercoralis	**Strongyloides venezuelensis**
Strongyloides venezuelensis	Toxocara sp.

Bold: Associated with both protection and pathology

ity to interact directly with specific receptors on immunocompetent cells (*Rose*, 2002; *Fairweather* and *Rose*, 2004).

Autoimmune disorders and allergies tend to cluster in families, suggesting an important genetic predisposition to the expression of disease. Studies in monozygotic twins have also identified the role of environmental factors, including infections, in the development of immunologically mediated disease processes (*Shoenfeld* et al., 2002). Although the mechanisms that govern the development of disease states are quite distinct and separate, some allergic and autoimmune diseases may exhibit common underlying mechanisms of expression. This opinion has been based on the observation of appearance of asthma and autoimmune conditions in the same patients, and the presence of autoantibodies in some allergic patients (*Rottem* and *Shoenfeld*, 2003). It has been proposed that altered T cell, mast cell, cytokine response and common genetic determinants may exist both for autoimmune as well as allergic diseases. Mast cells and their inflammatory cytokines, activation of protein kinase by such cytokines and T cell receptors now may represent areas of common disease susceptibility within the immune system for diseases such as asthma and autoimmunity (*Rottem* and *Shoenfeld*, 2003).

The influence of natural or induced infections, and vaccine induced immunologic responses on the outcome of allergic or autoimmune diseases is reviewed below.

NATURAL INFECTION-INDUCED IMMUNE RESPONSES

Allergic disorders

Role in protection

The pathogenesis of common allergic disorders involve development of allergen specific immune responses triggered by CD4+ (Th2) T cells, resulting in the expression of several immunoregulatory cytokines, including IL-4, IL-5, IL-9, IL-13. Such cytokines induce production of specific IgE and other immunoglobulin isotypes by B cells, recruitment of eosinophils, other inflammatory cells, and mucus production. Such a cascade eventually leads to IgE mediated degranulation and release of cytokines, chemokines and other pharmacologic mediators (including histamine, eotoxin) from mast cells and eosinophils, immune complex mediated cellular activation, local inflammation, development of smooth muscle contractibility, and eventually clinical expression of allergic symptoms (*Herz* et al., 2000).

Although genetic susceptibility is an essential component of the development of allergy, it is clear that a variety of environmental factors play a critical role in the mechanisms of protection against or the pathogenesis of clinical disease. The role played by different infectious agents in the outcome of allergic disease is outlined in Table 2. Many infectious agents which induce a potent Th1 type T cell response are associated with significant protection from allergic disorders. These include infection with *Mycobacterium tuberculosis*, *Mycobacterium bovis*, BCG, several probiotics, and some parasitic agents and viruses (*Trujillo* and *Erb*, 2003). Children immunized with BCG as neonates, and women with active tuberculosis prior to age 20 years, appear to have significantly lower incidence of asthma, atopic disease, and airway disease (*Marks* et al., 2003; *da Cunha* et al., 2004). BCG or immunization with inactivated BCG vaccine also seems to reduce allergen specific IgG and IgM serum antibody responses in mice and guinea pigs (*Trujillo* and *Erb*, 2003).

In additional studies, exposure to *Chlamydia trachomatis*, *Listeria*, several lactic acid bacteria and other probiotics have also been shown to suppress development of allergic responses by Th1 induced suppression of Th2 response. Suppression of allergic responses by IL-10 and TGF-β cytokines secondary to the induction of CDIIC+ cells independent of Th1 type of T cell response has also been proposed in animal models of airway hypersensitivity (*Sayers* et al., 2004; *Han* et al., 2004; *Repa* et al., 2003; *Matricardi* et al., 2000).

Limited evidence is available to suggest that infection with some helminthic agents is associated with lower incidence of atopic disease. These include infestation with *Schistosoma*, and hookworm. Infections in mouse model with *Strongyloides stercoralis* or *Nippostrongyloides brasiliensis* have been shown to suppress pulmonary allergic responses (*Wang* et al., 2001; *Wohllenben* et al., 2004). Clinical trials with live or killed commensals and probiotics have also provided interesting evidence to suggest suppression of allergic disease expression, including atopic dermatitis after maternal prenatal use of *Lactobacillus rhamnosus*, or intradermal application of killed mylobacterial vaccine, or feeding of *Lactobacillus* or *Bifidobacteria* species in infants (*Helin* et al., 2002; *Drachenberg* et al., 2001).

Infection with certain viruses such as hepatitis A virus appear to provide some protection against atopic diseases, based on an increase in the correlation

between levels of hepatitis A antibodies and reduced incidence of allergy. Additional data have suggested that viruses such as RSV, influenza A decrease the development of airway eosinophilia after airway challenge with allergens in experimental animal models. The anti-allergic effect appears to be associated with induction of prompt Th1 response by the virus in such situations (*Matricardi* et al, 2000; *Walzl* et al, 2000; *Bach*, 2002).

Role in Pathogenesis

Based on several recent studies, it is clear that infection induced Th1 responses do not necessarily protect against the development of allergy, but may in fact exacerbate its evolution (Table 2). Studies with *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Staphylococcus*, and *Bordetella pertussis* showed to enhance allergic inflammation in the bronchopulmonary tree. These effects may be mediated by induction of potent Th2 responses or via exotoxin (superantigen) mediated cytokine release (*Lieberman* et al, 2003; *Blasi*, 2004; *Hardy* et al., 2002; *Ennis* et al., 2004).

Most helminths induce very prominent Th2 responses and such responses should promote expression of allergy. Infections with certain helminths result in suppression of oral tolerance to allergens and enhancement of Th2 responses. This may explain increased allergic manifestation in children infected with ascaris, toxicara and other parasitic agents listed in Table 2. Antihelminthic treatment in such children results in prompt improvement in the clinical symptoms of asthma and urticaria (*Hurst* et al., 2001; *Demirci* et al., 2003; *Audicana* et al., 2002).

Although anti-allergic effects have been observed with RSV proteins and influenza A viruses in animal models, numerous publications have suggested that respiratory viruses are more commonly associated with airway hyperreactivity and respiratory allergy in man. In particular, RSV, rhinovirus, influenza virus, parainfluenza virus and metapneumovirus have been shown to induce wheezing in infants and children, and may pose a very significant risk for childhood asthma. Several mechanisms have been shown to contribute to viral induced allergic disease exacerbations. These include development of viral specific IgE response, induction of IL-13, and direct Th1 mediated airway hyperactivity. Recent data have also suggested that abnormal innate immune responses especially to RSV infection may be an important determinant of the severity of RSV disease, regardless of Th1 vs. Th2 T cell responses. In particular, activation of pulmonary dendritic cells, TLR activation, induction of IL-8 by lower airway epithelial cells (recruitment of neutrophils in airway), induction of IL-17 (increased mucous production) have been observed in association with viral induced respiratory allergic disease in human and experimental animal studies (*Grunewald* et al., 2002; *Welliver* et al., 2007; *Ogra*, 2004; *Garofalo* et al., 1999).

Autoimmunity

This information has been reviewed quite extensively in several recent publications (*Kamradt* et al., 2005; *Fairweather* and *Rose*, 2004; *Sandborg*, 2002; *Mackay* et al., 2008).

Role in protection

It is well known that induction of autoreactive T and B lymphocytes is an integral, albeit limited, component of the normal human lymphoid cell repertoire. However, under physiologic conditions such cells are quiescent or exhibit only minimal functional activity. It has been suggested that autoimmune

Table 3: Association of human infections with different autoimmune diseases

Disease	Possible aetiologic agent
Guillain-Barré Syndrome	CMV, EBV, **Campylobacter sp.**
Multiple sclerosis	EBV, measles, HBV, measles
Acute Disseminated Encepahlomyelitis (ADEM)	measles
Immune complex diseases: dermatomyositis polyarteritis nodosa (PAN), nephritis	**HBV and HBsAg carriers**
Myasthenia gravis	HSV, HCV
Lymphoproliferative disease	**EBV**
Rheumatoid arthritis	E. coli, M. tuberculosis, EBV, HBV, Proteus, Serratia
Arthritis	**B. burgdorferi**
Myocarditis	Coxsackie B virus, CMV, Chlamydia
Rheumatic fever	Group A Streptococcus
Systemic lupus erythematosus (SLE)	EBV
Insulin dependent diabetes mellitus (IDDM) type 1	Coxsackie B virus, rubella, CMV, mumps
Schizophrenia, thyroiditis, vasculitis syndromes	Parvovirus B-19

Bold: Strong evidence

disease-incidence may be a mirror image of the incidence of certain infections, especially, mycobacterial, helminthic and certain viruses (*Bach*, 2002). A number of recent epidemiologic studies have raised the possibility that some infections acquired during the first year of life are associated with reduced risk of diabetes mellitus, inflammatory bowel disease or multiple sclerosis later in life (Table 3). More importantly, studies carried out in non obese diabetic (NOD) mice and other rodents infected with *Salmonella*, *Schistoma mansoni*, BCG, mycobacteria, lactobacilli, *Heligmosomoides polysyrus*, and other helminths have demonstrated dramatic protective effects against development of diabetes in diabetic mice, and in other animal models against other autoimmune diseases such as EAE, and experimentally induced IBD and arthritis (*Madsen* et al., 1999; *Zaccone* et al., 2003; *Van der Kleij* et al., 2002; *Sharif* et al., 2001; *Elliott* et al., 2004). It appears that many such cell-associated bacterial and parasitic infections offer protection against autoimmunity by activation of CD4+ T cells, NKT cell expression of IL-10, and induction of CD25+ regulatory T (Treg) cells (*Madsen* et al., 1999; *Kamradt* et al., 2005).

Several recent studies have extended the observation in animal models to the treatment of autoimmune disorders in man. Probiotics have been employed for the treatment of inflammatory bowel disease, including ulcerative colitis or Crohn's disease. The use of probiotics appears to be beneficial in the management of pouchitis in patients with ulcerative colitis. Treatment with BCG has been attempted, but without success in the prevention or therapeutic management of diabetes mellitus, BCG therapy has been found to reduce magnetic resonance imaging

activity (MRI) in a few patients with multiple sclerosis. However, its therapeutic implications are not clear at this time (*Ristori* et al., 1999; *Gionchetti* et al., 2003; *Allen* et al., 1999). Other investigators have employed helminths in the therapeutic management of inflammatory bowel disease (*Sewell* et al., 2003). Oral administration of eggs of *Trichuris suis* in patients with Crohn's disease appears to be beneficial in decreasing the severity of the disease (*Summers* et al., 2005).

Role in pathogenesis

Although the data summarized above strongly suggest a beneficial role of many bacterial agents especially commensals and several helminths on the outcome of autoimmunity, equally impressive data are available to suggest that many autoimmune diseases are also triggered by infections (Table 3). Certain bacteria, namely group A streptococcus and Borellia have been characteristically associated with clinical disease such as rheumatic fever, and post infectious encephalitis, and lyme arthritis respectively (*Kamradt* et al., 2005; *Fairweather* and *Rose*, 2004). Studies in animal models have shown that certain transgenic mice do not develop EAE, spontaneous arthritis, or inflammatory bowel disease under pathogen-free conditions. However, such mice will develop diseases when bred under conventional microflora (*Kamradt* et al., 2005).

The most impressive association between infection and autoimmune disease has been observed with viruses. Studies with Theilers virus in mice have shown that intracerebral inoculation induces autoreactive T-cell responses against myelin antigens, possibly due to release of hidden or otherwise sequestered autoantigens (*Benoist* and *Mathis*, 2001; *Bach*, 2002). Other viruses clearly associated with the development of autoimmune disease processes include Coxsackie virus B4 (diabetes in transgenic mice), and rubella virus (congenital rubella and diabetes mellitus). Epstein-Barr virus infection may represent another possible candidate for viral induced autoimmune disease processes, in view of its potent immunoregulatory influence on B cell development and proliferation. The precise mechanisms underlying the development of autoimmunity after natural or induced infections remain to be defined. It has been proposed that both antigen-dependent as well as antigen-independent mechanisms are involved in the development of autoimmunity in genetically predisposed individuals (*Bach*, 2002).

Based on the information summarized above, it is suggested that any infection can be associated with the evolution of autoimmune immunologic reactivity. However, only a few agents have been clearly shown to be associated with the development of distinct immunologic markers of autoimmunity and expression of clinical disease. On the other hand, epidemiologic data collected over the past 4 decades have also suggested a strong relationship between a number of other human infections and the subsequent development of clinical autoimmune disease process as outlined in Table 3.

VACCINE INDUCED IMMUNE RESPONSES

Allergic disorders

Role in protection

Although the current discussions on vaccination related issues have largely focused on adverse effects of vaccine antigens or other vaccine components, there is interesting historical and some recent evidence to suggest that child-

hood vaccination may in fact provide protection against allergies (*Ennis* et al., 2005; *Gruber* et al., 2001a; 2001b; 2003). In a large epidemiologic study in Japan, conversion to tuberculin skin reactivity after natural infection or immunization with BCG was associated with significantly decreased incidence of asthma, hay fever, eczema and other atopic manifestations compared to subjects who continued to remain tuberculin negative. Tuberculin positive status appears to suppress the expression of IgE mediated atopic disease (*Shirakawa* et al., 1997).

Role in pathogenesis

Immediate type allergic hypersensitivity reactions to childhood vaccines occur with varying frequency with different vaccines in use at this time. Hypersensitivity reaction may be directed against the organism-specific vaccine antigens, other constituents necessary for the stability, adjuvants or other soluble vehicles included for delivery of the vaccine. These include gelatine, egg proteins, formaldehyde, chick proteins, thimerosol, aluminum, conjugating proteins, phenoxyethanol, antimicrobials, yeast, latex, and possible adventitious agents and tissue culture components in which the vaccine antigens are propagated (*Heidary* and *Cohen*, 2005; *Kelso*, 2007).

Solitary or multiple case reports of IgE mediated reactions have been observed with many childhood vaccines. These include both non-fatal as well as serious and rarely (2 cases) fatal anaphylactic reactions to diphtheria-tetanus booster, hypsensitivity reactions to HBV (about 1:1000,000 doses administered), hemophilus type B, reactivity to diphtheria conjugate proteins (4 cases), influenza vaccine (1 in 4 million doses), Japanese encephalitis (many late onset cases), pneumococcal conjugate (1 case), rabies (several late onset cases), tetanus (several cases), varicella (about 3 in 1 million doses), yellow fever (many cases).

Most of the hypersensitivity reactions reported to date with childhood vaccines seem to be associated with the nonvaccine antigen constituents such as gelatine (MMR, varicella, Japanese encephalitis), eggs (influenza, yellow fever), chicken proteins (yellow fever), aluminum (DPT, HIB, hepatitis A, pneumococcus), thimerosol (DT, HIB, HBV, typhoid, influenza, Japanese encephalitis) (*Kelso*, 2007). Many of these constituents have now been removed from more recent vaccine formulations. And, important lessons have been learned from prior use of some of these constituents. For example, development of painful and pruritic nodular lesions at the site of aluminum containing vaccines is the most frequent manifestation of hypersensitivity reaction in such vaccinees. Thimerosol is a common allergen but the clinical relevance of thimerosol allergy is relatively low. However, with the initiation of mass vaccination campaigns, the incidence of allergy in one setting increased from 6% in 1980 to 86% in 2001, after administration of thimerosol containing tick borne encephalitis vaccine. However, since 2001, most childhood vaccines employed in the United States are thimerosol free.

The development of hypersensitivity reactions to specific vaccine microbial antigens has also been reported, but is extremely rare. In one carefully conducted study, levels of IgE specific for tetanus toxoid were found to be significantly elevated in atopic subjects after immunization with DT vaccine. However, the levels declined to baseline levels over a 12-month period. Such increase in specific IgE did not promote allergic sensitization to allergens and did not promote atopic disease (*Dannemann* et al., 1996). With

other case-reports of hypersensitivity to vaccines, it is often not possible to separate reactivity to non-antigen components from specific microbial vaccine antigens.

Autoimmunity

Role in protection

As pointed out earlier, many naturally acquired bacterial and helminthic infections confer significant protection against development of autoimmunity. However, it remains to be seen if immunologic reactivity induced by vaccines, especially when it mirrors the reactivity observed after natural infection, can also offer similar protection. During early 1960's mass immunization campaigns with smallpox vaccine, an interesting bystander observation demonstrated that the incidence of diabetes mellitus declined precipitously during the peak of immunization (*Classen* and *Classen*, 1996; 1999). Studies have also shown elimination or decline in the incidence of subacute sclerosing panencephalitis after the introduction of measles vaccine in this country (*Campbell* et al., 2007). Data on other childhood vaccines relative to any possible protective role against autoimmunity are currently not available, although some studies have suggested that the timing of immunization and induced immunomodulation may prevent development of diabetes in murine models (*Classen*, 1996).

Role in pathogenesis

Several childhood infectious diseases have now been effectively controlled or eradicated in many parts of the world. At the same time, certain autoimmune disease states have shown a significant increase in their incidence and prevalence, often in the same regions where the childhood infection infections have been controlled through vaccination. Current medical literature and mass media is full of claims and counter claims regarding their possible relationship. One website designed for autoimmune diseases, claims that at least 60 such diseases ranging from alopecia areata to Wegener's granulomatosis are directly related to the use of vaccines in childhood.

Despite these claims, only a few well-defined autoimmune disease processes have been reported, albeit very rarely after childhood immunization (*Wrath* et al., 2003; *Schattner*, 2005; *Aron-Maor* and *Schoenfeld*, 2004; *Offit* and *Hackett*, 2003). For example, an earlier rabies vaccine prepared from rabies-infected brain was found to result in the development of acute disseminated encephalomyelitis in 0.1% of vaccinees (*Stuart* and *Krikorian*, 1928). Possible incidence of autoimmune diseases associated with other childhood vaccines is estimated to be as follows. Thrombocytopenic purpura, with measles vaccine alone (1:6000), with rubella vaccine alone (1:3000), with MMR (1:30,000); Guillian-Barré syndrome after swine influenza vaccine (1:100,000), other influenza vaccines (1:100,000). Acute demyelinating encephalomyelitis (ADEM) with measles vaccine is about 1:100,000 (*Chen* et al., 2001; *Zilber* et al., 1983). Arthritis has been reported after immunization with an outer surface protein A (ospA) of *Borella burgdorferi* vaccine in man, as well as in animal model after induced challenge with lyme spirochette (*Rose* et al., 2001; *Christopherson* et al., 2003).

In addition to the documented autoimmune effects summarized above, a large number of published reports have attributed vaccination to the development of multiple sclerosis, diabetes mellitus, autism, sudden infant death syndrome (SIDS), induction of immune dysfunction, chronic fatigue syndrome and other neurodevelop-

mental disorders. However, a number of large multicenter studies and several immunization safety reviews undertaken by the Institute of Medicine, National Academy of Science USA have consistently failed to demonstrate any link for the association of vaccines such as hepatitis B and MMR, and others, with autism, immune dysfunction, demyelinating neurologic diseases, multiple sclerosis, SIDS or diabetes mellitus (*Drutz*, 2007; *Schattner*, 2005).

DISCUSSION AND CONCLUSIONS

The information discussed in the preceding sections of this review suggests that acquisition of natural infections in childhood is an essential component of the maturation and development of immune response and induction of a diverse spectrum of immunoregulatory mechanisms. Acquisition of natural infections may be protective or pathogenic in the evolution of autoimmune or allergic diseases, based on underlying genetic susceptibility, and the nature of infecting organisms. Different infectious agents may exert strikingly different influences on the mechanism of protection against or the pathogenesis of autoimmune vs. allergic disease processes. Different agents may also exert strikingly different influences on the expression of disease. In general natural infections with helminths and mycobacterium are more protective and less pathogenic, while some cell associated viral infections may contribute more to the pathogenesis and development of autoimmune diseases. In addition to genetic susceptibility, other factors which influence the outcome of infections include, temporal pattern of the acquisition of the infection, age at the time of infection, route, localization and antigen burden, severity of infection, and modulation of the immune response by innate immune mechanisms. The principal immune mechanisms proposed to be responsible for development of infection-induced autoimmune reactivity include molecular mimicry, where antigenic epitopes of microorganisms closely resemble self-antigens. As a result, induction of immune responses to microbial antigens cross reacts with self-antigens and may induce autoimmunity. Other possible mechanisms relate to the bystander effects secondary to the tissue damage as a consequence of active infection, and exposure of otherwise sequestered (self) antigens. Several non-specific mechanisms may involve activation of the innate immune system, which is necessary and sometimes essential for development of adaptive B and T cell immune responses specific for each infectious agent. Abnormal or lack of intrinsic activation of innate immunity may result in loss of immunologic tolerance and development of abnormal T cell regulation for Th1 vs. Th2 type of cellular responses, which predispose to the eventual expression of physiologic, or abnormal (allergic or autoimmune immunologic) phenotypes (*Ogra* and *Welliver*, 2008). Thus, it appears that the development of transient and varying degree of autoimmune reactivity is a consistent feature of most naturally acquired infections.

The introduction of many new vaccines associated with emergence of increased frequency of allergic and autoimmune disorders in our society has lead to the current concerns about the risk of vaccine-induced immunologically mediated diseases. In retrospect, it is remarkable that a large number of successful and highly effective vaccines were developed and used

Table 4: Induction of different cytokine profiles by environmental factors and their disease association*

	Increased Th1 responses	Increased Th2 responses
Environmental factors	Normal mucosal bacterial flora	Diet and processed foods in developed world
	Inflammatory cytokines	Cow's milk and formula
	Breast feeding	Antibiotics
	Infectious agents	Infectious agents
Disease associations	Autoimmune thyroiditis	Leishmania; Toxoplasma
	Exp. autoimmune uveoretinitis	Candida; mycobacteria (M. tuberculosis; M. leprae)
	Crohn's disease	HIV, atopic dermatitis
	EAE; MS; IDDM	Asthma; allergic rhinitis

*Ogra and Welliver, 2008

extensively for childhood immunization long before the acquisition of our current knowledge about the immune system in early childhood. It has been now demonstrated that prenatal and postnatal periods in general favour Th2 T cell cytokine profile, and the profile shifts toward a Th1 type response by preschool age. The shift toward Th1 T cell response is largely driven by common childhood infections, and there is a delayed or incomplete shift toward Th1 responses in atopic subjects. Increased Th1 T cell responses have been associated with autoimmune thyroiditis, EAE, MS, diabetes mellitus and Crohn's disease. On the other hand, increased Th2 T cell response have been associated with diseases due to *Toxoplasma*, *Leishmania*, *Candida*, HIV, mycobacteria, as well as in atopic and allergic disorders such as asthma, atopic dermatitis, and allergic rhinitis (Table 4) (*Ogra* and *Welliver*, 2008).

It is clear now that most primary immunizations are given during the period in childhood, which favours Th2 responses. By 6 months of age, most children will have received as many as 16 different microbial vaccines. Because of the elimination of smallpox, poliomyelitis, and significant decline in mortality and morbidity associated with other vaccine preventable infectious diseases, concerns have now shifted toward the relative risk of childhood vaccines, rather than the dangers of natural infection, which still prevail in many parts of the world. The information summarized above provides evidence for the safety and effectiveness of existing vaccines in the prevention of several serious infectious diseases. However, it is also now recognized that no vaccine developed to date is completely safe and or completely effective in each and every immunized individual. Some vaccinees may have an adverse reaction, and some may not be fully protected. Some existing vaccines have been clearly associated with the development of transient autoimmune disorders such as thrombocytopenic purpura, and Guillain-Barré syndrome. However, such side effects are relatively rare (1 in 30,000 to 1 in 1,000,000). There are other immunologic alterations observed after

childhood immunization. These include increased IgE responses to tetanus and diphtheria toxoids, increased class switch for mRNA for IgE after MMR immunization, possible immune enhancement with prior priming for Japanese encephalitis, spontaneous reversion to virulent phenotypes after oral administration of live attenuated (Sabin) poliovaccine, and development of vaccine associated paralytic polio in some (1 in 10,000 to 1 in 1,000,000 doses of OPV administered) in vaccinated subjects, and development of intussusception after administration of an earlier rhesus reassortant rotavirus vaccine.

The biological significance of the many immunologic alterations observed after immunization must be assessed in the context of associated clinical symptoms. For example, it may not be surprising to elicit laboratory markers of immunologic hypersensitivity or autoimmunity after immunization in a manner similar to natural infection. However, such immunologic reactivity does not necessarily reflect development of established allergic or autoimmune disease. The human immune system is well endowed with other compensatory mechanisms to prevent development of such diseases. However, it is important to monitor the induction of such laboratory findings with existing as well as with next generation of vaccines which may contain, different or more potent adjuvants, other carrier proteins, or other unique antigenic epitopes, which may mimic pathogenic processes associated with the development of natural disease.

It is neither advisable, nor possible at this time, to completely eliminate pathogenic or disease-producing microorganisms from our environment. The goal of future development of new and continued usage of existing vaccines is to induce an optimum degree of protection against disease with the lowest possible rate of adverse side effects, including the development of allergic and autoimmune disease processes. Until we are able to develop highly effective vaccines with no side effects whatsoever, the rationale for the use of existing vaccines should consider each specific situation, the burden of natural disease, its global magnitude, morbidity and mortality; epidemiologic nature of the disease relative to endemic and epidemic spread, relative risks associated with natural disease; long term effects of the vaccine, and the societal acceptance of the vaccine in a changing global population base.

Finally, it must be emphasized that the recent increase in the incidence of many allergic and autoimmune diseases may have more to do with the overwhelming environmental alterations and changes in global ecology than with the prevention of childhood infectious diseases by immunization practices.

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