Review Article

Mechanisms of Disease

The Effect of Infections on Susceptibility to Autoimmune and Allergic Diseases

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INFECTIOUS agents can induce autoimmune diseases in several experimental settings, some of which have clinical counterparts. A variety of mechanisms have been invoked to explain these observations, including molecular mimicry and an increase in the immunogenicity of autoantigens caused by inflammation in the target organ.[1] Paradoxically, infectious agents can also suppress allergic and autoimmune disorders. In this review, I will summarize the evidence that the main factor in the increased prevalence of these diseases in industrialized countries is the reduction in the incidence of infectious diseases in those countries over the past three decades. This concept is not new. In 1966, for example, Leibowitz et al. suggested that the risk of multiple sclerosis is increased among persons who spent their childhood in a home with a high level of sanitation.[2] About 20 years later, Strachan observed that the risk of allergic rhinitis was inversely linked to birth order and the size of the family. He proposed that infections within households in early childhood have a role in preventing allergic rhinitis.[3] Since then, numerous epidemiologic and experimental studies have sought to clarify and extend this so-called hygiene hypothesis concerning asthma and other allergic diseases and autoimmune disorders.

CONTRASTING EPIDEMIOLOGIC TRENDS IN DEVELOPED COUNTRIES

Epidemiologic data provide strong evidence of a steady rise in the incidence of allergic and autoimmune diseases in developed countries over the past three decades. The incidence of many diseases of these two general types has increased: asthma,[4] rhinitis,[5] and atopic dermatitis,[6] representing allergic diseases, and multiple sclerosis,[7,8] insulin-dependent diabetes mellitus (type 1 diabetes) — particularly in young children[9] — and Crohn's disease,[10] representing autoimmune diseases. The prevalence of asthma, hay fever, and atopic dermatitis doubled in Swedish schoolchildren between 1979 and 1991,[11] and in Lower Saxony, Germany, the incidence of multiple sclerosis also doubled from 1969 to 1986.[8] The incidence of Crohn's disease more than tripled in northern Europe from the 1950s to the 1990s.[10] The incidence of these disorders apparently began to increase in the 1950s and continues to do so today, although the incidence of some of these diseases may have plateaued.

Concomitantly, there has been an obvious decrease in the incidence of many infectious diseases in developed countries as a result of antibiotics, vaccination, or more simply, improved hygiene and better socioeconomic conditions. Figure 1 shows the estimated incidence of tuberculosis, rheumatic fever, measles, and mumps in the United States and of hepatitis A in France over a 50-year period. Intestinal infections are notable, because their frequency has decreased in developed countries as compared with less-developed countries, particularly among children. Moreover, the age at which colonization of the intestinal flora occurs differs among countries: intestinal colonization with gram-negative bacteria, for instance, occurs later in developed than in less-developed countries, both quantitatively and qualitatively.[16,17] The high prevalence of parasitic infections, notably with plasmodia and schistosoma in southern countries, contrasts with the absence of these diseases in developed countries. Furthermore, the frequency of infestation by minor parasites such as *Enterobius vermicularis* (pinworms) over the past decade has decreased in developed countries.[18,19]

THE GEOGRAPHIC DISTRIBUTION OF ALLERGIC AND AUTOIMMUNE DISEASES

The North–South Gradient

Allergic and autoimmune diseases are not evenly distributed among continents, countries, well-circumscribed regions within a given country, or ethnic groups. An examination of the distribution reveals several important and probably interrelated phenomena. One is the north–south gradient: the incidence of disease decreases from north to south in the Northern Hemisphere (and reciprocally from south to north in the Southern Hemisphere). This gradient is clearly seen in Figure 2 in the cases of multiple sclerosis and

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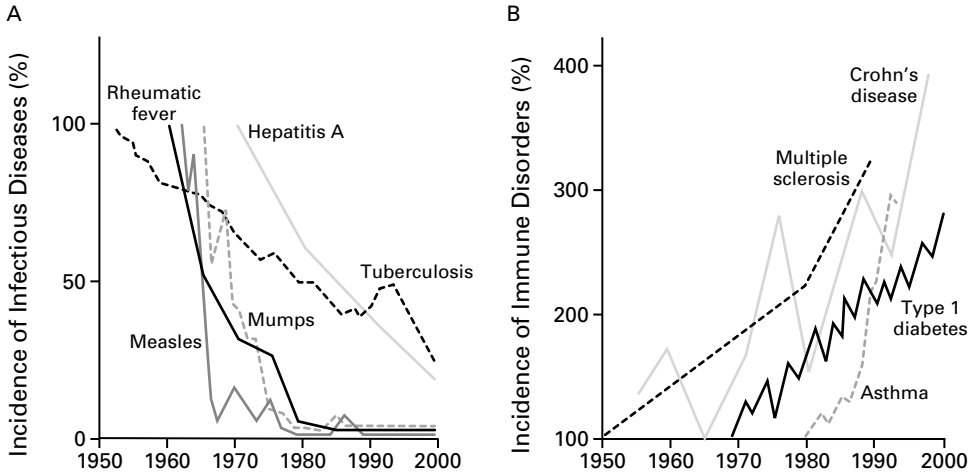

Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Joussemet et al.[12] In Panel B, data on immune disorders are derived from Swarbrick et al.,[10] Dubois et al.,[13] Tuomilehto et al.,[14] and Pugliatti et al.[15]

type 1 diabetes in Europe. A comparison of Europe and Africa reveals a similar and even clearer trend,[22] although the epidemiologic data are less well documented in Africa. There are similar geographic differences in Europe with respect to allergy[23] and Crohn's disease[24]; in North America with respect to multiple sclerosis,[25] type 1 diabetes,[26] and Crohn's disease[27]; and in Australia with respect to multiple sclerosis.[28]

Are these differences real? Perhaps, owing to deficiencies in medical facilities, allergic and autoimmune diseases are underdiagnosed in less-developed countries. This general explanation is, however, unlikely because severe diseases like multiple sclerosis and type 1 diabetes are rarely misdiagnosed. Moreover, the differences in frequency also involve southern countries with ample medical resources, such as Greece and Spain.

Genetic Factors

There are several explanations for the gradient other than underdiagnosis. One is the role of genetic factors. For example, in Japan, there is a low frequency of HLA alleles (DR3 and DR4-DQB1*0302) that increase the likelihood of type 1 diabetes, and the incidence of the disease is also low. Conversely, the incidence of type 1 diabetes is high among residents of Sardinia (as compared with residents of neighboring regions) as well as in first-degree descendants of Sardinians who migrated to continental Italy.[29]

Environmental Factors

The contribution of genetic factors to the north–south gradient seems small, however, as compared with the contribution of environment. Environmental factors could account for the rapid increase in the incidence of allergic and autoimmune diseases in developed countries. There are striking data on the incidence of multiple sclerosis, type 1 diabetes, and asthma in populations migrating from one country to another in which the rates of these disorders differ. The rate of development of type 1 diabetes among the children of Pakistanis who migrated to the United Kingdom is the same as the rate among nonimmigrants in the United Kingdom (11.7 per 100,000), or about 10 times as high as the incidence of type 1 diabetes in Pakistan (1 per 100,000).[30,31] In Israel, multiple sclerosis is common among immigrants from Europe and rare among immigrants from Africa or Asia. By contrast, among native-born Israelis of European, African, or Asian origin, the prevalence of multiple sclerosis is as high as that among the European immigrants.[32] It is also notable that the frequency of systemic lupus erythematosus is dramatically lower in western Africans than in black Americans, two populations derived from the same ethnic group but exposed to different environments.[33] Conversely, Britons migrating to northern Australia have a decreased frequency of multiple sclerosis,[34] providing a negative control for the positive migration data, which in principle could represent underdiagnosis.

Interactions between Genetic and Environmental Factors

The degree to which genetic and environmental factors influence susceptibility to autoimmune and allergic diseases is still ill defined. The best hint derives from the concordance rates of such diseases in mono-

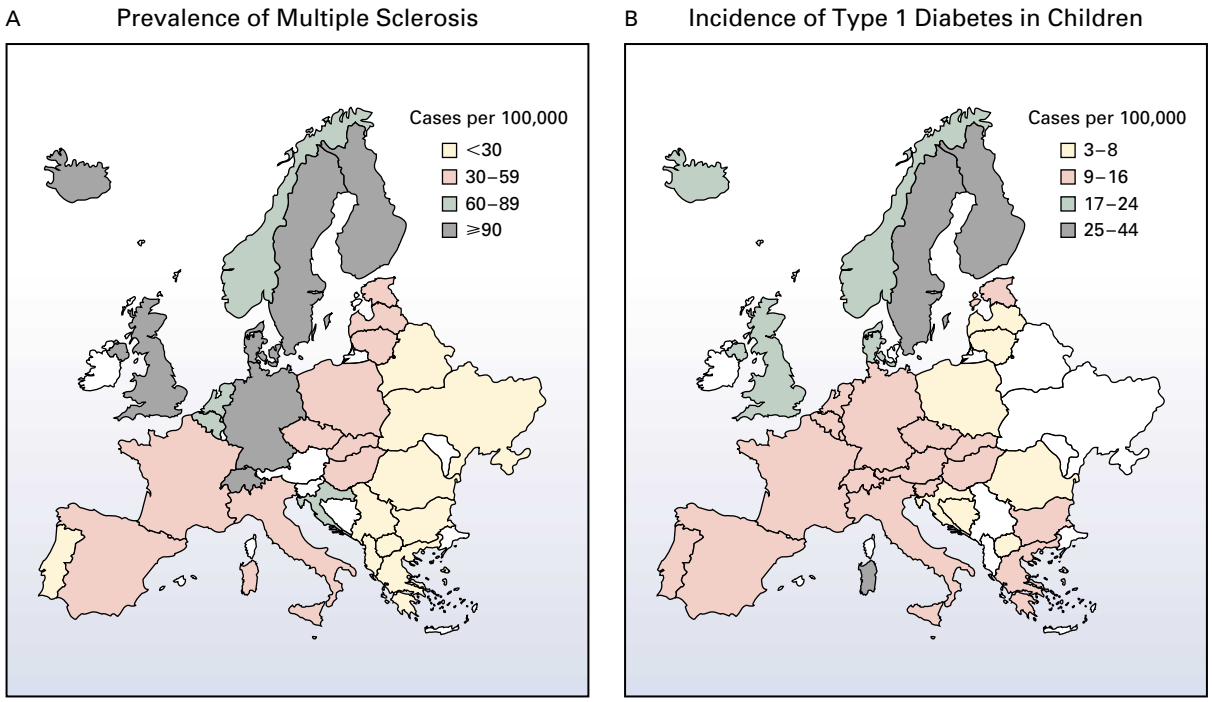

Figure 2. The North–South Gradient in the Prevalence of Multiple Sclerosis (Panel A) and the Incidence of Type 1 Diabetes Mellitus (Panel B) in Europe.

Adapted from Kurtzke[20] and Green and Patterson.[21]

zygotic twins. The rate is 25 percent in the case of multiple sclerosis,[35] 40 percent in the case of type 1 diabetes,[36] and 75 percent in the case of asthma.[37] One may assume that the concordance rate is directly related to penetrance of the disease, with the proviso that it is impossible to include in such analyses pairs of twins in which both twins have all the predisposing genes but are disease-free. Major progress has recently been made in identifying chromosomal areas that include genes that predispose persons to multiple sclerosis,[38] type 1 diabetes,[39] and asthma,[40] but very little information is available on the genes themselves, with the exception of HLA genes in autoimmune diseases. A crucial task is to identify which of these genes directly modulates sensitivity to inciting or protective environmental factors. An example is the observation in patients with atopic diseases of unique polymorphisms of the genes encoding interleukin-10 and transforming growth factor β (TGF-β),[41] two cytokines that might contribute to the protective effect of infections on allergic diseases.

Socioeconomic Status

An obvious factor in the north–south gradient is socioeconomic differences. Several studies have found a lower frequency of immunologic diseases in populations with a low socioeconomic status. Figure 3 shows the positive correlation between the gross national product and the incidence of asthma, type 1 diabetes, and multiple sclerosis in 12 European countries. In regions of Yorkshire[43] and Northern Ireland,[44] there is a statistically significant positive correlation between the low incidence of type 1 diabetes and certain socioeconomic indexes (unemployment, lack of a car, crowded housing conditions, and living in rental housing rather than purchased property). Similar data have been reported for Crohn's disease in the Canadian province of Manitoba.[45] Also striking is the difference in the incidence of asthma between residents of former East Germany and West Germany (the incidence is higher in the more developed West Germany), despite their common genetic background.[46]

Some infections in European countries may be distributed according to a south–north gradient that is a mirror image of the gradient for autoimmune diseases. This has been shown in the case of hepatitis A virus (HAV) infection.[47] Among Italian military recruits, atopy was less common in HAV-seropositive recruits than HAV-seronegative subjects.[48] Low socioeconomic levels and high temperatures, two common features of southern countries, may predispose inhabitants to infections in a number of ways; less stringent

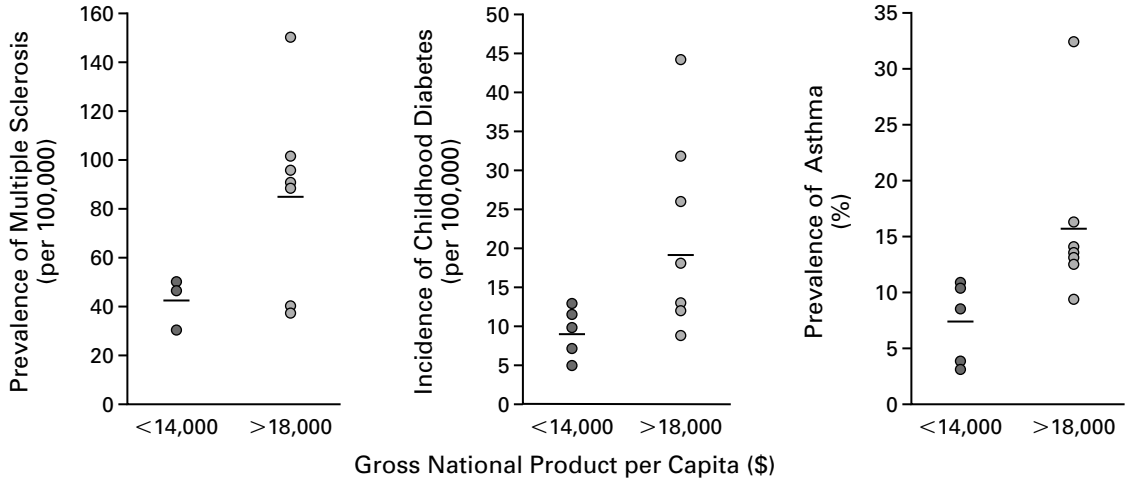

Figure 3. The Frequency of Multiple Sclerosis, Type 1 Diabetes Mellitus, and Asthma in 12 European Countries According to the Gross National Product per Capita.

Adapted from Kurtzke,[20] Green and Patterson,[21] and Stewart et al.[42]

control of microbial contamination of water and food, an increased risk of bacterial proliferation with higher ambient temperatures, and poorer housing conditions may all affect the risk of contamination between persons.

Childhood Infection

When infection is an incriminating factor it often occurs early in childhood. In Yorkshire, a case–control study demonstrated a correlation between the incidence of type 1 diabetes and the degree of social mixing, including attendance at day-care centers, and the number of infections that occur before one year of age.[49] Young children with older brothers and sisters at home and those who attend a day-care center during the first six months of life subsequently have a lower incidence of asthma[50] and type 1 diabetes[49] than children who do not attend a day-care center and who have no older siblings. Children in small families tended to have a decreased incidence of atopy when they attended a day-care center in early childhood.[51]

Another influential factor is the quality of medical care, which varies substantially from country to country with respect to the use of vaccines and antibiotics. The administration of antibiotics to children has been suspected to increase the risk of asthma and allergy. Droste et al. observed that the use of antibiotics in the first year of life increased the risk of asthma or other allergic diseases in children with a genetic predisposition to atopy.[52] Antibiotics might act by decreasing the number of infectious episodes or by modifying intestinal flora. The composition of the digestive flora, indeed, differs between newborns in whom allergy develops at a later age and those in whom atopy does not develop.[53,54]

Other Factors

Other factors that may not influence the rate of infection should not necessarily be dismissed. The climate (notably the extent of exposure to sunlight) and a number of culturally based differences in behavior, notably diet, may also be important. Air pollution may have a role in asthma. But even though air pollution can worsen the clinical status of patients with asthma, it does not appear to affect the incidence of asthma. No correlation has been established between pollution indexes and the incidence of asthma.[55] German reunification provided an opportunity to study the effects of air pollution on the development of asthma and atopy. Several studies found a lower prevalence of asthma, atopic sensitization, and hay fever among residents of cities of the former East Germany, which were more polluted than West German cities.[46,56] Similarly, the prevalence of asthma in Athens, Greece, is relatively low, despite the high levels of air pollution.[57] The incidence of asthma is not lower in the countryside than in cities,[58] except in persons raised on animal farms, where one may assume that children are exposed to animal pathogens.[59]

In 1999, Braun-Fahrländer et al. tested the hypothesis that the lower prevalence of allergic diseases among persons living in rural as compared with urban environments was linked to something other than air pollution.[60] They found that children whose parents were farmers and who lived on their parents' farms were less subject to allergies than other children

from the same rural region who were not raised on a farm. A more recent study carried out in Austria, Germany, and Switzerland confirmed these findings and showed that allergies were less frequent when the children were exposed early and for a prolonged period to farm animals and cow's milk.[59] Data reported by Braun-Fahrländer et al. in this issue of the *Journal* show an inverse relation between endotoxin levels in bedding and the incidence of atopic diseases among children living in rural areas.[61] Other risk factors may include organ damage by environmental toxins and the immunomodulatory effect of vitamin D deficiency. In experiments in animals, vitamin D prevents or decreases the intensity of autoimmune diabetes and experimental allergic encephalomyelitis.[62] In humans, vitamin D deficiency may influence the risk of type 1 diabetes[63,64] and multiple sclerosis,[65] but the data are inconclusive.

IS THE DECREASED INCIDENCE OF INFECTIOUS DISEASES CAUSALLY RELATED TO THE INCREASED INCIDENCE OF IMMUNOLOGIC DISEASES?

There is anecdotal evidence that exposure to infectious diseases is associated with decreased manifestations of immune-related diseases. Measles has been reported to ameliorate the severity of the nephrotic syndrome[66] and atopic dermatitis[67,68] and transiently to suppress cutaneous delayed-hypersensitivity responses to tuberculin.[69,70] Recently, it was reported that the deliberate administration of a nonpathogenic lactobacillus to pregnant women with atopy and, ultimately, to their newborns significantly decreased the incidence of atopic dermatitis in the newborns.[71] Similarly, the administration of probiotics (which are live, nonpathogenic microbes incorporated into food) to infants with atopic dermatitis improved the skin lesions.[72] Children who received antibiotics during infancy had a higher incidence of allergy and other atopic disorders than children who had not received antibiotics[52,73] — a finding in keeping with the observation that oral kanamycin enhances the production of cytokines that promote allergic reactions in infant mice.[74] In addition, regular anthelmintic treatment of children in a slum area of Caracas, Venezuela, where helminths are endemic, was associated with an increased incidence of immediate hypersensitivity to environmental allergens (on the basis of skin tests and specific IgE antibody tests).[75]

Animal Models

The best evidence of a causal relation between infections and allergic or autoimmune diseases derives from animal models. It has been consistently observed that autoimmune diseases in susceptible strains of mice or rats develop earlier and at a higher rate among animals bred in a specific pathogen-free environment than among animals bred in a conventional environment. In nonobese diabetic (NOD) mice and in BB rats, the use of cesarean delivery and isolated living conditions increases the incidence of diabetes from 40 percent to 80 percent[76] (and Chatenoud L: personal communication) (Fig. 4). A similar effect of the use of specific pathogen-free conditions has been reported in rats with collagen-induced arthritis[77] or adjuvant arthritis[78]; the effect was abrogated in the latter case by treatment with neomycin.

Diabetes is prevented in NOD mice by infecting the young mice with mycobacteria,[79] lymphocytic choriomeningitis virus,[80] murine hepatitis virus,[81] lactate dehydrogenase virus,[82] or schistosoma[83] and filariae.[84] Infection of lupus-prone NZB mice or (NZB×NZW)F1 hybrid mice with lactate dehydrogenase virus or *Plasmodium berghei* prevents lupus.[85,86] Treatment with killed bacteria (complete Freund's adjuvant)[87] or bacterial extracts (streptococci[88] or klebsiellae[89]) offers a similar degree of protection against diabetes in NOD mice. Treatment with mycobacteria also protects against experimental allergic encephalomyelitis[90,91] and inhibits the production of IgE antibodies, and the administration of *Mycobacterium bovis* and *M. vaccae* can attenuate the late-phase response, airway hyperresponsiveness, and eosinophilia in bronchoalveolar-lavage fluid in a mouse model of bronchial asthma.[92]

UNDERLYING MECHANISMS

Type 1 and Type 2 Helper T Cells

How infections protect against allergic and autoimmune diseases is unknown. The development of most autoimmune diseases depends on the cytokines interleukin-2 and interferon-γ produced by type 1 helper T cells (Th1), whereas the development of allergic diseases requires interleukin-4 and interleukin-5, both of which are produced by type 2 helper T cells (Th2). The reciprocal down-regulation of Th1 cells by Th2 cytokines and of Th2 cells by Th1 cytokines raises the possibility that these cytokines are involved in the infection-mediated protection against allergy or autoimmunity. Contrary to initial reports,[93] there is a trend toward an association between allergic and autoimmune diseases in individual patients: the frequency of atopic diseases is increased in patients with diabetes and rheumatoid arthritis.[94,95] These observations would fit with the concept of common mechanisms underlying infection-mediated protection against autoimmunity and allergy.

Regulatory T Cells and Cytokines

In NOD mice and in rats with experimental allergic encephalomyelitis — a demyelinating autoimmune disease — the protection against these conditions afforded by treatment with mycobacteria can be trans-

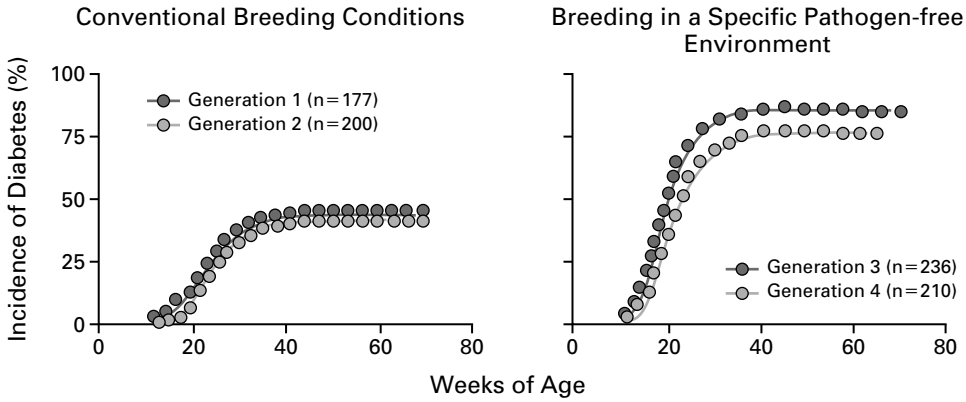

Figure 4. Effect of Infections on the Incidence of Diabetes in Female Nonobese Diabetic Mice.

The incidence of diabetes, which is normally stable in successive generations bred in a conventional environment (generation 1 and generation 2), increases immediately after breeding conditions are changed to a specific pathogen-free environment through the use of cesarean delivery and isolated living conditions (generation 3 and generation 4).

ferred to uninfected animals by CD4+ T cells,[96] and protection is abrogated by treatment with cyclophosphamide, a drug that may act selectively on regulatory T cells.[91,96] In NOD mice, the protection against diabetes afforded by the administration of killed mycobacteria may involve the production of Th2 cytokines within the islets,[97] and such protection can be nullified by treatment with antibodies against interleukin-4 and interleukin-10.[98] However, since mycobacteria protect NOD mice from diabetes even if the animals lack functional interleukin-4 and interleukin-10 genes,[99] other mechanisms may be responsible for this effect. Considerable attention has been focused on CD4+ T cells that express the α chain of the interleukin-2 receptor (CD25), since the depletion of these cells in nonautoimmune mice induces a polyautoimmune syndrome.[100] The mechanism of action of these CD25+ regulatory T cells is still ill defined but may involve transforming growth factor β (TGF-β)[101]; it is not clear whether infections activate these cells. Natural killer T cells, which have properties of both natural killer cells and T cells, may also contribute importantly to immunoregulation.[102]

Interleukin-10, which is produced by Th2 cells, monocytes, and macrophages, slows the progression of autoimmune and allergic diseases in experimental models.[103] Production of interleukin-10 is increased in a number of infectious diseases, and this cytokine probably helps suppress the immunopathologic complications of such infections.[103] For example, the unresponsiveness of T cells in in vitro models of lepromatous leprosy can be reversed by the addition of neutralizing antibody against interleukin-10.[104] Interleukin-10 may also play a part in allergic diseases by shortening the survival of activated (lipopolysaccharide-stimulated) eosinophils.[105] Two groups of investigators have found that there is considerably less interleukin-10 in the lungs of patients with asthma than in the lungs of control subjects,[106,107] although there is a contradictory report.[108] Conversely, schistosoma infection in Gabonese children is associated with increased serum levels of interleukin-10 and a decreased incidence of immediate hypersensitivity to house-dust mite antigens,[109] and the oral administration of lactobacillus, which protects against atopy, stimulates the production of interleukin-10.[110] In any case, interleukin-10 is not the only factor since, as already mentioned, the administration of killed mycobacteria protects against diabetes in NOD mice in which the interleukin-10 gene has been knocked out.[99]

Taken together, the data suggest that infectious agents stimulate the production of regulatory cells whose effects extend beyond the responses to the invading microbe (bystander suppression).[111,112] Interleukin-10 and TGF-β, which may be produced by CD25+ and other regulatory T cells,[113] can inhibit both Th1 and Th2 responses and are plausible candidates as mediators of this regulation. It is of interest in this context that *M. vaccae*–induced protection against allergic bronchial inflammation is mediated by allergen-specific CD4+ CD45 RB^{low} T cells and inhibited by neutralizing antibodies against interleukin-10 and TGF-β.[114]

Other Mechanisms

A second mechanism with relevance to the influence of infection on allergy and autoimmunity is antigenic competition, in which the immune response

to an antigen is decreased by a concomitant immune response against an unrelated antigen.[115,116] The competition is maximal when the unrelated antigen is administered a few days after the administration of the first antigen. Antigenic competition can affect both antibody production (including that of IgE) and cell-mediated immune responses as well as autoimmune and allergic responses.[115,116] The mechanisms of antigenic competition remain unknown despite numerous investigations.[117,118]

The transfer of maternal antiviral antibodies to newborns may also have a role in the susceptibility to autoimmune diseases. Zinkernagel suggested that decreased exposure of women to particular viruses before pregnancy may subsequently reduce the degree of protection against these viruses afforded to their newborns.[119] Exposure to these viruses could provoke an immune response in the children that could ultimately lead to an autoimmune disease. This hypothesis could apply to the development of type 1 diabetes, in which rubella virus and coxsackie B virus have been implicated.

Another mechanism by which bacteria and viruses could protect against immune disorders is related to Toll-like receptors (TLRs), which are receptors for various bacterial components. TLR2 serves as a receptor for peptidoglycan and bacterial lipoproteins, TLR4 as a receptor for gram-negative lipopolysaccharide, TLR5 as a receptor for flagellin, and TLR9 as a receptor for the CpG motif of bacterial DNA.[120] When they bind these bacterial ligands, TLRs stimulate mononuclear cells to produce cytokines, some of which could down-regulate allergic and autoimmune responses. A TLR-mediated effect probably explains the protective effect of the CpG motif against diabetes in NOD mice.[121] Investigation of the role of TLRs in human allergic and autoimmune diseases is just beginning.

There are other mechanisms through which infectious agents may have immunosuppressive properties that are not related to the immune response to specific antigens. Superantigens, which are components of some bacterial products or of viral proteins, may induce the deletion or, sometimes, the activation of T cells expressing a given T-cell receptor *V* gene. The possible role of superantigens in protection against immune disease is illustrated by the fact that experimental allergic encephalomyelitis is prevented by treatment with staphylococcal enterotoxin B.[122] Staphylococcal enterotoxin B has also been shown to inhibit the development of lupus nephritis in MRL/1pr mice.[123]

Recent studies have indicated that measles-induced immunosuppression could be mediated by the direct effect of two measles virus proteins on mononuclear cells.[124] A large variety of parasitic infections are associated with generalized immunosuppression, an effect that is apparently not directly related to the antiparasitic immune response.[125-127]

CLINICAL IMPLICATIONS

The relation between the reduction in the incidence of infectious diseases and the increase in the incidence of allergic and autoimmune diseases, on the one hand, and the apparent protective effect of infections against immune-mediated diseases, on the other hand, have clear clinical implications. A major problem with these correlations is that the infections contributing to protection or susceptibility are ill defined. Moreover, certain infectious agents can trigger allergic or autoimmune diseases. Two lines of research are needed: one should focus on strengthening the epidemiologic evidence, especially through the use of prospective studies. Some allergic and autoimmune diseases are amenable to prospective epidemiologic investigations because they occur early in life (such as atopic dermatitis, asthma, and type 1 diabetes), thereby reducing the survey time. The second line of research should attempt to reduce the incidence of selected allergic and autoimmune diseases by innocuous immunostimulation. Positive results involving treatment with a mycobacterial extract[128] and probiotics[71,72] have recently been reported in patients with atopic dermatitis. Vaccination with bacille Calmette–Guérin produced negative results in patients with type 1 diabetes, possibly because the duration of treatment was too short.[129,130] This approach has produced encouraging results in patients with multiple sclerosis,[131] and it should be investigated further once the treatment is found to be safe.

Vaccination strategies should be examined in the context of the hygiene hypothesis, notably in relation to vaccination with bacille Calmette–Guérin. The problem is complex. Vaccinations may cause immunostimulation and thus have a favorable effect, or they may prevent "protective" infections and thus have an unfavorable effect. It is important to stress that there are no solid data indicating either a positive or a negative role of vaccinations in the development of autoimmune or allergic diseases. The potential benefit of antibiotic therapy in situations in which the pathogenic role of a bacterium is doubtful should be carefully assessed. In addition to the problem of antibiotic resistance, unnecessary treatment with antibiotics could reduce the degree of physiological immunostimulation afforded by commensal bacteria.

There is a certain irony in the fact that we must now search for new ways to reproduce the infectious diseases against which we have been fighting with great success over the past three decades. The challenge is an important one because of the high morbidity of allergic and autoimmune diseases. In fact, it might extend to other immune disorders, notably non-Hodg-

kin's lymphomas, the frequency of which is also increasing in developed countries.[132,133]

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